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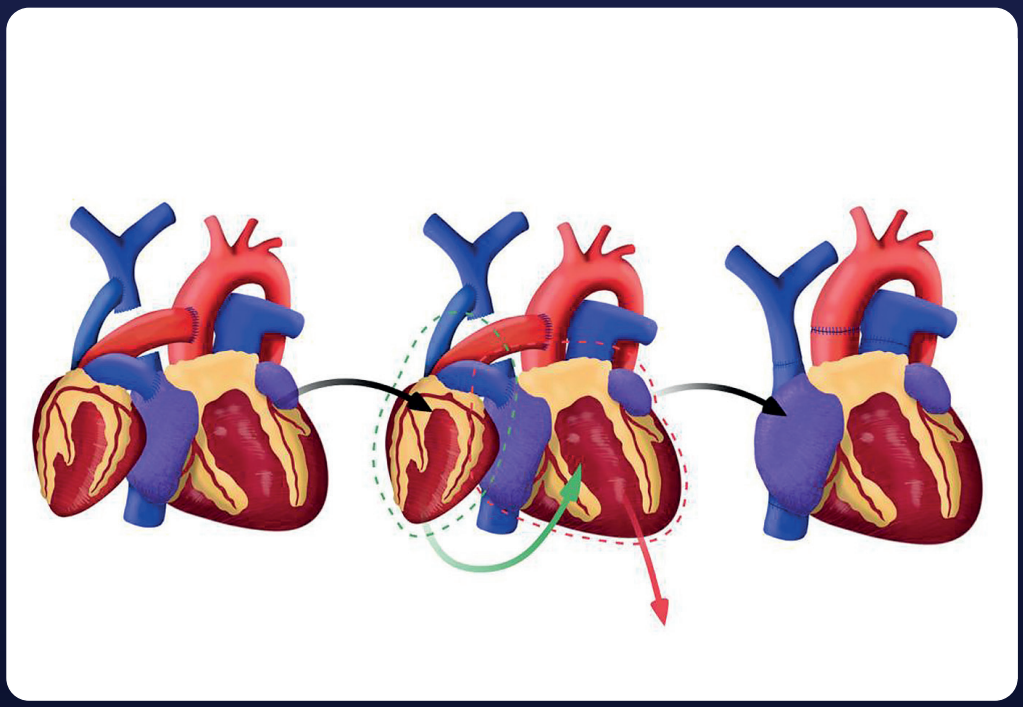

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Special Article

How to Implement a Heart Transplant Program for Patients with Advanced Heart Failure

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Introduction

Patients with heart failure (HF) refractory to guideline-directed medical therapy should be considered for advanced therapies, such as heart transplantation (HT), ventricular assist devices, or even palliative care in cases where these procedures are contraindicated or unavailable.[1] In this scenario, HT is the standard treatment.[1] Brazil has shown a significant increase in the number of transplants in recent years, but this number is still not compatible with the number of patients who require this treatment.[2] Furthermore, most transplants are concentrated in few regions and centers[2] (Figure 1). The following factors limit the growth in the number of HTs performed in Brazil: few qualified transplant centers, inadequate care for donors, critical condition of recipients, and limited access to medium- and long-term circulatory assist devices. Transplant centers aim to optimize recipients' clinical condition, to create logistical conditions to increase the efficiency of organ procurement, and to train professionals, thus generating a positive impact on the number and the outcomes of transplants. The organization of a transplant center with a multidisciplinary team is essential to improve not only the care provided to the recipient, but also the entire process involved in HT, including organ procurement. Transplant centers are composed of a broad multidisciplinary team responsible for evaluating and optimizing recipients' clinical conditions, evaluation of donors, operationalization of procurement, perioperative care, and long-term care of HT recipients (Figure 2). Teams are usually composed of the following: clinical cardiologists, cardiovascular surgeons dedicated to HT, nurses, biomedical doctors, intensive care specialists, infectious disease specialists, pathologists, immunologists, and others.

In this article, we will describe the functioning of one of the transplant centers in Brazil, which performs approximately 50 adult HTs annually and which works on a dedicated basis 24 hours a day, 7 days a week, with emphasis on the importance of a multidisciplinary team and each member's respective functions.[3]

Keywords

Heart Transplantation; Heart Failure; Interdisciplinary Research.

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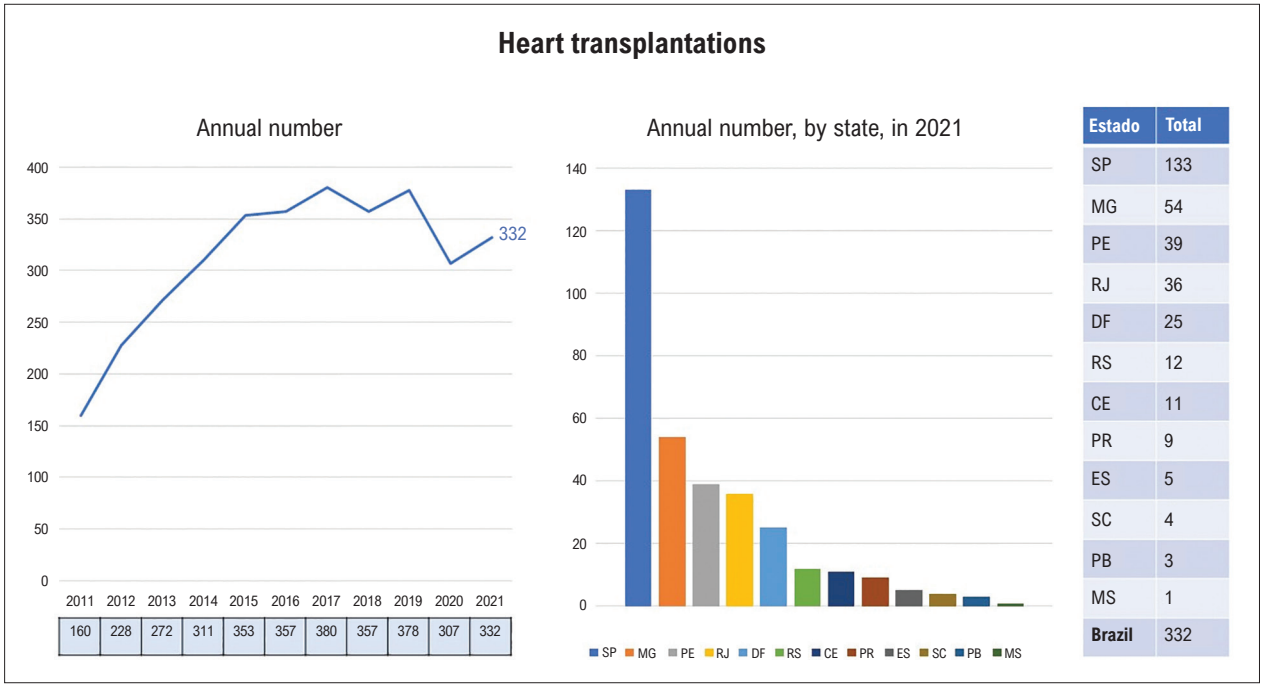
How is a transplant center team formed?

Clinical cardiologist

Training a cardiologist specializing in HF and transplantation is fundamental in order to improve care for patients with advanced cardiovascular disease. In recent years, there has been an increased incentive to train cardiologists in this area due to advances in the treatment of HF, the emergence of new treatment modalities, and the complexity of immunosuppressive therapy during the post-transplant period.[4] In 2010, a group of societies published a document with the competencies required of specialists in HF and HT, highlighting that patients with stage D HF should be evaluated by these professionals.[5] This specialty was formally recognized by the American Board of Internal Medicine and by the Heart Failure Association/European Society of Cardiology, in 2013 and 2014, respectively.[4]

When evaluating patients, before indicating HT, the cardiologist must detect reversible causes of HF that could be amenable to surgical intervention or other specific treatments. When this is not the case, the evaluation of the patient for HT begins. At this point, the objective is to assess whether there are indications and/or potential contraindications to HT, by means of adequate interpretation of the clinical condition and complementary exams, such as ergospirometry test, right heart catheterization, viral serology, immunological panel, and others.[6,7] These exams are essential in deciding whether or not to include a patient in the waitlist for HT. Once included in the waitlist, the patient is monitored, in either an outpatient or a hospital environment, with the transplant center team until the time of the procedure. The clinical cardiologist also participates in donor evaluation. Clinical and anthropometric characteristics of the donor, as well as the brain death process are obtained by the procurement nurse by means of a form sent by the transplant center. The information is passed on to the clinical and surgical team who, together, define whether the donor is favorable for the HT. During the procurement process, it is necessary to identify, by means of data on medical history, physical examination, and laboratory tests, whether any change occurred in the condition that would make the transplant unfeasible at that moment. Subsequently, immunosuppressive therapy and antibiotic prophylaxis are also defined, which are individualized and defined together with the team's infectious disease specialist. In the perioperative care of HT, the cardiology specialist faces the challenges and peculiarities of the postoperative period of HT, namely, primary graft dysfunction, acute right ventricular dysfunction, acute rejection, and infections.[8] Late follow-up after HT takes place in the same transplant center where the procedure was performed. Medical follow-up of these patients consists of periodic assessment of graft



Estado	Total
SP	133
MG	54
PE	39
RJ	36
DF	25
RS	12
CE	11
PR	9
ES	5
SC	4
PB	3
MS	1
Brazil	332

Figure 1 – *Heart transplantation statistics. Adapted from: Associação Brasileira de Transplante de Órgãos.*[2]

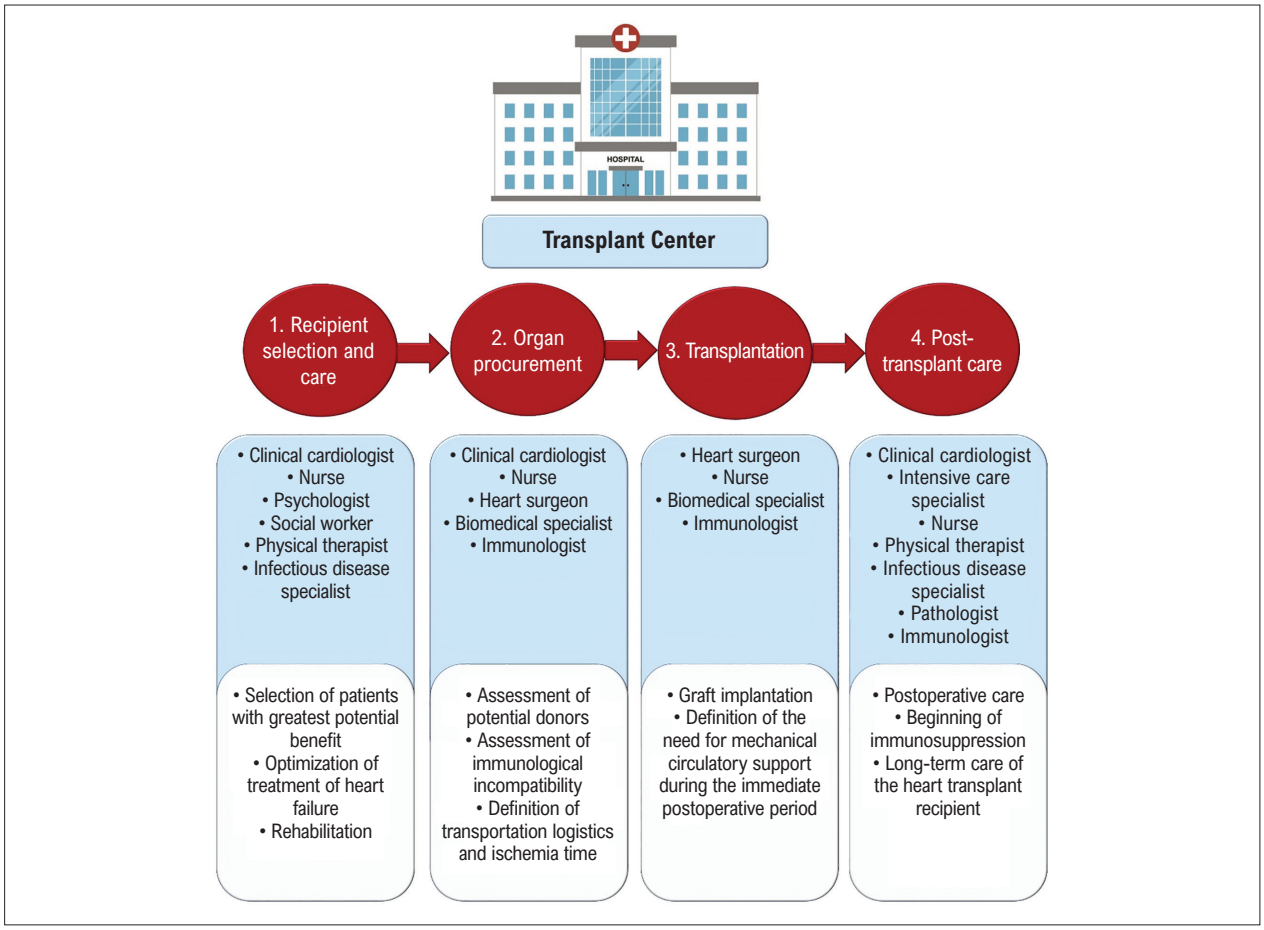


Figure 2 – *Role of the multidisciplinary team in different phases of heart transplantation.*

function, adjustment of immunosuppressive medications, and control of late complications that may occur, including acute rejection, opportunistic infections, pathologies related to the use of immunosuppressants (systemic arterial hypertension, diabetes mellitus, hypercholesterolemia, osteoporosis, and others), reactivation of Chagas disease, graft vascular disease, and neoplasms.[1]

Cardiovascular surgeon

The heart surgeon plays crucial roles. In addition to the surgical procedure itself, he or she acts during the process of evaluation of the recipient, procurement, and the postoperative period. In order to outline the surgical strategy and individualize the procedure, it is essential for the surgeon to get to know the recipient by participating in meetings with the entire transplant center team. Procurement is the first stage of the surgical procedure. Joint evaluation of donor data with the clinical team is crucial for better results. During the procurement process, the surgical team analyzes the logistics to be applied in order to minimize the graft ischemia time. This analysis is especially important in cases of remote procurement. Synchrony between the procurement and implant teams is also worth underscoring. The transfer of the recipient to the operating room occurs only after meticulous evaluation of the graft by the procurement team.

Other medical specialties

In addition to the cardiologist and the heart surgeon, three other medical specialties are directly involved in the different phases that involve HT.

The immunologist plays a crucial role in defining the compatibility of the donated organ with the recipient, by carrying out virtual and real cross-matching, in addition to working together with the clinical cardiologist in the post-HT period in the identification of specific antibodies against the donor, which are the substrate for antibody-mediated rejection.

The pathologist also plays an important role in defining the presence of both cellular and antibody-mediated rejection, in addition to providing data on the explanted heart, which often makes it possible to identify previously unknown pathologies and, thus, define conditions that should be investigated in the transplant recipient's relatives.

Finally, the infectious disease specialist assists the clinical cardiologist at different moments of the process, from pre-transplant care, especially in services where most transplants occur in a priority condition, where patients are hospitalized for many months while waiting for a heart and are, therefore, subject to infections related to prolonged hospitalization, until the follow-up after HT, guiding prophylaxis and/or treatment of opportunistic infections and infections related to the surgical procedure or hospitalization.

Assisting nurse

During the pre-HT phase, patients who are candidates require careful evaluation by the entire multidisciplinary team. In patients undergoing outpatient evaluation, the assisting nurse schedules all the appointments with other professionals. For hospitalized patients, the nurse works as a coordinator so that these professionals can make their evaluations in a synchronized and early manner.

The nurse's assessment aims to evaluate the recipient's conditions, habits, and adherence to drug treatment; to update the patient's vaccination schedule; to educate; and to create or improve conditions so that the patient can be included in the HT waitlist. It is also up to the nurse to interview and evaluate the caregiver of the potential HT candidate. Together with the psychology and social service team, the nurse assesses the family nucleus and identifies whether there is a caregiver capable of assuming the responsibility of caring for the HT candidate after the procedure. After inclusion in the waitlist, the nurse communicates with the patient and the caregiver regarding all the general guidelines related to the waiting process, how the selection of donors occurs, and the criteria for compatibility with the recipient. The patient on the waitlist is accompanied by the nurse in scheduled consultations and in educational meetings with caregivers. During this period, the nurse's role is important to resolve doubts and to reduce the anxiety of patients and family members, thus strengthening the bond with them.[9]

Procurement nurse

During initial evaluation of a potential donor, the nurse's role is fundamental to the procurement process, involving discussion about the clinical and management conditions of the potential donor and the immunological interfaces in relation to the recipient, in addition to the logistics of the entire process. When a donor becomes available, the transplant center informs the place of offer and time of procurement, blood type, mechanism of death, time of brain death, occurrence and duration of cardiorespiratory arrest, doses of vasoactive drugs, urinary output, presence of infection and use of antibiotics, medical history, habits and addictions, immunological evaluation, use of blood products, electrocardiogram, chest X-ray, and, when available, echocardiogram and coronary angiography. At this moment, the procurement nurse verifies this information together with the Brazilian Organ and Tissue Procurement Service and the hospital where the donor is located. Subsequently, the procurement nurse communicates this verified information to the clinical cardiologist, initiating a brief discussion about the case, together with the surgical team, regarding whether to accept or refuse the proposed donor and, consequently, whether or not to perform the HT. Whenever possible, the procurement nurse goes to the hospital, evaluates the donor, and suggests strategies to minimize the potentially deleterious effects of the brain death process.

Psychologist

HF and depression are frequently associated, especially in highly limited patients who are being evaluated for inclusion in the transplant waitlist. The psychologist's role, in both psychological evaluation and follow-up of HT candidates, is fundamental to deciding whether the patient

is emotionally prepared to be included in the waitlist and to endure the waiting time for an organ, which is, in most cases, long. The psychologist can even identify new problems that need to be solved together with the medical team. The long waiting time for a compatible organ, in both inpatients and outpatients awaiting heart transplantation, generates feelings of anxiety and, often, depression, which must be identified by the attending psychologist and promptly treated. However, the psychologist's role also extends to the post-HT phase. Many changes occur within a short timeframe, and the patient needs to adapt to a new life, gaining confidence to return to work and general activities that were limited by HF.[9]

Social worker

The objective of social assessment of HT candidates is to identify socioeconomic and educational factors that may be considered a risk for the patient after the transplant is performed. The social service team analyzes the patient's and caregiver's abilities to accept and adhere; the identification of the caregiver within the family nucleus; the assessment of socioeconomic conditions such as family income, level of education, housing conditions, and profession of the patient/provider; and, finally, the patient's conditions related to travel to the hospital when called for transplantation. Furthermore, the social service team can promote, together with family members, structural changes that allow the transplanted patient to live in the residence in question. After performing the HT, this team must then verify that the interventions proposed to overcome the difficulties have really been implemented and that conditions are adequate for the patient to be discharged.

Biomedical doctor

The biomedical specialist plays a fundamental role during organ procurement. Once a potential donor has been identified, the biomedical specialist assists in evaluating the entire logistics, under the supervision of the procurement surgeon, with the aim of minimizing graft ischemia time during procurement, especially when procurement is done remotely. In addition to this assessment, the biomedical doctor assists the surgeon in the act of procurement, either directly in the operation or indirectly by assisting in the preparation and infusion of the graft preservation solution.

Logistics from procurement to transplantation

Prolonged ischemia time, particularly longer than 4 hours, is an independent risk factor for early graft failure and death.[1] For this reason, in continent-sized countries like Brazil, the issue of procurement logistics is of the utmost importance. Approximately 50% of procurements occur at distances greater than 100 km, which makes it difficult to use ambulances. In these cases, cooperation with the Military Police and Civil Police make it possible to use helicopters, and partnerships with the Brazilian Air Force and the Secretary of State make it possible to use airplanes for remote procurement. Moreover, as procurement occurs at unpredictable moments, it is fundamental to have a full team available 24 hours a day, 7 days a week.

Conclusion

The structuring of a HT center involves training and synchronizing the work of an extensive multidisciplinary team. The objectives of this team are to select recipients with an appropriate profile, to optimize their preoperative clinical conditions, to create procurement logistics that minimize ischemia time and immunological incompatibilities, and to provide long-term care to HT recipients. A clinical cardiologist with experience and specialization in HT plays a central role in this team. Therefore, we believe that it is essential for the Brazilian Ministry of Health to support the creation of residency programs for an additional year in HT, as well as specialized supplementary programs in hospitals with large volume, structure, and tradition in performing this procedure. In this manner, it will be possible to expand transplant centers in Brazil and to provide life-saving treatment to patients who need it.

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Long-Term Ventricular Assist Devices: Where are We in Brazil?

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The use of long-term ventricular assist devices (VADs) as a therapeutic option in patients with advanced heart failure (HF) refractory to drug therapy is well established worldwide. The latest update of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) reported more than 27,000 VAD implants between 2010 and 2019, with approximately 3,000 implants annually in recent years. In addition, 12-month survival rates after implantation reached 82%, with significantly improved quality of life and functional capacity.[1]

The technological development of VADs in the last decade has dramatically changed the type of device used. Between 2010 and 2014, axial-flow devices accounted for most VAD implants. Since 2017, centrifugal-flow VADs with magnetic levitation have had a significant increase in the number of implants, accounting for 75% of implanted devices in 2019.[1]

This technological advancement, combined with increased expertise in the selection and care of patients with a VAD, has allowed gains in survival. Recent data show that the median survival of patients with a VAD is approaching 5 years.

Another trend in recent years, especially in the United States, has been the shift from VAD indication as a bridge to heart transplantation (HT) to destination therapy. This was encouraged by a change in the heart allocation policy by the United Network for Organ Sharing (UNOS) in 2018, which decreased the priority of patients on the HT waiting list with a previously implanted VAD, reducing their chance of transplantation compared with patients treated with intravenous inotropes or with percutaneous mechanical circulatory support.[2]

Until 2017, just under half of implants had destination therapy as a strategy. In 2019, more than 70% of VADs were implanted for this purpose.

Despite advances and promising results with the use of VADs, the rates of device-related events and the need for hospitalization after implantation remain high. More than 60% of patients undergoing a VAD implant are estimated to develop relevant complications and require hospitalization in the first year after the procedure.[1]

These data further support the need for continuous development of new technologies and improvements in VADs. In the Momentum 3 study, which compared axial-flow devices vs centrifugal-flow devices with magnetic levitation, the rates of neurological events were significantly lower in patients with the newer devices.[3] Thus, with the increase in the number of patients receiving next-generation devices, the rates of complications, thromboembolic events, and hospitalizations are expected to gradually reduce.

In Brazil, the first VAD was approved by the Brazilian Health Regulatory Agency (*Agência Nacional de Vigilância Sanitária*, ANVISA) in 2000. Since then, few national studies have been published on the topic.[4] Data on the experience of national excellence centers are also limited.

Data provided by the companies that sell VADs in Brazil indicate that, since 2010, approximately 80 devices have been implanted in the country (one third of which are centrifugal-flow devices), mainly in the last 4 years. Resources for the few VAD implants in Brazil were obtained from health care providers and court decisions, philanthropic programs subsidized by the Brazilian Ministry of Health, private funding, or donations from manufacturers.

The following are major obstacles for a more widespread use of VADs in Brazilian patients with advanced HF:

- High cost of the devices marketed in Brazil.
- A lack of feasibility and cost-effectiveness studies of VADs in hospitalized patients on the HT waiting list in Brazil.
- Questionable interpretation of VAD coverage regulations in ANVISA's list of procedures, which allows health insurance companies to question VAD coverage.

Despite these barriers, Brazilian programs for VAD implantation in selected patients are being developed, although some aspects must be considered and discussed.

Centralizing VAD implant procedures and patient care in regional excellence centers, preferably with experience and capacity to support patients with advanced HF and HT, would be an important strategy to obtain positive results to support this therapy.

The high costs involved in VAD implantation and the high rates of associated complications require good clinical

Keywords

Heart-Assist Devices; Heart Failure; Cardiogenic Shock.

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results to support this type of procedure. Thus, a rigorous selection of patients with low morbidity and mortality risk would be advisable when implementing a VAD program.

In addition, the scarcity of resources for VAD implantation in centers with well-established HT programs places patients with limitations for HT (such as the presence of severe pulmonary hypertension and increased immune sensitization) high in the priority list to receive this therapy.

Finally, the creation of a Brazilian registry on the experience of VAD implantation would be a good strategy to understand the country's reality and difficulties and to propose solutions according to the best medical practices.

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Heart Transplant from a Genetically-Modified Pig: A Paradigm Shift?

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Heart transplant remains the therapy of choice for patients with end-stage heart failure but is limited by chronic shortage of donated organs. Mechanical circulatory support (MCS) devices, with modern designs, have been used as destiny therapy, yielding better results that have positively impacted patient survival.[1] The indications for MCS have significantly increased and become part of the current context of potential candidates for transplant, be it as destiny therapy, bridge-to-transplant or bridge-to candidacy. However, there remains a considerable number of patients who would benefit from the transplant if the availability of donated organs was higher. According to the Brazilian Organ Transplant Association (ABTO), approximately 400 heart transplants are performed yearly in Brazil, but the demand for this procedure is 1,600 per year, *i.e.*, many patients die waiting for an organ.

A possible solution for this issue is xenotransplantation, the process of transplanting organs from other animals, which has gained increasing interest in the last years[2,3] for a combination of reasons. First, the efficacy of preclinical models has improved, with an increase in survival time of xenografts. Second, the rapid advances in genome editing, particularly the advent of CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), which allowed the generation of donor pigs with multiple genetic protection modifications; what used to take years can now be done in months, with more accurate and comprehensive results. Third, the spectrum of the porcine endogenous retrovirus (PERV) significantly reduced. There is no evidence of PERV transmission in clinical trials of preclinical models, and novel treatment options and even elimination of these viral diseases are now available.[4] Due to its potential, the importance of xenotransplantation as a solution for the shortage of human organs and tissues remains a great hope for the transplant community, especially for the patients who face advanced disease and high mortality while waiting for a donated heart.

Keywords

Heart Transplantation; Transplantation, Heterologous; Allergy and Immunology; Genetically Modified Animals; Swine

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Many questions and ethical concerns have been raised about xenotransplantation. The risk of infection transmission from pigs may require a lifelong surveillance not only for transplant recipients but also for their family members. Another issue concerns the performance of animal experiments with a specific purpose of producing genetically engineered pigs for transplants and to save lives. Discussions among the community, regulatory agencies and animal protection agencies have played an important role in the advancement of research, that may become true in a near future.[5]

This year, with enthusiasm, we received the news of the first heart transplant from a pig to a male patient at the University of Maryland Medical Center. The regulatory agency of the U.S.A federal government (Food and Drug Administration) had approved xenotransplantation under "compassionate use" rules for emergency situations. The patient had refractory heart failure, severe sarcopenia, was in prolonged extracorporeal membrane oxygenation (ECMO), and considered not eligible for conventional heart transplant according to the medical staff.

The patient died approximately 50 days after the transplant, due to progressive cardiac hypertrophy and severe diastolic dysfunction. The patient had been transitioned back to ECMO support until the end. Biopsy and pathologic examination did not reveal any signs of humoral or cellular rejection. Many hypotheses have been proposed, that will probably be elucidated in the final publication of the data. One of the hypotheses is that the patient heart was affected by porcine cytomegalovirus, which may have contributed to refractory and irreversible dysfunction. Also, the physiological functioning and even gravitational aspects could have affected the graft function.

This pioneering experiment provided valuable indications for the possibility of the normal functioning of a genetically modified pig heart in a human person while the immune system is adequately suppressed. It is important that the valuable insights from this case guide future research and indications of the procedure.

The application of this groundbreaking research in a patient was only possible due to numerous previous work that helped to define the genetic engineering required to overcome the feared immunological and infectious barriers. This research started more than 30 years ago and constructed the basis for making this procedure feasible.

The reason for choosing pigs as donors was these animals have a shorter gestational period and time to maturity (around one year) and similar size for organs as compared with humans. Pigs have long been used in Human Medicine, for example for skin grafts and cardiac

valve implants. However, organ transplantations are far more complex than the use of highly processed tissues. The gene-edited pigs were produced by Revivicor (United Therapeutics Corporation, Virginia, USA), one of the several animal biotechnology companies at the frontiers of knowledge focused on producing organs for transplantation into humans. According to available information, 10 genes were supposedly manipulated – three knockout genes, one gene was inactivated to prevent hypertrophy and six human genes were inserted into its genome.

The next challenge was to neutralize the effect of pre-existing antibodies (AB) and manage potential incompatibility between the complement and the coagulation systems, and infection of the receptor by endogenous retroviruses.

The introduction of the CRISPR technology into xenotransplantation increased the speed of genetic manipulation in pigs. Thanks to this technology, researchers cannot only produce knockout and knock-in animas targeting multiple genes, but also exclude the expression that increases the risk of specific viral diseases. Genetically modified pigs using the CRIPSR technology have been used in several important studies involving AB and coagulation dysfunction. Today, there are more than 26 types of gene-edited pigs available for xenotransplantation research.[6]

Endothelial injury may occur within minutes due the activity of pre-existing AB against pig specificities. The AB-antigen binding triggers a hyperacute rejection after reperfusion of the xenograft. To prevent this complication, using genetic engineering, the three main genes responsible for the α-1,3-Gal, β4Gal and Neu5Gc proteins were inactivated by gene knockout, creating the triple-gene knockout pig.

The activation of the complement pathway and changes in the coagulation system may lead to the xenograft dysfunction within days or weeks, and consequent loss of the graft. At the human blood-porcine endothelial interface, porcine thromboregulatory molecules such as thrombomodulin, endothelial protein C receptor (EPCR), and thrombin activatable fibrinolysis inhibitor interact inappropriately with human coagulation pathway molecules. This can result in thrombotic microangiopathy in the xenograft and disseminated intravascular coagulation in the receptor.

To prevent the production of new AB or increase in pre-existing AB, the use of anti-CD40 monoclonal AB has been proposed, along with other components of a more comprehensive immunosuppressive regimen.[7]

The cardiac xenotransplantation, performed by Mohiuddin et al. evidenced the possibility of the long-term survival of cardiac grafts of genetically modified pigs.[8] Genetic modifications in pigs, combined with an intensive immunosuppressive therapy, based on a chimeric anti-CD40 monoclonal antibody, prevented humoral rejection and dysregulation of systemic coagulation pathway, promoting the cardiac xenograft survival, in addition to controlling inflammation and coagulation.[9]

Some lessons can be learnt from this first, groundbreaking case. Preoperative clinical conditions, such as sarcopenia, prolonged inactivity, and infections, made difficult the prompt recovery of the patient after transplantation. In this case the patient had pancytopenia, which prevented the use of the ideal immunosuppressive regimen. The severe interstitial edema, with myocardial necrosis and no cellular infiltrate, which led to ventricular dysfunction, will need to be better understood, including whether or not there was an influence of immunological components.[10]

We are truly experiencing an important paradigm shift in the field of transplantation. In the next years, we will witness great progress and research continuation towards feasible, safe and effective procedure in clinical practice. The University of São Paulo is planning the construction of a pig facility, focusing on research to make suitable clinical transplantation within the next five years. Again, research and science are playing their role in the progress of humanity. The future is happening now, right in front of our eyes.[11]

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Editorial

Biologic Left Ventricular Assist: A New Strategy for Patients with Advanced Heart Failure with Pulmonary Hypertension

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Pulmonary arterial hypertension due to increased vascular resistance is a clinical condition that directly impacts the prognosis of patients with heart failure (HF), and it is considered one of the main contraindications to orthotopic heart transplantation.[1] Although hemodynamic values vary in the literature, there is a consensus that pulmonary artery systolic pressure above 50 mmHg, transpulmonary gradient above 15 mmHg, and pulmonary vascular resistance above 3 Wood units, when unresponsive to vasodilators, contraindicate orthotopic transplantation.[2] Therapeutic strategies to decrease or reverse this condition are a challenge in clinical practice, which, if resolved, may allow definitive treatment of HF with orthotopic transplantation.

The use of long-term continuous-flow left circulatory assistance devices as a bridge to candidacy is a reality in large transplant centers in developed countries. Several studies have demonstrated that device implantation not only leads to the expected eligibility for orthotopic transplantation in some patients; it also improves the quality of life of patients for whom it ends up remaining as the target therapy. In a study recently carried out by Ruan et al, it was demonstrated that, approximately 6 months after device implantation, there was a reduction and stabilization of pulmonary pressure.[3] The reversal of pulmonary hypertension through left assistance devices is possible, given that there is an important decrease in filling pressures by means of the continuous emptying of the left ventricle.[4]

Heterotopic transplantation is a technique that was initially conceived by Christian Barnard in 1974 as an alternative to circulatory support in cases of graft failure due to primary dysfunction or hyperacute rejection and in cases of pulmonary hypertension. In addition to these three classic indications, over time, two other indications were added, namely, when there is a substantial mismatch in weight between the donor and recipient and when the graft is considered marginal (long ischemia times, high doses of vasopressors and/or inotropes, and segmental alterations on echocardiogram).[5] The use of the heterotopic technique as a form of ventricular support was described by Barnard; however, in the configuration initially proposed, support is biventricular, and the left and right circulation are connected in parallel. This model of circulation causes the native heart to progressively stop its mechanical activity, which can cause arrhythmias, formation of intracavitary thrombi followed by emboli, in addition to increasing the incidence of endocarditis. These complications were responsible for the discontinuation of the technique.[6]

In 2011, Jake and Hannah Copeland published an alteration of Barnard's heterotopic transplant technique by means of parallel connection of the left ventricle and only decompression of the right ventricle. This modification proved to be effective in cases where right ventricular function is normal, which is similar to the indications for implantation of left mechanical assistance. This model of heterotopic transplantation can be considered biologic left ventricular assist (bio-LVA).[7]

In 2020, Gaiotto et al. proposed a modification of the Copeland technique, in which the superior vena cava drainage is directly connected to the right atrium of the implanted heart, keeping the right ventricle functioning and in series with the cranial segment of circulation. This model was proposed for patients with fixed pulmonary hypertension with contraindication to orthotopic transplantation. Once left assistance is performed with this model, a drop in pulmonary pressure and the feasibility of conventional transplantation are expected. Knowing that the heart in the heterotopic position maintains left and right ventricular function by modification of the previously described technique, in a subsequent moment, the native heart can be explanted and the other heart can be repositioned in an orthotopic position (Figure 1). This proposal with both stages was already carried out in 2021, and the result was surprising. The patient, who had a contraindication to conventional transplantation and was in palliative care, underwent heterotopic implantation as a "bridge to candidacy." In less than 40 days, there was a significant drop in pulmonary pressure, and the second stage was successfully performed. He did not have access to the long-term mechanical device due to the high cost.

There is still a lot to be studied regarding this topic, and we understand that we need to perform other cases for better conclusions. The fact is that, as of now, with only one case performed, the technique conceived by Gaiotto et al. has already shown to be promising, as it may provide a low-cost and effective alternative for patients with fixed pulmonary hypertension.[8] Could this be the rebirth of heterotopic transplantation, this time with a new configuration? This could give hope to patients in palliative care who will never have access to long-term mechanical devices.

Keywords

Heart Transplantation; Heart Failure; Hypertension, Pulmonary

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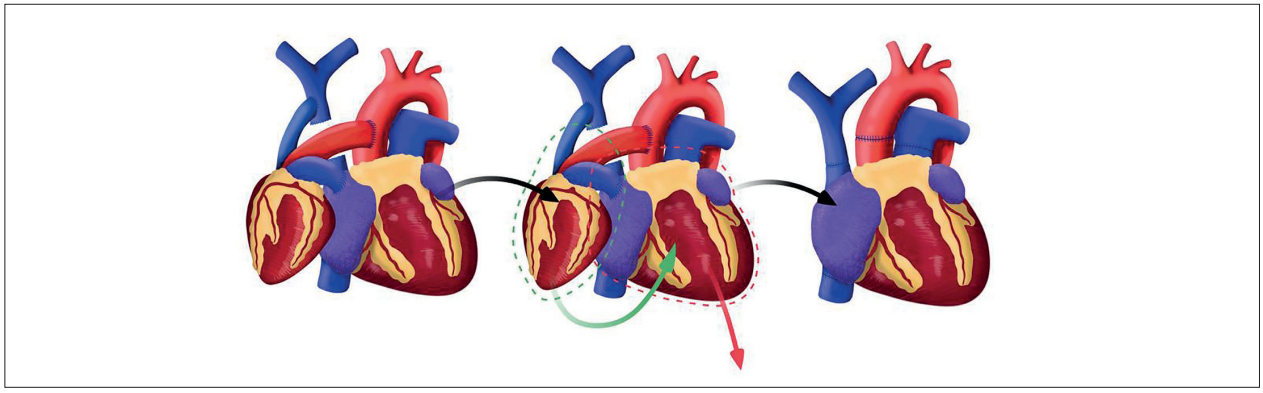

Figure 1 – *Images demonstrating the technical modification of heterotopic transplantation and, subsequently, the final aspect of the second stage of the procedure.*

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Original Article

Association of Age with Optimal Medical Therapy in Patients with Chronic Heart Failure

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Abstract

Background: **The adherence to guideline-directed medical therapy in patients with heart failure (HF) remains suboptimal.**

Objectives: **We evaluated the association between age and adherence to guideline-directed medical therapy in patients with chronic HF and explored whether polypharmacy and comorbidities might explain this association.**

Methods: **We performed a cross-sectional study of 374 patients with chronic HF and left ventricle ejection fraction < 50% (23 to 89 years old, 33% women) between 2018 and 2019. GDMT was defined as using HF-related disease-modifying medications at the target dose according to guidelines. Patients were classified in 3 age groups (23 to 57, 58 to 67, and 68 to 89 years old).**

Results: **Older patients were less likely to receive optimal therapy (33% versus 24% versus 15%, p < 0.001 for each age category, respectively). After adjusting for potential confounders, the chances of receiving medical therapy at optimal dose significantly reduced for each age-decade increase (OR 0.66 [95% confidence interval 0.48 – 0.92], p = 0.013). The proportion of this association that was explained by polypharmacy (0% [0% – 3.5%]) or comorbidities (7% [0% – 41%]) was negligible.**

Conclusion: **We found that age was inversely associated with optimal drug therapy for HF, and polypharmacy or comorbidities do not appear to explain this.**

Keywords: **Heart Failure; Drug Therapy; Polypharmacy; Aging.**

Introduction

Heart failure (HF) affects 26 million people worldwide and is increasing in prevalence.[1] The expenditures are notable and will raise considerably in an aging population. HF has high mortality and morbidity, and treatment with different class of drugs can improve survival of these patients, as demonstrated in clinical trials.[2-10] Therapy using these drugs at target doses similar to those used in trials are paramount to modify the natural course of the disease, and they have been recommended by HF-related guidelines, which has been denominated guideline-directed medical therapy (GDMT).[11]

Despite the substantial evidence accumulated in the last 3 decades, the adherence to GDMT remains low. A previous study showed that only 1% of eligible patients with HF simultaneously received the target doses of angiotensin converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB)/angiotensin II receptor-neprilysin inhibitor (ARNI), beta-blocker, and mineralocorticoid receptor antagonist (MRA) therapy recommended by guidelines.[12] Failure to achieve the target dose has been associated with worse survival.[13] The reasons for low compliance to GDMT are complex and likely multifactorial. A few studies have explored these reasons and suggested that drug optimization appear to be lower among older patients with HF, when compared to younger ones, but other factors may also play a role in the low treatment compliance, such as low income and health illiteracy.[14-16] However, there is a lack of studies evaluating rates of compliance to GDMT in low- and middle-income countries.

We, therefore, aimed to analyze the relation between age and GDMT in patients with HF treated in an institution from a middle-income country. We also explored whether the number of prescribed medications (polypharmacy) and number of comorbidities can help explain this association, as they might contribute to poor adherence to treatment.

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Methods

Study population

This is a cross-sectional observational study approved by the local institutional ethics committee under protocol number 3.227.412. We included consecutive patients over 18 years old referred to the Heart Failure Outpatient Clinic of the *Santa Casa de Misericórdia de Curitiba*, a tertiary university center dedicated to specialized care of patients with HF from Brazil's Unified Public Health System (SUS), from May 2018 to February 2019 in Curitiba, Paraná, Brazil. All of them were first diagnosed with HF and received medical treatment in primary care centers from SUS. They should be referred to the specialized center if they have been hospitalized for HF, or if they were considered refractory to medical treatment. Inclusion criteria were previous diagnosis of HF and left ventricle ejection fraction (LVEF) below 50%, measured by an echocardiogram performed within the previous 12 months. The patients were approchead during their routine consultation, and all the data were collected during the visit and from medical records. All patients provided written informed consent. Those who refused to participate in the study or had insufficient information, such as missing data on echocardiogram or laboratory exams, were excluded.

Exposure

Patients' ages were defined according to birth date as registered in medical records and evaluated as a continuous variable. The patients were also classified into 3 groups according to age tertiles: the first tertile from 23 to 57 years old, the second from 58 to 67 years old, and the third from 68 to 89 years old.

Outcome

The outcome was the proportion of patients under GDMT, i.e. using optimal medical treatment as recommended by the 2018 Brazilian Heart Failure Guidelines (*Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda*).[17] Patients were considered under GDMT if they were using the following drugs at the target dose according to European Society of Cardiology guidelines (Supplemental Table 1): 1) a HF-specific beta-blocker (carvedilol, metoprolol succinate or bisoprolol); 2) either an ACEI, ARB or ARNI; and 3) a MRA if symptomatic (New York Heart Association [NYHA] class II to IV).

Other covariates

Sex, etiology of HF, NYHA functional class, and creatinine blood levels were obtained from medical records. Blood pressure was measured during the patient's visit as recommended by international guidelines.[11,17] Height was measured in orthostatic position using a calibrated anthropometer, and weight was systematically measured on a calibrated scale. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared.

Time from the diagnosis of HF was the period in months between the diagnosis of HF and the date the patient was included in the study. The moment of diagnosis was estimated during patient interview based on either the first hospitalization due to HF or when they started to present typical symptoms of HF and were told they had HF, whichever happened first.

We estimated the severity of the disease by calculating the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score, which is a score that predicts the 1- and 3-year mortality in patients with HF.[18,19] This score combines 13 independent clinical variables such as LVEF, age, systolic blood pressure (SBP), BMI, creatinine levels, NYHA class, sex, current smoking status, diabetes, chronic obstructive pulmonary disease (COPD), first diagnosis of HF > 18 months, beta-blocker, and ACEI/ARB (Supplemental Table 2).

Polypharmacy and comorbidities

We defined polypharmacy as the use of medications belonging to pharmacologic classes other than those in the GDMT definition (i.e. ACEI, ARB, ARM, ARNI, or HF-specific beta-blocker).[11,17] They include medications related to HF, such as ivabradine, digoxin, loop diuretic, thiazide, hydralazine, and nitrate, as well as to comorbidities, such as statins, antiarrhythmics, anticoagulants, aspirin, clopidogrel, and others. For instance, if the patient was taking enalapril, carvedilol, digoxin, furosemide, statin, and aspirin, polypharmacy should be counted as four. As they are part of GDMT definition, enalapril and carvedilol did not count toward polyphamarcy.

The number of comorbities were defined according to the presence of hypertension, diabetes, coronary artery disease, chronic kidney disease, and COPD.

Statistical analyses

Continuous variables were evaluated for the Gaussian distribution of the data and were compared among the 3 age tertiles using ANOVA or Kruskal-Wallis test accordingly. Categorical variables were compared among groups using chi-squared test. To evaluate the independent association between age and GDMT, we performed multivariate logistic regression analysis with age as a continuous variable adjusted for sex, BMI, etiology of HF, LVEF, SBP, heart rate, NYHA functional class III/IV, MAGGIC score, and creatinine blood levels. Finally, we added polypharmacy and comorbidities to the model as potential mediators for the association between age and GMDT based on the previous hypothesis that elderly patients might take a greater number of medications and/or have more comorbidities, which might lead to less treatment optimization for HF due to drug side effects and lack of compliance. Structural equation models were built to assess the direct and indirect effects of age and to estimate the percentage of the total effect that is mediated by polypharmacy. All analyses were performed using Stata version 15 (Stata Corp, College Station, TX, USA).

Results

Study population

We evaluated 504 patients with HF from May 2018 to February 2019. Those with LVEF ≥ 50% (n = 123) or missing data (n = 7) were excluded, resulting in 374 patients for the present analysis. The mean age of the patients was 61 ± 12 (range 23 to 89) years old; 21 (6%) patients were octogenarians, and 33% were women. Table 1 displays the patients' characteristics according to age tertiles. Older patients had lower BMI, were more likely to present the ischemic and Chagas etiologies of HF, and had higher creatinine blood-levels and MAGGIC score, as compared to younger ones. LVEF, SBP, heart rate, functional class, and duration of HF were similar across age tertiles (Table 1). The proportion of patients using sodium-glucose cotransporter-2 inhibitors was very small (1 [0.8%], 1 [0.8%], and 2 [1.7%], p value = 0.48, in the three age tertiles, respectively).

Age and guideline-directed medical therapy

Older patients were less likely to receive optimal medical therapy according to GDMT. For each age decade increase, the chance of receiving optimal medical therapy significantly reduced (OR 0.67 [95% confidence interval 0.56 – 0.82], Table 2). This association remained significant after adusting for potential confounders, such as sex, BMI, etiology of HF, LVEF, SBP, heart rate, NYHA functional class III/IV, MAGGIC score, and creatinine blood levels (OR 0.66 [95% confidence interval 0.48 – 0.92], Table 2, Figures 1 and 2). There was no interaction between age and GDMT association and sex (p for interaction = 0.51).

Table 1 – Patient characteristics according to age tertile

Age tertiles	First tertile 23 a 57 y n=130	Second tertile 58 a 67 y n=128	Third tertile 68 a 89 y n=116	p value
Female, n (%)	39 (30)	42 (32.8)	42 (36.2)	0.59
BMI, kg/m²	29.6 ± 6.6	27.9 ± 5.2	26.5 ± 4.8	< 0.001
Etiology of HF, n(%)				< 0.001
Ischemic	41 (31.5)	53 (41.4)	59 (50.9)	
Chagasic	5 (3.8)	9 (7.0)	15 (12.9)	
Other	84 (64.6)	66 (51.6)	42 (36.2)	
Ejection fraction, %	33.4 ± 8.5	33.1 ± 8.9	32.1 ± 7.9	< 0.42
SBP, mmHg	112.1 ± 19.4	109.1 ± 18.8	110.2 ± 21.3	0.48
Heart rate, bpm	73.4 ± 13.7	71.9 ± 14.1	71.5 ± 13.1	0.53
NYHA 3 or 4, n(%)	35 (26.9)	34 (26.6)	32 (27.6)	0.98
Hypertension (%)	77 (59.2)	87 (67.9)	88 (75.9)	0.005
Diabetes (%)	31(23.8)	37 (28.9)	47 (40.5)	0.005
Coronary artery disease (%)	48 (36.9)	62 (48.4)	71 (61.2)	< 0.001
Chronic kidney disease	9 (6.9)	16 (12.5)	27 (23.3)	< 0.001
COPD	3 (2.3)	8 (6.2)	10 (8.6)	0.031
2 or more comorbities	49 (37.7)	67 (52.3)	80 (68.9)	< 0.001
Target dose according to GDMT, n(%)				
ACEI/ARB or ARNI	71(54.6)	60 (46.9)	45(38.3)	0.013
BB	80 (61.5)	71 (55.5)	57 (49.6)	0.06
MRA*	64 (80.0)	63 (80.8)	69 (75.0)	0.44
GDMT	43 (33.1)	31 (24.2)	17 (14.7)	< 0.001
MAGGIC score, points	12.9 ± 5.5	17.3 ± 6	24.2 ± 5.3	< 0.001
EGFR, mL/min per 1.73m²**	81.7±25.3	72.6±21.2	54.9±24.4	< 0.001
Onset of HF, years	3.3 [1.4-6.0]	4.2 [1.4-7.7]	2.6 [1.2-6.0]	0.35

*ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; ARNI: angiotensin receptor-neprilysin inhibitors; BB: beta-blocker; BMI: body mass index; COPD: chronic obstructive pulmonary disease; Cr: creatinine; EGFR: estimated glomerular filtration rate; HF: heart failure; GDMT: guideline-directed medical treatment; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; SBP: systolic blood pressure. *Only for symptomatic patients **EGFR was estimated by the CKD-EPI formula.[30]*

Table 2 – Association between age and guideline-directed medical therapy after accounting for potential confounders

	N	OR	95% CI	p value
Age, for each 10-year increase				
Unajusted	374	0.67	(0.56-0.82)	<0.001
Adjusted for model 1	358	0.71	(0.57-0.88)	0.02
Adjusted for model 2	334	0.66	(0.48-0.92)	0.013

Model 1: Adjusted for sex, body mass index, etiology of heart failure, left ventricle ejection fraction, systolic blood pressure, heart rate, New York Heart Association functional class III/IV, and creatinine blood levels. Model 2: Adjusted for Model 1 + MAGGIC score. CI: confidence interval; OR: odds ratio.

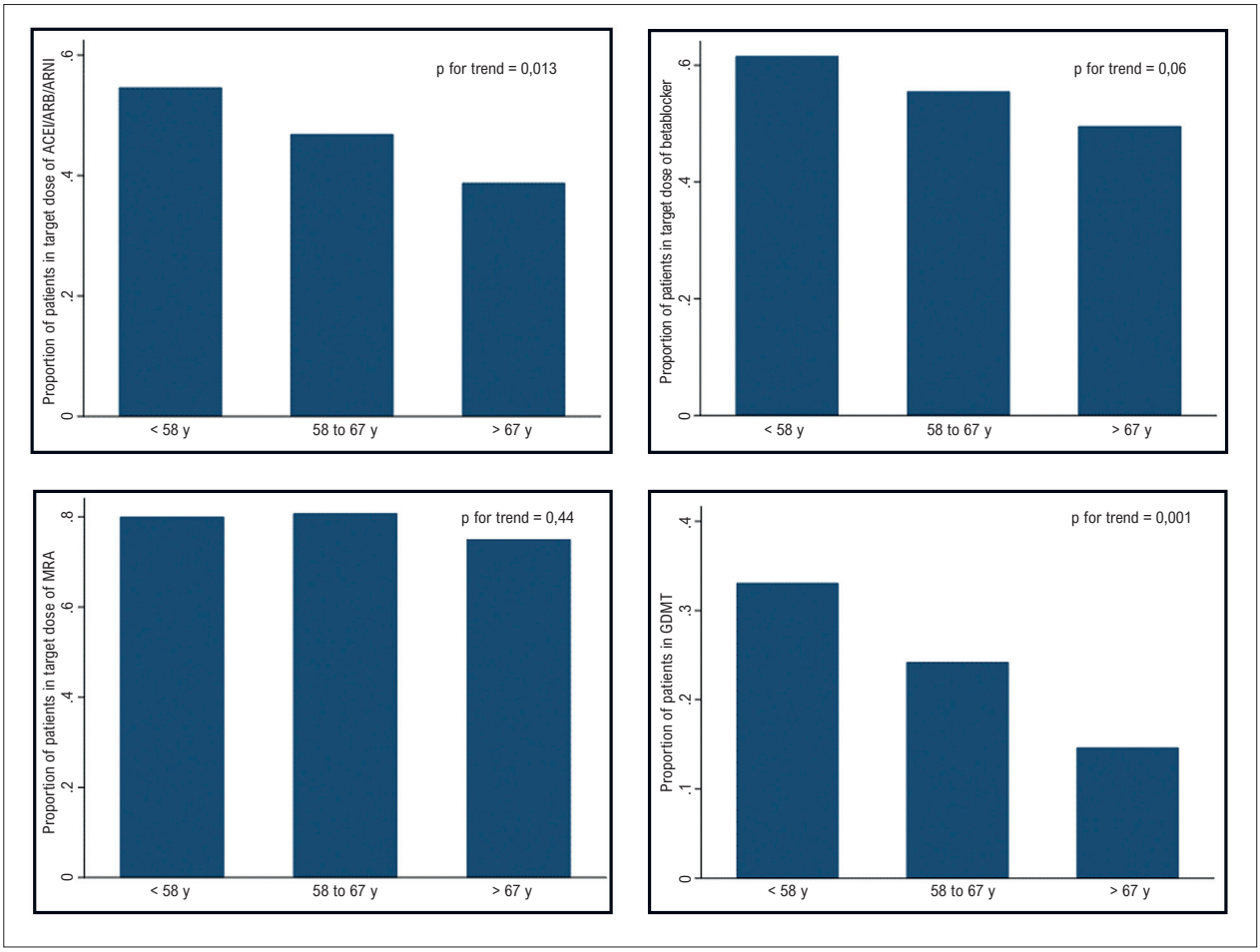

Figure 1 – *Proportion of patients at target dose of each heart failure medication as recommended by guidelines according to age tertiles. ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; ARNI: angiotensin receptor-neprilysin inhibitors; GDMT: guideline-directed medical treatment; MRA: mineralocorticoid receptor antagonist.*

Polypharmacy and comorbidities

Older patients were more likely to use bisoprolol instead of carvedilol as HF-specific beta-blockers (Table 3). They were also more likely to use loop diuretics and statins (Table 3). Use of ACEI, ARB, MRA, digoxin, thiazide, hydralazine, nitrate, antiarrhythmic, anticoagulant, aspirin, and clopidogrel were similar between the age tertiles (Table 3). The proportion of the association between age and GDMT mediated by polypharmacy was 0% (0% – 3.5%). We also analyzed the number of comorbidities (hypertension, diabetes, coronary artery disease, chronic kidney disease, and COPD) to evaluate whether a high proportion of comorbidities might explain the inverse association between age and GDMT. We found that the number of comorbities mediated only 7% (0% – 41%) of this association.

Original Article

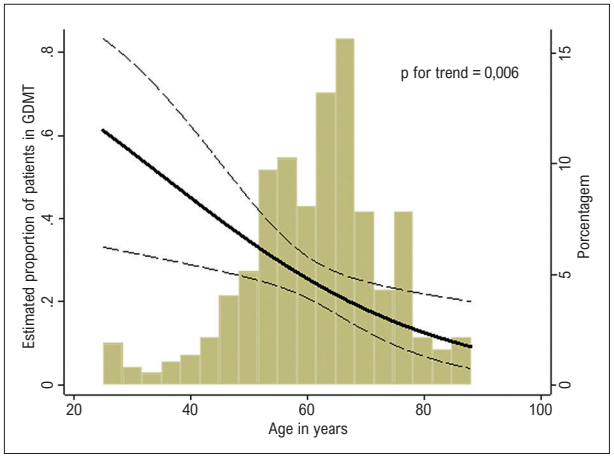

Figure 2 – *Association between medical treatment of heart failure according to guidelines and age after adjusting for potential confounders GDMT: guideline-directed medical treatment.*
**Adjusted for sex, body mass index, etiology of heart failure, left ventricle ejection fraction, systolic blood pressure, heart rate, New York Heart Association functional class III/IV, MAGGIC score, and creatinine blood levels*

Discussion

In this study of patients with chronic HF in a middle-income country, we found that optimal medical therapy for HF was significantly lower in elderly patients, compared to younger ones. This inverse association between age and optimal medical therapy was independent of heart rate, SBP, and disease severity. Also, this does not appear to be explained by polypharmacy or by the number of comorbidities, indicating treatment complexity, among elderly patients. It is noteworthy that the proportion of patients in GDMT was low across all ages. Our results show that there is much room for improvement in therapy for HF in clinical practice, which has the potential to improve survival in these patients.

Previous studies had suggested that older age can be related to lower rates of reaching target doses for HF-related medications.[15] In a study from Japan, it was shown that the presciption rates according to GDMT were significantly lower in patients 80 years old or older.[14] Another study, a survey from 36 countries worldwide found an inverse association between age and likelihood of receiving beta-blockers at the target dose in patients with HF with reduced ejection fraction.[15,20] They also found that rates of use of ACEIs and beta-blockers at target dose were quite

Table 3 – Association between use of medications and age categories

	First tertile	Second tertile	Terceiro tercil	p value
	23 to 57 y n=130	58 to 67 y n=128	68 to 89 y n=116	
Disease-modifying medications				
Carvedilol, n(%)	98 (75.4)	86 (67.2)	66 (56.9)	0.002
Metoprolol succinate, n(%)	11 (8.5)	11 (8.6)	12 (10.3)	0.61
Bisoprolol, n(%)	18 (13.8)	27 (21.1)	35 (30.2)	0.002
ACEI, n(%)	67 (51.5)	55 (43)	48 (41.4)	0.11
ARB, n(%)	34 (26.2)	47 (36.7)	30 (25.9)	0.98
ARNI, n(%)	24 (18.5)	22 (17.2)	27 (23.3)	0.36
MRA, n(%)	103 (79.2)	98 (76.6)	88 (75.9)	0.53
Other HF-related medications				
Ivabradine, n(%)	16 (12.3)	3 (2.3)	4 (3.4)	0.003
Digoxin, n(%)	34 (26.2)	24 (18.8)	24 (20.7)	0.29
Loop diuretic, n(%)	88 (67.7)	88 (68.8)	90 (77.6)	0.09
Thiazide, n(%)	19 (14.6)	15 (11.7)	10 (8.6)	0.15
Hydralazine, n(%)	32 (24.6)	29 (22.7)	21 (18.1)	0.22
Nitrate, n(%)	31 (23.8)	25 (19.5)	23 (19.8)	0.43
Other medications				
Statin, n(%)	75 (57.7)	93 (72.7)	90 (77.6)	<0.001
Antiarrhythmic, n(%)	14 (10.8)	5 (3.9)	9 (7.8)	0.34
Anticoagulant, n(%)	31 (23.8)	27 (21.1)	37 (31.9)	0.16
Aspirin, n(%)	63 (48.5)	79 (61.7)	66 (56.9)	0.17
Clopidogrel, n(%)	10 (7.7)	8 (6.2)	14 (12.1)	0.24

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; ARNI: angiotensin receptor-neprilysin inhibitors; HF: heart failure; MRA: mineralocorticoid receptor antagonist.

low (28% and 15%, respectively), and adherence to guidelines varied across different regions around the world, which may result from different cultural and economic aspects.[15] Althought they included 5 continents, countries in South America were under-represented in this survey. Our study describes the rates of guideline-based prescriptions of drugs in HF in a Brazilian city, adding that older patients were also less likely to receive optimal medical therapy.[20] Conversely, we found higher rates of ACEIs and beta-blockers at target dose than those previous reports, probably reflecting patients treated in a referral center for HF, with access to medications free of cost.

The reasons for lower prescription according to guidelines in elderly patients are multifactorial. It has been suggested that elderly individuals are prone to hypotension and bradycardia, and these were important reasons for non-prescription of guideline-recommended medications in the QUALIFY survey.[15] Nevertheless, we did not find significant differences in SBP and heart rate among age tertiles in our study, and GDMT rates remained lower among elderly patients after adjusting for these parameters.[15] Therefore, there might be other factors, such as concern related to adverse effects and treatment inertia, which help explain the lower treatment optimization in this population. There is a well documented "risk-treatment paradox" in HF, where patients with a higher risk of mortality tend to receive less GDMT prescription.[12,21] Elderly patients are usually more complex, with more severe disease and co-morbidities, displaying higher mortality risk. Such complexity results in more unstable conditions that are more difficult to manage, and physicians may feel insecure in optimizing HF-related medications. Moreover, elderly patients may be less likely to report effort dyspnea, and physicians are less prone to optmize treatment when patients report themselves as asymptomatic. Also, physicians may prefer drugs that improve symptoms, with fewer potential adverse effects, instead of prescribing drugs that improve survival in elderly patients.[20]

Treatment complexity due to higher prevalence of comorbidities among elderly patients may also be a barrier to optimal medical treatment.[16] Cognitive impairment, which is prevalent in elderly patients with HF, has been reported as related with poor medication adherence.[22] On the other hand, an analysis from the QUALIFY study suggested that patients with HF and multiple comorbidities, such as coronary artery disease, hypertension, diabetes mellitus, vascular disease, and stroke/transient ischemic attack, were more likely to be at target dose of ACEIs, ARBs, and MRAs, which is expected, as these class of drugs are also indicated for these conditions.[15] This suggests that the presence of these comorbidities might actually contribute to optimal medical treatment for HF. Despite the mixed evidence, our results suggest that neither polypharmacy nor number of comorbidities accounted for the association between age and optimal medical treatment in HF.

Although they are excluded from most trials, elderly patients with HF are likely to benefit from GDMT.[23-25] An observational study showed that GDMT was associated with lower mortality in elderly patients with HF, and this association was consistent amont those 80 years old or older.[24] Our study highlights that there is much room to improve survival of patients with HF in clinical practice, particularly elderly patients. Efforts should be made to increase rates of GDMT in clinical practice, improving medical training and reducing medical inertia. For instance, a strategy called "start low go slow" for titration of the drugs and delivery of frequent educational reinforcements may help achieve the target dose for HF drugs in elderly patients.[25,26] Additionally, public policies may help improve comunication and establish goals for GDMT among patients with HF. Dissemination of cardiology guidelines and multidimensional practice-specific performance improvement interventions were associated with an increase in the use of GDMT.[15,27] A multilevel intervention that increases social support by relatives and healthcare providers and integrates different models of care, such as home care, telemedicine, primary care, and HF clinics, can help patients deal with treatment complexity and improve medical treatment.[20,25,28,29] Better rates of GDMT help reduce hospitalizations, with a significant economic impact.

Our study has some limitations that deserve attention. This is a cross-sectional study, which prevents us from establishing a temporal sequence relating patients aging and use of optimal drug doses. Furthermore, this design is subject to survival bias. We also cannot exclude the possibility that the differences and relations observed are due to other unmeasured confounding variables, such as income and education level. In addition, this is a single-center study of patients from SUS, and previous diagnosis of HF and LVEF below 50% may not necessarily reflect practices of others centers. The following specific characteristics of our study popuation should be noted: around 75% in NYHA funcional class I and II, which may reflect symptom improvement after treatment; 20% of patients used ARNI, even though this drug had elevated costs and it was not provided by the government at the time of the study; amost one third used ARB, even though they should be used only in patients who are intolerant to ACEI. Finally, the term "polypharmacy" has been defined in different ways in the literature, most commonly as the use of 5 or more medications, and no standard definition has been stablished.[30]

Conclusion

In this study of patients with HF in a middle-income country, we found that, overall, the rates of medical therapy of HF at the target dose was low. These rates were significantly lower in elderly patients, when compared to younger ones, and this does not appear to be explained by polypharmacy or the higher presence of comorbidities among the elderly.

Author Contributions

Conception and design of the research: Fernandes-Silva MM; Acquisition of data: Koga VAA, Dall'Asta L, Jacyntho TLP, De-Marchi LC, Mulinari RP, Ladeira BA, Nemeth MERF; Analysis and interpretation of the data: Koga VAA, Fernandes-Silva MM; Statistical analysis: Dall'Asta L, Fernandes-Silva MM; Writing of the manuscript: Koga VAA, Dall'Asta L, Jacyntho TLP, De-

Marchi LC, Mulinari RP; Critical revision of the manuscript for intellectual content: Silvestre OM, Bonatto MG, Moura LAZ, Fernandes-Silva MM.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

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Original Article

Cost-Effectiveness of Heart Transplantation: Data from a Referral Center in the Central-West Region of Brazil

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Abstract

Background: **In Brazil, heart transplantation is fully funded by the Brazilian Unified Health System.**

Objectives: **The objective of this study is to explore, for the first time, the cost-effectiveness profile of heart transplantation in a convenience sample, in a referral center in the Central-West Region of Brazil.**

Methods: **Costs related to transplant hospitalization were evaluated, including those related to the surgical procedure, as well as hospitalization in the intensive care unit and in the inpatient ward, until patients were discharged. Costs associated with professional remuneration, fees, materials, and medications were computed. In order to assess effectiveness, post-transplant survival was used. For survivors, survival time was censored until the last contact recorded in the medical records of the transplant clinic. The cost-effectiveness ratio was expressed in Brazilian reals (BRL) per year of life saved.**

Results: **We observed that the cost-effectiveness ratio was 25,806 BRL/year of life saved. Considering the average survival projected by Kaplan-Meier analysis, the cost-effectiveness ratio was 6,842 BRL/year of life saved.**

Conclusion: **This result demonstrates a good cost-effectiveness ratio when compared to international studies that have evaluated this parameter. We did not, however, assess the micro-costing of the program and its feasibility for the institution. Given that this is a single-center study, the evaluation of other transplant centers is necessary in order to better elucidate this scenario.**

Keywords: **Heart Transplantation; Cost-Benefit Analysis; Capital Financing; Unified Health System.**

Introduction

Heart failure is considered an epidemic disease in the modern world. It affects approximately 1% to 2% of the adult population, and it is the leading cause of hospitalization in the South American population, with significant mortality.[1,2]

Heart transplantation is considered the gold standard therapy for heart failure that is refractory to medical treatment. It should be considered as a treatment for patients who remain in New York Heart Association functional classes III and IV, with recurrent hospitalizations and unfavorable prognostic markers notwithstanding full medical and surgical therapy.[3–5]

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The first heart transplantation in Brazil took place in 1968, at Hospital das Clínicas in São Paulo. Currently, approximately 380 heart transplants are performed annually. This complex procedure is financed by the Brazilian Unified Health System (SUS) of the Ministry of Health, in accordance with Law 9.434, of 1997.

Health managers have sought to better understand the implementation of new health technologies by means of tools to assess their efficiency and their real benefit to the population. These analyses are important to decisions to incorporate new technologies, evaluate medications, and reflect on the costs of new or already incorporated procedures. Cost-effectiveness analysis is one of these tools to broaden debates on the topic.

Accordingly, the objective of this study is to explore, for the first time, the cost-effectiveness profile of heart transplantation in a convenience sample in Brazil. In order to do this, we consecutively analyzed the cohort of patients undergoing transplantation at our institution, computing the real costs and comparing them to absolute survival during follow-up and to actuarial survival.

Methods

Study design

This is a descriptive cost-effectiveness study, based on observational cost and survival data from a retrospective cohort of patients who consecutively underwent heart transplantation. Considering the single-center study design, this is an exploratory and hypothesis-generating study.

The research project received approval from the Institutional Research Ethics Committee, waiving the requirement to obtain an informed consent form, given that it comprises retrospective collection of coded secondary data, from the hospital's management system.

Sample selection and follow-up

All adults (≥ 18 years) who underwent heart transplantation at the Cardiology Institute of the Federal District (ICDF, acronym in Portuguese) were included in this analysis, from the beginning of the program (May 2009) until April 30, 2017, when follow-up analysis was performed for this study.

The ICDF is a private, non-profit institution that provides mixed care for patients in the public and supplementary systems. All transplants were financed by the SUS, of the Ministry of Health.

Data collection

Data were collected from a clinical-epidemiological source from the heart transplantation program. Before acquisition, data were duly coded, so that it was not possible to identify patients. The following were collected: demographic and clinical characteristics, cause of the cardiomyopathy that led to transplantation, and death with respective cause. The program Business Intelligence (QlickView®, QlikTech, Pennsylvania, EUA, 2007) was used to obtain cost data.

Definitions of survival and mortality

Survivors' survival time was censored until the last contact registered in the medical records of the transplant clinic. During follow-up, the maximum life span after transplantation was recorded in individuals who died. The evolution of medical records was analyzed to define the causes of death, classified as follows: death related to the transplant procedure; death not related to the transplant procedure, which was subdivided into heart disease-related and non-heart disease-related. Surgery-related deaths were defined as those due to complications from the transplant procedure, such as primary graft dysfunction (cardiogenic shock), bleeding, nosocomial infection, or perioperative stroke. Cardiac death unrelated to surgery was defined as due to rejection (defined by evidence of rejection on endomyocardial biopsy), allograft vascular disease (coronary atherosclerosis), or immunosuppression-related infection. Finally, non-heart disease-related death was defined as death due to pathologies not associated with transplantation, for example, external causes or neoplasms unrelated to the transplant.

Definitions of cost

Costs were defined as the absolute amount spent by the hospital to perform each procedure, regardless of the amount transferred through the SUS. Therefore, this information reflects the real cost of the procedure and not the cost to the health system.

The overall cost of transplantation was generated during the entire hospital stay, subdivided into surgery costs (material, medications, procedures, room fees, and professional remuneration) and hospitalization costs (material, medications, procedures, hospital stay fees, and professional remuneration). The amounts spent on organ harvesting surgery and staff mobilization were not considered, because these results were not available in the hospital system.

Cost-effectiveness analysis

Time was described as median and interquartile range due to non-normal distribution. Normality was assessed using the Kolmogorov-Smirnov test. Survival time was defined by the time elapsed between transplantation and death or by the time censored in the maximum follow-up of survivors in the other individuals. It was described as median and interquartile range. The cost of transplantation was described as mean ± standard deviation. Kaplan-Meier analysis was used to project total life span after transplantation and calculate cumulative probability of survival. Clinical outcomes were described as an overall percentage considering all procedures and were expressed as proportions, with their respective 95% confidence intervals. We reported p values to 3 decimal places with p values less than 0.001 reported as $p < 0.001$. For all tests, we used the two-tailed alpha significance level = 0.05. Residual examination provided an assessment of model assumptions for the regression analyses.

The cost-effectiveness ratio was expressed in Brazilian reals (BRL) per year of life saved and calculated as a fraction whose numerator was the sum of each patient's hospital cost, and the denominator was the sum of years of life after transplantation for each patient. This analysis did not consider cost after hospital discharge, seeing that it would consist of a combination of factors related to the procedure and factors inherent to remaining alive, whose discrimination could be inaccurate. Therefore, the decision was made to focus the analysis on the "investment" related to the surgery. Years of life saved were defined as the entire life span after transplantation, under the hypothetical premise that the patients would have received the new organ on their last day of life in the absence of the transplant.

Given that the overall survival time is underestimated due to the study's short follow-up, the cost-effectiveness ratio was secondarily calculated using the projected survival time in Kaplan-Meier analysis.

Statistical analyses were performed using the program SPSS, version 25 (SPSS Inc, Chicago, Illinois, USA).

Results

Sample characteristics

Between May 2009 and April 2017, 154 patients received transplantations. Patients' age ranged from 49 ± 12 years,

and 59% were men. Donors were 29 ± 12 years old, and 79% were male. Among the causes that led to transplantation, Chagas cardiomyopathy was predominant, accounting for 69% of the cases, followed by the other causes illustrated in Figure 1. The immunosuppressive regimen was tacrolimus in 60% of the patients and mycophenolate in combination with a calcineurin inhibitor in the others.

Post-transplant evolution

The majority of deaths occurred during the same hospitalization period as the transplant (63%), divided into 17 deaths due to primary graft dysfunction (28%), 12 deaths due to infection (20%), and 6 deaths due to stroke (10%). After discharge, there were 25 deaths, distributed as follows: 6 due to rejection, 11 due to infection, and 8 unrelated to heart disease. The causes of death are displayed in Figure 2.

Median time between transplantation and the date of this analysis was 2.2 years (interquartile range = 0.90 to 3.9), at which point 66% of patients were alive. Post-transplant survival time (until death or total follow-up time in survivors) showed a median of 1.27 years (interquartile range = 0.32 to 3.2), with a total gain of 196 person-years during this period. According to the Kaplan-Meier analysis, the estimated survival time after transplantation was 4.8 years (95% confidence interval = 4.1 to 5.5), with a cumulative survival probability of 52% (Figure 3).

Cost-effectiveness

With respect to cost, it ranged from a minimum of 11,909 BRL to a maximum of 137,596 BRL, with an average of 32,844 ± 21,768 BRL. The total cost of the 154 transplants was 5,058,013 BRL. Of this amount, about 40% came from the surgical procedure and the rest from hospitalization. The amplitude in costs is due to increased expenses in cases of extracorporeal membrane oxygenation or renal replacement therapy in some patients, in addition to costs with antibiotic therapy.

Using the absolute lifetime observed in this period during which 65% of patients were censored, the cost-effectiveness ratio was 25,806 BRL/year of life saved. Considering the average survival of 4.8 years projected by the Kaplan-Meier analysis, the cost-effectiveness ratio is reduced to 6,842 BRL/year of life saved.

Discussion

This study explores the potential cost-effectiveness ratio of heart transplantation in Brazil. A favorable ratio was demonstrated between investment and clinical benefit in only 2.2 years of follow-up.

The World Health Organization recommends, as a reference, 3 times the gross domestic product per capita per year of life saved in order to consider an intervention advantageous from the economic point of view, which, in 2017, was equivalent to the value of 29,463 dollars. Considering the short follow-up time, our crude analysis underestimates the years of life saved due to the large number of patients censored (still alive when follow-up was interrupted). Even so, the cost-effectiveness value obtained

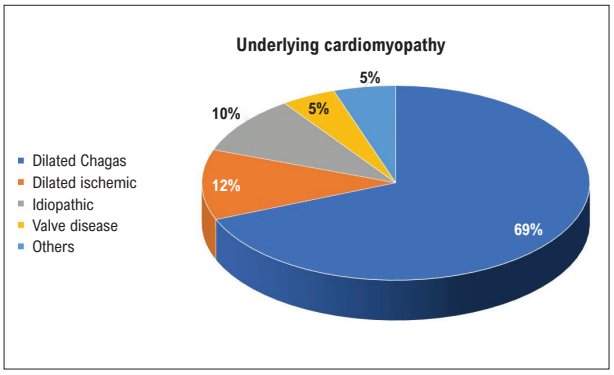

Figure 1 – *Distribution of the causes of heart failure that led to transplantation*

is about 25% of the limit proposed by the World Health Organization. The outlook becomes more favorable when we apply the mean survival estimated by the survival function, which suggests a cost-effectiveness ratio of 6,842 BRL/year of life saved.

Studies involving cost-effectiveness in patients undergoing heart transplantation are scarce. Evans demonstrated that the overall cost-effectiveness ratio of heart transplantation in the United States was estimated at 44,300 dollars/year of life saved.[6] Our results are advantageous in relation to those that have been described in developed countries, whose costs related to transplantation are much more significant than in Brazil.[7]

The survival rate of heart transplant recipients from 2009 (when this analysis began) to 2017 was 66%. According to survival function, we estimated that 50% of patients would be alive at 4.8 years. Accordingly, for this follow-up period, the magnitude of the death reduction is 50% in relative terms and 50% in absolute terms, with a number needed to treat of 2. This explains why, even though it is a high-cost procedure, it is economically efficient, even when circulatory support is required in the context of primary graft failure.[8]

It is necessary to recognize that our survival numbers are below international references.[9] This may be due to the severity with which our patients are operated, the low accessibility to the system (selection of more severe patients), and the congested waiting line for transplantation; other factors such as socioeconomic level, comorbidities (the majority of patients had Chagas disease), and limited volume of transplants per center can also contribute negatively. Accordingly, this makes it more difficult in our environment to obtain ideal results. This gives greater relevance to our data, which suggest that, in less favorable scenarios, the magnitude of the benefit may be sufficient to generate cost-effectiveness.

Cost-effectiveness thresholds are arbitrary, and they serve only to guide analysis. The decision to implement an intervention is more complex. For example, more important than categorizing an intervention as cost-effective is the comparison of the efficiency profile with other interventions that compete to be subsidized by the same health system. In this sense, cost-effectiveness is not the same as low cost, and we must remember that we are dealing with a high-cost therapy.

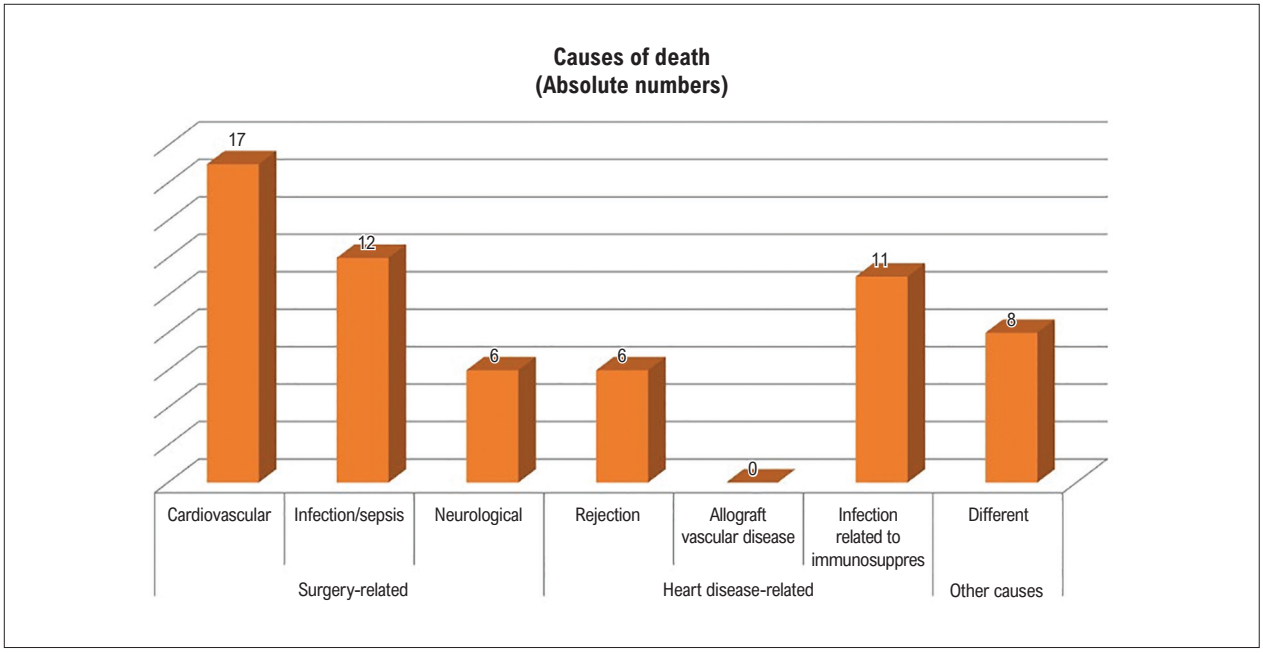

Figure 2 – *Causes of death: related versus not related to transplant surgery. Other causes represent causes not related to heart disease.*

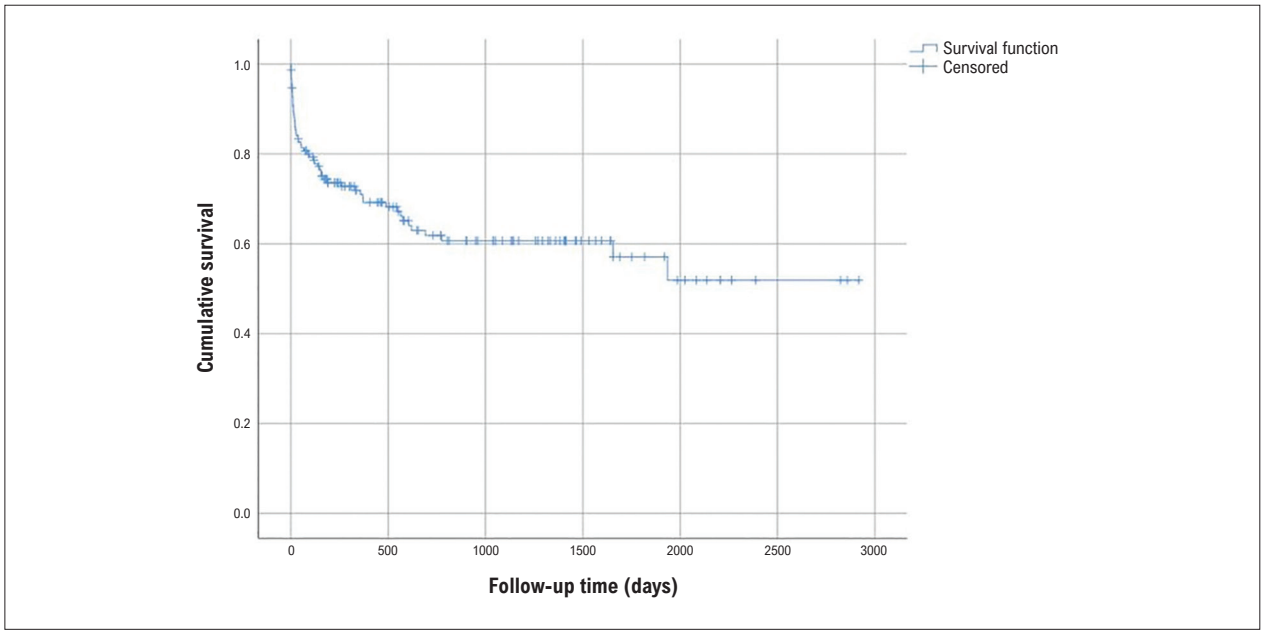

Figure 3 – *Cumulative survival.*

It is important to emphasize that cost-effectiveness analysis does not take into consideration the financial viability of a transplantation program. The analysis under consideration refers to the impact of heart transplantation on society. Based on the data presented, there is benefit in a program with these characteristics for a health system such as Brazil's. On the other hand, programs are recognized to be underfunded, when analyzing the micro-costing of heart transplants in Brazil.[10,11]

It is necessary to recognize limitations to our analysis, which make our study insufficient to be considered definitive. First, this is a single-center study, with a convenience sample of the real situation in Brazil. Second, certain costs inherent to the transplantation process were not considered, such as pre-transplant evaluation and management, logistics and transport for organ harvesting, hospitalizations, and post-transplant follow-up. The impacts in relation to returning to work and social security, with financial and psychosocial influence on

the patient and on society, were also not analyzed. Another important point to be evaluated is the quality of life after transplantation, which was not evaluated in this study. Finally, our follow-up was short, and this study should be reproduced with a longer follow-up period.

Conclusion

In conclusion, this exploratory, single-center study suggests a favorable cost-effectiveness ratio for heart transplantation, and it should serve as a springboard for a multicenter study to reassess this issue with greater external validity, including generalization at the level of Brazil. Considering that this procedure is publically funded, this knowledge is of paramount importance to making decisions and adapting health policies in this area.

Author Contributions

Conception and design of the research: Biondi RS, Correia LC, Vieira NW, Barzilai VS, Chaves RB, Monte GU, Atik FA; Acquisition of data: Biondi RS, Vieira NW, Rocha Júnior EF, Araújo MCCL, Faria LR, Lucas PFS, Araujo JS, Araújo APC, Barbosa AA, Monte GU; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Biondi RS, Correia LC, Vieira NW, Barzilai VS, Chaves RB, Rocha Júnior EF, Araújo MCCL, Faria LR, Lucas PFS, Araujo JS, Araújo APC, Barbosa AA, Monte GU, Atik FA; Statistical analysis: Biondi RS, Correia LC, Monte GU, Atik FA; Writing of the manuscript: Biondi RS, Correia LC, Barzilai VS, Chaves RB, Monte GU, Atik FA.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

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Original Article

Cognitive Frailty and Depressive Symptoms in Heart Transplant Candidates: Rational and Study Design

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Abstract

Background: **Patients with advanced heart disease have impaired cognitive abilities and higher probability of depressive symptoms. These factors contribute to negative outcomes of treatment, such as the development of comorbidities, higher hospitalization and mortality rates, poor treatment compliance and self-care, and decrease in quality of life and functionality.**

Objective: **To describe the prevalence and to evaluate the impact of cognitive frailty in patients in the waiting list of heart transplantation, with death while waiting transplantation and priority transplantation as clinical outcomes.**

Methods: **Longitudinal, prospective study evaluating cognitive frailty in 150 patients with advanced heart failure referred to transplantation in a hospital in Sao Paulo. Volunteers older than 18 years of age, hospitalized or in outpatient care, in the waiting list of transplantation will be considered eligible and will be assess within one month after being included in the waitlist. Cognitive performance will be assessed using the Montreal Cognitive Assessment and the battery of neuropsychological test Wechsler Abbreviated Scale of Intelligence (WASI). The symptoms of depression will be assessed by the Beck Depression Inventory.**

Results: **The study will allow to describe the prevalence of cognitive frailty and its relationship with treatment outcomes in a Brazilian population.**

Conclusion: **Data from this study will allow the analysis of associations between cognitive profile and severity of heart failure in patients referred to transplantation and their effects on clinical outcomes.**

Keywords: **Cognitive Frailty; Heart Failure; Heart Transplant.**

Introduction

Frailty is understood as a state of increased vulnerability to stressors associated with loss of physiologic reserve. Frail patients, when exposed to stressors, have increased likelihood of decompensation, adverse events, functional decline and disability. In cardiac patients, frailty has also been associated with higher hospitalization rate and comorbidities and has been suggested as a strong predictor of unfavorable clinical outcomes and mortality. Compared to non-frail individuals, frail patients with heart failure (HF) show higher rates of mortality (16.9 vs. 4.8%) and hospitalization (20.5 vs. 13.3%).[1,2]

Patients with HF are at higher risk of cognitive frailty. The reasons are not clear, but may be associated with hemodynamic, vascular, and inflammatory issues that may occur in the process of cardiac failure.[3] Functional changes in the white and grey matter of the brain are detected in imaging tests. Decreased blood flow to the brain, reduced cardiac output, altered cerebrovascular reactivity and altered blood pressure seem to be the main mechanisms involved in the pathogenesis of cognitive impairment in HF.[4]

Cognitive impairment in HF involves several domains, including learning memory, late memory, working memory, attention, executive function and psychomotor speed. Cognitive changes affect self-care ability of patients, *i.e.*, the active decision-making in dealing with the incident disease, promoting health maintenance and making behavioral changes towards a specific treatment. In practical terms, these changes can cause relevant difficulties in the management of cardiac patients, especially regarding the

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understanding of disease, compliance to instructions and drug therapy.[4,5]

Cognitive and mood changes in frail patients with HF have been shown to play a key role in disease progression, disability conditions and death. Many studies have recognized frailty as a multisystem measure that includes not only physical damages, but also psychosocial and cognitive problems. Therefore, identification and management of these conditions are important clinical challenges nowadays.[1,4-6]

Objective

The present study aims to evaluate the impact of cognitive impairment in patients in the waiting list of heart transplantation, with death while waiting transplantation and priority transplantation as primary clinical outcomes.

Method

Study design and population

Adult patients (older than 18 years), with diagnosis of advanced HF, of different etiologies, in the waiting list of heart transplantation of the *Hospital do Coração do Hospital das Clínicas da Faculdade de Medicina da USP* will be invited to participate in the study within 30 days after being included in the list. Patients admitted to the wards or to the intensive care units, and outpatients in the waitlist for transplantation will be considered eligible. Patients will be given information about the study, and those who accept to participate will sign an informed consent form, according to the 466/2012 resolution, and receive a copy of the document. The research protocol was approved by the local ethics committee from *Hospital das Clínicas da Faculdade de Medicina da USP* (CAAE 97526818.4.0000.0068).

Patient assessment will be preferably performed at the same visit. The three assessment instruments will be administered on the same day, except for patients with complications or institutional requirements for temporary interruption of the study. Eventual administration of the instruments on separate days will not affect the results. The battery of neuropsychological tests predicts the interruption of the tasks after a sequence of consecutive errors, which reduces the likelihood of aversion to the task or excess exposure to frustration or distress in case of poor performance. All patients will also be assessed for physical frailty according to the Fried criteria.[7]

A brief sociodemographic interview will be administered, including data on marital status, religion, self-reported race, monthly income, occupation and work activity, diagnosis awareness, psychiatric history, life habits and lifestyle. Clinical data of patients will be collected in the electronic chart and the database will be constructed using the REDCap software.

Inclusion criteria

- patients aged older than 18 years of both sexes;
- patients with diagnosis of heart failure of different etiologies, in the transplant waiting list at the Heart Institute.

Exclusion criteria

- patients with medical conditions that prevent the administration of assessment tools for cognition and/or depression (sleepiness, depressed conscious level, delirium or mental confusion, among others) or the performance of tasks involved in the assessment.
- Incomplete assessment protocol, due to clinical decompensation or refusal to continue participation.

Materials

Cognitive performance will be assessed using the Montreal Cognitive Assessment (MoCA) and the Wechsler Abbreviated Scale of Intelligence (WASI). The MoCA is a cognitive screening test that has been shown to be a practical and effective tool in the distinction of performance between adults with normal cognition and adults with decreased cognition. The battery of tests evaluates eight cognitive domains, with a maximum score of 30 points (Table 1).[8]

WASI is a quick measure of intelligence, individually administered to people aged 6-89 years. The instrument provides information about total intelligence quotient (Total IQ), executive IQ (eIQ) and verbal IQ (vIQ) using four subtests: (vocabulary, block design, similarities, and matrix reasoning) that evaluate several cognitive aspects, including verbal comprehension, visual information processing, spatial and non-verbal reasoning, and fluid and crystallized intelligence. The time of administration of the WASI varies from 30 to 60 minutes, according to patient performance. The scale can also

Table 1 – Structure of the Montreal Cognitive Assessment (MoCA)

Cognitive Domain	Task	Points
Executive functions	Trail Making Test (adapted)	1 point
	Phonemic verbal fluency	1 point
	Verbal abstraction	1 point
Visuospatial ability	Clock drawing	3 points
	Copy two-dimensional figure (cube)	1 point
Memory	Name recall	5 points
Attention and work memory	Recall of digits (forward order)	1 point
	Recall of digits (backward order)	1 point
	Sustained attention (target detection)	1 point
	Serial 7 subtraction	3 points
Language	Name 3 unfamiliar animals	3 points
	Repeat 2 syntactically complex sentences	2 points
	Phonemic verbal fluency	
Orientation	Temporal	4 points
	Spatial	2 points

In the Brazilian population, for adults with 12 years of schooling, the cutoff point is 12 years. Then, scores ≤ 26 points will be classified as frailty.

measure TotalIQ using only two subtests (vocabulary and matrix reasoning) within 15 minutes. This battery, derived from and similar to the Wechsler family, was created to meet the need of a quick and reliable measure of intelligence in the clinical and research contexts. The test was normalized and validated to the Brazilian population in the end of 2014.[3,9,10]

Tables 1 and 2 describe the structure of the tests, the cognitive functions assessed, and the frailty criteria used in the study.

The Beck Depression Inventory (BDI) will be used to evaluate depression. The BDI is a self-report measure consisting of 21 items, aimed at measuring the presence and the severity of depressive symptoms. The instrument must be applied by a psychologist and can be used in adolescents (>13 years) and adults. The time for administration is approximately 10 minutes, but there is no maximum time to complete the test. The patient will answer items that evaluate feelings of sadness, pessimism, hopelessness, unhappiness, guilt, punishment sensitivity, self-disgust, self-blame, suicidal ideation, crisis of crying, irritability, social withdrawal, distortion of body image, work inhibition, fatigue, somatic concern, and changes in sleep, appetite, body weight and libido. Results < 13 points indicate absence of depressive symptoms; 14-19 points indicate mild depression; 20-28 points moderate depression, and 29-63 points severe depression.

Table 2 – Structure of the Wechsler Abbreviated Scale of Intelligence WASI

Task	Area	Domains analyzed
Cubes	Execution	Visuospatial organization and processing ability
		Speed of perception and organization
		Problem solving
Matrix reasoning	Execution	Fluid ability and perception organization
		Planning and prediction ability
		Visual and perceptual-motor coordination
		Attention
Vocabulary	Verbal	Lexical competencies
		Linguistic entrenchment
		Expression of thought
Similarities	Verbal	Logical thought and abstraction Formation of concepts and categories Ability to integrate and synthesize concepts Mental flexibility Immediate memory
Similarities	Verbal	Logical thought and abstraction
		Formation of concepts and categories
		Ability to integrate and synthesize concepts
		Mental flexibility
		Immediate memory

Scores of 90-110 are classified within the population mean; therefore, scores ≤ 90 will be classified as frailty.

Clinical outcomes

Primary:

- death while waiting transplantation and priority transplantation;

Secondary:

- death while waiting transplantation
- correlation of cognitive frailty with physical frailty

Statistical analysis and sample calculation

Continuous data of each variable will be compared to a normal curve using the Kolmogorov-Smirnov test and classified as parametric and non-parametric. Parametric data will be expressed as mean and standard deviation, and asymmetric data as median and interquartile range, lower quartile (25^{th} percentile) and upper quartile (75^{th} percentile). Data will be analyzed by parametric survival models, not necessarily considering the proportionality of risks over time.

For sample size calculation, we considered the primary endpoint of the study, and a proportion between frail and non-frail patients of 4:1. A rate of events of 30% within six months was adopted to achieve a statistical power of 80%, an alpha error of 0.05 and to detect a two-fold increase in the risk of the primary endpoint in six months. Thus, the estimated sample was 150 patients. To evaluate the relationship between cognitive frailty and death while on waitlist for heart transplantation, we will use the subdistribution hazard model by Fine and Gray, considering transplantation as the competing event.

Study limitations

This was a single-center study conducted in a quaternary referral hospital, which may cause selection or ascertainment bias. In addition, in our institution, most transplantations have been conducted in patients who have top priority in receiving heart transplants, which indicates higher severity of the study population. Finally, socioeconomic and cultural status of the Brazilian population differs from that of other countries, which may affect the external validation of the study.

Conclusion

The international literature indicates that there is a direct relationship between cognitive frailty and worse outcomes of heart transplantation. There are few data on this theme in Brazil and for this reason, we believe it is important to assess and to describe how this condition affects patient survival. The study will allow to evaluate the relationship between cognitive frailty and death while on waitlist in a quaternary hospital in Sao Paulo, Brazil.

Author Contributions

Conception and design of the research: Oliveira FM, Ikeda ET, Bacal F, Marcondes-Braga FG, Mangini S; Acquisition of data: Oliveira FM, Ikeda ET; Analysis and interpretation of the data: Oliveira FM, Seguro LFBC, Avila MS, Campos IW, Marcondes-

Braga FG, Mangini S; Statistical analysis: Fernandes-Silva MM, Marcondes-Braga FG; Writing of the manuscript: Oliveira FM, Marcondes-Braga FG; Critical revision of the manuscript for intellectual content: Seguro LFBC, Avila MS, Campos IW, Marcondes-Braga FG, Mangini S, Santos MVB, Feltrim MIZ, Lage SHG, Bocchi EA, Issa VS, Gaiotto FA.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

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Original Article

Review Article

I NEED HELP: How to Indentify Patients with Advanced Cardiac Dysfunction?

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Abstract

Heart failure (HF) is a clinical syndrome characterized by inadequate tissue oxygen supply. In spite of the best current approach to heart diseases, population aging in individuals with heart disease has resulted in increased incidence of HF.

In Brazil, HF represents the second leading cause of hospitalization due to cardiovascular diseases, and it has high mortality in its most advanced stage. The difficult recognition of therapeutic refractoriness can often lead to delays in referral to specialized centers that are able to promote reduced symptoms, improved quality of life, and increased survival.

Therapeutic options are limited in advanced HF, and heart transplantation is the therapy of choice. Organ availability is a major limitation, making circulatory support an increasingly present reality, with improved results.

Definition

The term advanced heart failure (HF) encompasses the group of patients with chronic HF who evolve with progressive worsening of cardiac function and symptoms. Ultimately, these patients progress to refractoriness to standard treatment guided by the current guidelines. Thee patients' prognosis is limited, with mortality reaching 25% to 75% in one year. Accordingly, in order to guarantee favorable outcomes, they require advanced therapies, such as heart transplantation, support with a mechanical circulatory assist device, and/or palliative care.[1]

Numerous classification systems have been created to characterize patients with HF and to select advanced cases. The assessment of functional class proposed by the New York Heart Association (NYHA) defines individuals with symptoms at rest or during any physical activity as class IV. In 2001, the American College of Cardiology (ACC) and the American Heart Association (AHA) described stage D patients as those requiring specialized interventions due to the presence of refractory symptoms despite optimal medical therapy. The Interagency Registry for Mechanically Assisted Circulation (INTERMACS) classification was developed to stratify the risk of patients with advanced HF and to establish prognosis and urgency of intervention. Table 1 shows the classification systems together.[2]

The definition of advanced HF has evolved over the past decades. The Heart Failure Association of the European Society of Cardiology (HFA-ESC) update from 2007 to the 2018 document introduced a new concept for classifying these patients. Although left ventricular ejection fraction (EF) is frequently reduced, it is not a mandatory criterion for the diagnosis of advanced HF, given that it can develop in patients with HF with preserved ejection fraction (HFpEF) as well. Extracardiac organ dysfunction due to HF (for example, cardiac cachexia, kidney dysfunction, and liver dysfunction) or pulmonary hypertension may be present, but they are not required for definition of advanced HF. The updated HFA-ESC 2018 criteria are displayed in Table 2.[3]

HF risk scores were developed from specific cohorts, including the group of patients with acute HF, HF with reduced EF, and/or HFpEF. They are important tools in clinical decision-making, to the extent that they accurately assist in adaptation and identification of the need for disease-modifying treatments, advanced therapies, or the indication of end-of-life care. It has been observed that they are still underused in clinical practice and that their results should not be analyzed in an isolated manner.[4]

There are different risk scores for HF, including Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM),[5] Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico-Heart Failure (GISSI-HF),[6] Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC), and Seattle Heart Failure Model (SHFM).[7] MAGGIC seems to have the best discriminatory power for one-year mortality.[4]

Incidence

It is estimated that approximately 64.3 million people worldwide are living with HF, approximately 1% to 2% of the adult population in developed countries,[8] and the disease has been characterized as a global pandemic. Over the decades, great difficulty has been observed in establishing HF criteria that are easy to reproduce, followed by the challenge of obtaining reliable data in some regions of the world.

Keywords

Heart Failure; Heart Transplantation; Classification

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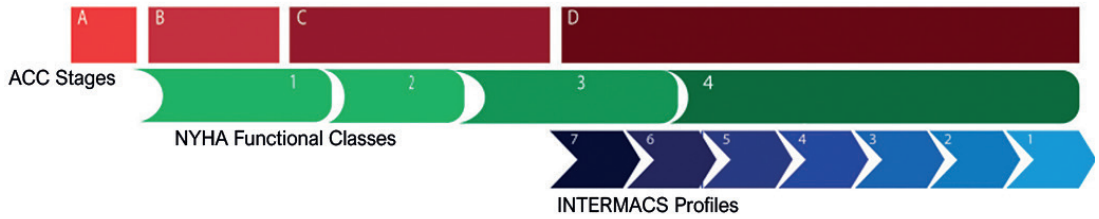
Table 1 – Stages and symptoms of heart failure in different classification systems



ACC stages	NYHA functional classes	INTERMACS profiles
A: Patients at risk of developing heart failure, without functional or structural heart disease	**I:** No limitation of routine physical activity	**I:** Severe cardiogenic shock
B: Structural heart disease, without symptoms of heart failure	**II:** Mild symptoms during routine physical activity	**II:** Progressive decline despite inotrope use
C: Structural heart disease. Prior or current symptoms of heart failure	**III:** Symptoms during less than ordinary physical activities. Important limitation. Comfortable only at rest.	**III:** Stable, but inotrope dependent
D: Heart failure refractory to clinical treatment, requiring specialized intervention in heart failure centers	**IV:** Severe limitation to any physical activity without discomfort. Symptoms at rest.	**IV:** Frequent hospitalizations
		V: Housebound, exertion intolerant
		VI: Exertion limitation
		VII: NYHA III

Adapted from Truby LK, Rogers JG[2] Stages of heart failure as described by the American College of Cardiology (ACC), New York Heart Association (NYHA) functional classes, and the Interagency Registry for Mechanically Assisted Circulation (INTERMACS).

Table 2 – Criteria for defining advanced heart failure

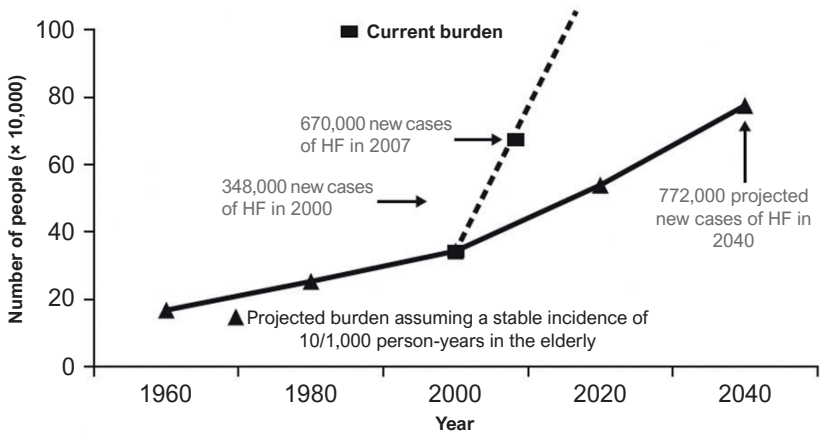
1.	Severe and persistent symptoms of HF (NYHA III or IV).
2.	Severe ventricular dysfunction defined by at least one of the following: • LVEF ≤ 30% • Isolated right HF • Non-operable severe valve abnormalities • Non-operable severe congenital abnormalities • Persistently high BNP or NT-proBNP values and data showing severe diastolic dysfunction or LV structural abnormalities, according to the definition criteria for HFpEF
3.	Episodes of pulmonary or systemic congestion requiring high doses of intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing more than 1 unplanned visit to the emergency department or hospitalization within the past 12 months
4.	Severe impairment of exercise capacity, with inability to exercise or low 6MWTD (< 300 m) or pVO_2 (< 12 to 14 ml/kg/min), estimated to be of cardiac origin

Adapted from Metra et al.[1] 6MWTD: 6-minute walk test distance; BNP: B-type natriuretic peptide; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; LV: left ventricle; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; pVO_2: peak exercise oxygen consumption.

It is historically predominant in male individuals,[9] but the recent inclusion of HFpEF and HF with mildly reduced EF has statistically increased the representation of women in this syndrome.[3] Incidence is lower in young people, around 3 to 5 per 1,000 inhabitants in Europe, and it increases substantially in those over 70 years of age.[10]

Several models have shown acceleration in new cases of HF from the turn of the millennium, with nearly 915,000 new cases in the United States in 2016[11] (Figure 1). This greater number of new patients is added to those with prolonged survival due to the best medical and invasive treatment, in addition to the global increase in life expectancy, thus corroborating a substantial increase in the prevalence of the disease.

In Brazil, there are few multi-center analyses of the situation of HF; however, a group from Paraíba[12] managed to



The annual incidence of heart failure (HF) reported in the United States (squares and dotted line) exceeds the projected annual incidence (triangles and solid line), calculated based on a stable incidence of 10/1,000 person-years in the elderly. Source: Lam et al, 2011. Reproduced with permission, John Wiley & Sons.

Figure 1 – *Burden of heart failure*

demonstrate a reduction in the national mortality rate. It is, however, worth noting, that there is an increase in hospital mortality rates and hospitalization time, indicating a lack of appropriate treatment for the most severe disease forms.

Measurement of individuals with advanced HF is even more complex than that of HF *lato sensu*, and it is subject to variations in the definition criteria, with scores that are not very accurate; nevertheless, the ADHERE registry[13] found, in the mid-2000s, that 5% of hospitalizations were related to advanced HF. These data seem to underestimate these patients with severe HF, given that, in 2019 in the United States, more than 3,000 patients were treated with a left ventricular assist devices; around 3,000 patients received heart transplants, and an additional 3,500 patients were waiting in line to receive an organ.[2]

How to Identify It

HF has a challenging clinical course that poses difficulties even to experienced clinicians, seeing that it is a chronic disease whose evolution can be subtle over time, giving patients and healthcare staff a false sense of clinical stability.

Unlike other chronic diseases, HF may have a fluctuating survival curve with clinical improvement after a severe episode of decompensation and subsequent reestablishment of functional class. These individuals can, with the support of optimal medical therapy, still have reasonable survival. Others will maintain worsening of symptoms and high mortality in a short timeframe. The limit between these two scenarios is tenuous and imprecise, making it of the utmost importance to develop warning signs in advanced HF. (Figure 2)

The addition of biomarkers, arrhythmic load, exercise performance, and EF evolution bring greater objectivity when establishing the best moment for referral; however, there is no consensus among the leading societies as to what these markers should be. In spite of this, advanced NYHA functional class (III/IV), optimized drug therapy, and episodes of decompensation requiring hospitalization are unanimously recognized as markers of worse prognosis.[2]

A useful mnemonic that can help identify patients who require referral to centers specializing in HF treatment is "I NEED HELP". It integrates aspects related to clinical history, hospitalizations, drug intolerance, EF, symptoms, and end-organ dysfunction (Table 3).[14]

The factors listed in this mnemonic device are not the only ones of concern, but, in multivariate analyses of several clinical trials, they were shown to be important predictors, and the presence of any one of these factors indicates that the opinion of a referral center should be sought.

EF is an important variable. In patients with HF with reduced EF, for every 10% reduction in EF, a significant increase occurs in events related to sudden death and death due to HF.[15] However, difficulties are often observed in the risk stratification of patients with preserved EF. Patients in this population are equally severe when they have other warning signs, and their diagnosis ends up being delayed, with the addition of a limited therapeutic arsenal.

The NYHA classification is one of the most widely used to describe the severity of symptoms. It allows clinical evaluation, helps in therapeutic management, and also has an excellent prognostic ratio. However, there are limitations, as it depends on self-reported symptoms, which are influenced by each patient's subjectivity. In these individuals, the use of the cardiopulmonary exercise test (CPET) provides more accurate information, highlighting warning signs even in asymptomatic individuals, and it is a great instrument for calibrating risk and providing prognosis

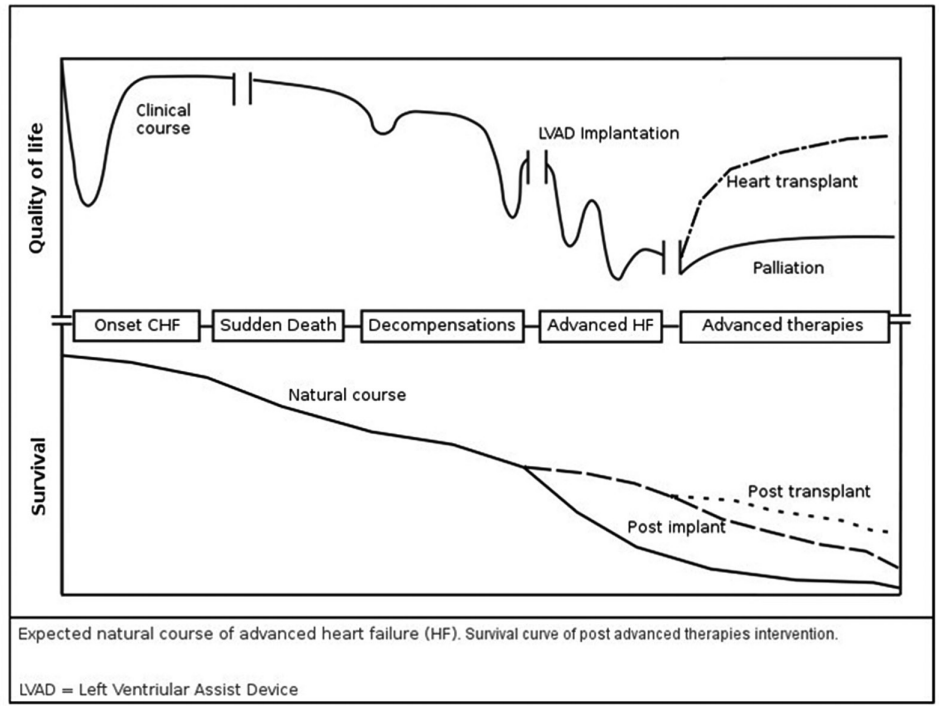


Figure 2 – *Clinical Course of Advanced HF.*

Table 3 – "I NEED HELP" mnemonic for identifying patients with advanced heart failure

I	Inotrope dependent/intolerant to optimized therapy
N	Persistent NYHA III/IV
E	Ejection fraction below 20%
E	Persistent edema, refractory to progressive doses of diuretics
D	Defibrillator (recurring appropriate shock)
H	Recurring hospitalizations and emergency department visits in the last 12 months
E	Persistent elevation in natriuretic peptides
L	End-organ damage
P	Systolic blood pressure persistently below 90 mmHg

NYHA: New York Heart Association.

for individuals with advanced HF. In patients with HFpEF and HF with mildly reduced ejection fraction, CPET also maintained accuracy, with excellent correlation of peak VO_2 and ventilatory response (VE/VCO_2 slope).[16]

B-type natriuretic peptide (BNP) is a biomarker with great prognostic utility. A persistent elevation in BNP indicates risk of events and mortality. In a systematic review that analyzed 19 studies, for every 100 pg/mL increase in plasma BNP, a 35% increase was observed in the relative risk of death.[17]

Inotropic therapy, taken alone, is a marker of in-hospital death,[18] and it should be used exclusively in patients in shock; therefore, patients who required inotropic therapy coming from a hospitalization should have priority in post-discharge reassessment.

Another even more challenging scenario of refractoriness is that of patients with cardiogenic shock (CC), who may have an acute presentation (first-time diagnosis) or have a chronic disease that has evolved with low output and perfusion deficit. In these cases, temporary inotropic and/or mechanical support are fundamental until etiological diagnosis has been made and prognosis established. To this end, a shock team with protocols for fast and accurate action is essential to avoid multiple organ failure.[19]

In order to improve recognition and agility in interventions in CC, the Society for Cardiovascular

Angiography and Interventions (SCAI) proposed a new classification in 2019 (Figure 3), subdividing CC into five stages, with a focus on tissue perfusion and signs of dysfunction organic. Stage A patients at risk for shock, and stage B represents beginning of shock. Identification of and action upon these stages improve prognosis and have an impact on survival.[20]

Another important point is hemodynamic monitoring with a pulmonary artery catheter, which becomes fundamental in the diagnosis of CC, bringing more therapeutic precision. Recently, the Cardiogenic Shock Working Group (CSWG) evaluated invasive monitoring in 1,414 patients with CC, showing that guided therapy reduced mortality in this population.[21]

Around the world, treatment centers for advanced HF indicate that patients receive late referral. Multiple strategies are needed to improve the recognition and care for these patients in both the acute and chronic phases, thus allowing the use of advanced therapies.

Management of advanced HF

As previously indicated, patients with advanced HF present high complexity and elevated mortality; for this reason, they should be followed up in specialized HF centers.[14,22] These centers aim to rule out reversible causes of HF and guarantee the use of all possible medical therapies, including resynchronization therapy and valve management, when applicable, in addition to critical multidisciplinary support in order to identify eligibility for more advanced therapies.

In this stage, patients show signs of clinical refractoriness to optimized medical and non-medical treatments recommended by national and international guidelines.[3,14,22] Previously well-tolerated disease-modifying medications may require dose reduction or even suspension. Different degrees of tissue hypoperfusion may determine the association of inotropes. The progressive deterioration of renal function may require a combination of diuretics, intravenous diuretic therapy, or even renal replacement therapy.[2,3,14,22]

As a therapeutic plan for advanced HF, HF centers basically have three available options:

1. Heart transplantation: Heart transplantation is the treatment of choice in the absence of contraindications (Table 4). The number of heart transplantations is growing, with more than 5,000 procedures performed worldwide each year. Brazil has also managed to increase the number of cases in recent years with 380 transplants in 2017, but this is still below the population's need, which is estimated to be 1,649 transplants/year.[23] A major limiting factor is organ availability, leading to the option of circulatory assistance devices for selected cases.

2. Circulatory assist devices: These devices promote symptomatic improvement and allow satisfactory survival when compared to the results of heart transplantation. They are interesting options in some cases where heart transplantation is contraindicated (target therapy), and they can be used as a "bridge to heart transplantation" or as a "bridge to recovery".[2,3,14,22]

Today, there is a wide range of different types of circulatory assist devices available. The choice of device will depend on the therapeutic goals, the patient's severity or degree of hemodynamic instability, the team's skills in dealing with different support methods, and the availability of the methods at each institution.[22]

Devices are classified by manufacturers according to the support time expected for the method, as follows:

- Short-term circulatory assist devices: intra-aortic balloon pump, Impella®, and extracorporeal membrane oxygenation;
- Medium-term circulatory assist devices: Centrimag®;
- Long-term circulatory assist devices: Heart Mate III®.[22,23]

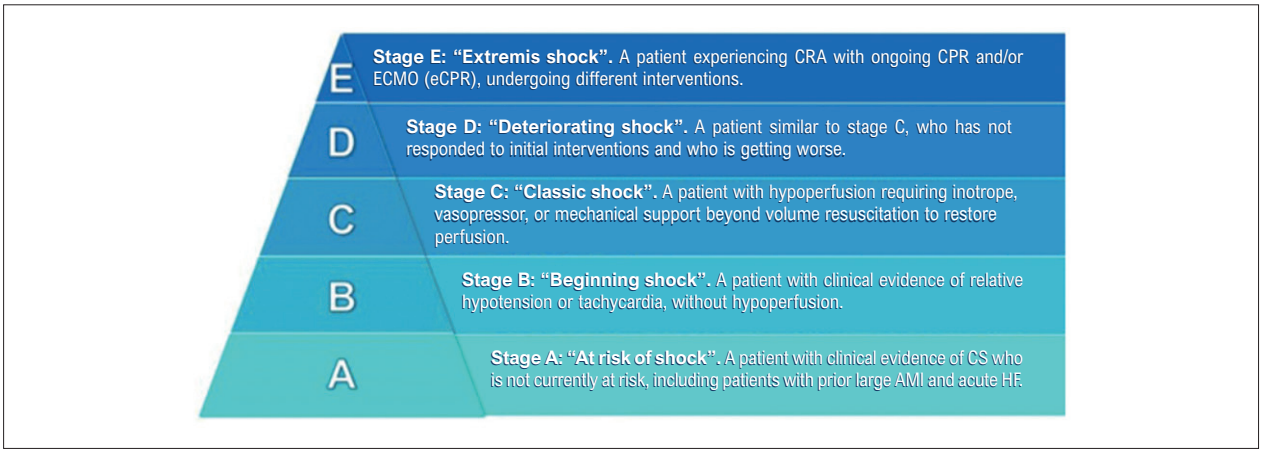


Figure 3 – *Classification of the Society for Cardiovascular Angiography and Interventions (SCAI) for cardiogenic shock. Adapted from: Baran DA et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock. Catheter Cardiovasc Interv. 2019; 94(1): 29-37. AMI: acute myocardial infarction; CRA: cardiorespiratory arrest; CPR: cardiopulmonary resuscitation; CS: cardiogenic shock; ECMO: extracorporeal membrane oxygenation; HF: heart failure.*[20]

The INTERMACS classification proposed in 2011 allows prognostic assessment and specifies the urgency for indication and implantation of circulatory assist devices in advanced HF. For the most severe and unstable patients (INTERMACS 1) implantation of circulatory assist devices is recommended within hours. In these cases, due to the high mortality and complexity, short-term methods are suggested, preferably with peripheral and rapid implantation. For patients in INTERMACS 2, implantation of short- or medium-term devices can be considered. For patients classified as INTERMACS 3 (stable, using inotropes) implantation of medium-term devices is recommended. Patients with INTERMACS classification greater than 4 can be assessed for elective implantation of long-term devices (Table 5).[2,3,14,22,24,25]

3. Palliative care: This option is for patients for whom heart transplantation and circulatory assist devices are not indicated or available. This form of care is ideally performed by specialists focused on quality of life and symptomatic control. Indications for devices such as pacemakers and defibrillators are reassessed. Palliative care is able to minimize rehospitalizations and humanize treatment in HF.[2,3,14,22]

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Author Contributions

Conception and design of the research: Miranda JSS; Acquisition of data: Miranda JSS, Fatorelli A, Salles V; Analysis and interpretation of the data: Salles V; Writing

Table 4 – Indications and contraindications for heart transplantation

Indications (Class I)	Possible contraindications
– Advanced HF with dependence on inotropic drugs and/or mechanical circulatory support – Advanced HF with persistent NYHA functional class IV in spite of optimal treatment, in the presence of other poor prognostic factors – Advanced HF with peak VO2 lower than or equal to 12 ml/kg/min while using beta-blocker or lower than or equal to 14 ml/kg/min in patients intolerant to beta-blockers	– Over 70 years of age – Active drug use, tobacco use, alcoholism – Uncontrolled psychiatric disorders, dementia syndromes or severe mental retardation, comatose states – Neoplasms without cure criteria – Non-adherence to proposed therapy before heart transplantation – Coexistence of comorbidities that limit the patient's life to less than 1 year – Fixed pulmonary hypertension;

HF: heart failure; NYHA: New York Heart Association.

Table 5 – INTERMACS classification[22,25]

Profile	Description	Hemodynamic state	Timeframe for intervention
I	Severe cardiogenic shock	Persistent hypotension, notwithstanding use of inotropres and IABP, associated with organ dysfunction	Hours
II	Progressive decline, despite use of inotropes	Deterioration in renal function, liver function, and nutrition and lactatemia, despite optimized doses of inotropic agents	Days
III	Stable, but inotrope dependent	Clinical stability under inotrope therapy, but with a history of failure to wean from inotropes	Weeks to months
IV	Frequent hospitalizations	Signs of fluid retention, symptoms at rest, and frequent emergency department visits	Weeks to months
V	Housebound, exertion limitation	Pronounced limitation to activity, comfortable at rest, despite fluid retention	Variable urgency, depending on nutritional state and degree of organ dysfunction
VI	Exertion limitation	Moderate exertion limitation and absence of signs of hypervolemia	Variable urgency, depending on nutritional state and degree of organ dysfunction
VII	NYHA III	Hemodynamic stability and absence of hypervolemia	Not indicated

IABP: intra-aortic balloon pump; NYHA: New York Heart Association.

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Review Article

Invasive Cardiopulmonary Hemodynamic Assessment in Patients with Advanced Heart Failure: How to Interpret?

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Abstract

Invasive cardiopulmonary hemodynamic assessment by means of a pulmonary artery catheter is an important tool for evaluating patients with advanced heart failure. It makes it possible to definitively diagnose pulmonary hypertension and, when pulmonary hypertension is present, to classify it as isolated post-capillary or combined pre- and post-capillary. Its use is mandatory in evaluation for heart transplantation and mechanical circulatory assist device implantation. Furthermore, it can be very useful in the management of cardiogenic shock.

Introduction

The use of catheters for invasive cardiac assessment has been described since the beginning of the twentieth century.[1] However, it was only starting in the 1970s that pulmonary artery catheters (PAC) began to be used for hemodynamic assessment at the bedside of critical patients. Their use became popular in subsequent years, to the extent that, by the end of the 2000s, approximately 1.5 million catheters were being sold annually in the United States.[2] Studies with negative results for routine use of PAC in critical patients in intensive therapy[3] and in patients with symptomatic heart failure (HF) with signs of severity but without cardiogenic shock[4] led to a reduction in their use. However, more recent data on patients with cardiogenic shock in the contemporary era incorporating the use of mechanical circulatory assist devices in treatment have demonstrated an association of PAC use with greater survival.[5]

Currently, PAC are recognized as useful and recommended in some clinical scenarios, including the following:[6-8]

- assessment of valvular and congenital diseases, especially when there is disagreement between the clinical and echocardiographic findings, as well as in the assessment of pulmonary hypertension (PH) and pulmonary reactivity before correction;
- diagnosis, prognostic assessment, and reactivity test to guide therapy for pulmonary arterial hypertension;
- early diagnosis of HF with preserved ejection fraction in patients with dyspnea;
- assessment and management of patients with advanced HF, both for indication of advanced therapy (transplantation or mechanical circulatory assist devices) and for assistance in management of cardiogenic shock.

Keywords

Heart Failure; Hemodynamic Monitoring; Pulmonary Hypertension

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Definition and classification of pulmonary hypertension

One of the main objectives of using PAC in advanced HF is assessment of PH. The definition of PH has recently been modified, and it is currently diagnosed in the presence of mean pulmonary artery pressure (mPAP) above 20 mmHg at rest, thus reducing the previously used cut-off value of 25 mmHg.[9]

A study with invasive assessment of 1,187 healthy individuals showed that the mean value for mPAP was 14.0 ± 3.3 mmHg, and this value was independent of sex and ethnicity.[10] Considering this normal value, mPAP > 20 mmHg would be 2 standard deviations above. Moreover, observational studies have demonstrated that small elevations in pulmonary pressure (mPAP between 20 and 25 mmHg) have a prognostic impact on symptoms, hospitalization, and mortality.[11] In a meta-analysis of 15 studies, the risk ratio for mortality was 1.52 among patients with mPAP of 19 to 24 mmHg when compared to patients with lower pressures.[12]

PH is currently classified into 5 groups that combine clinical conditions with similar pathophysiological mechanisms, clinical presentation, hemodynamic characteristics, and therapeutic management (Table 1).[9,13]

Pulmonary hypertension in heart failure

The main characteristic of group 2 PH is the presence of elevated pulmonary artery occlusion pressure (PAOP) (> 15 mmHg), which reflects increased left ventricular filling pressure. This group accounts for 65% to 80% of patients with PH.[14]

Group 2 PH results primarily from increased left ventricular filling pressures due to systolic and/or diastolic ventricular dysfunction or to aortic or mitral valve disease. This increased left chamber pressure is transmitted retrogradely to the pulmonary circulation (post-capillary component). Persistent elevation of pressure in this area leads to endothelial dysfunction with increased vasoconstrictor action, decreased available nitric oxide, and desensitization of vasodilation induced by natriuretic

peptides.[15] Subsequently, activation of inflammatory mediators and metabolic factors occurs, which will lead to vessel remodeling, with intimal fibrosis and hypertrophy of the middle layer of pulmonary arterioles, which are histological changes similar to those observed in primary pulmonary arterial hypertension.[16] The prevalence of PH in the population with HF with reduced ejection fraction is estimated at 40% to 75%.[14]

According to the presence or absence of functional or morphological alteration of pulmonary arterioles associated with the post-capillary component, PH in HF can be further classified as isolated post-capillary or combined pre- and post-capillary (Table 2). What indicates the presence of alterations in the pulmonary vasculature is increased pulmonary vascular resistance (PVR), which is calculated by dividing the transpulmonary gradient (TPG) by the cardiac output.[9] In turn, TPG corresponds to the difference between mPAP and PAOP, where > 15 mmHg indicates the presence of an associated pre-capillary component.[17]

Indications for use of pulmonary artery catheter in patients with advanced heart failure

Invasive cardiopulmonary hemodynamic assessment by PAC continues to be an important tool in patients with advanced HF (Figure 1). The main recommendations for the use of PAC in patients with advanced HF are as follows:

- Patients being evaluated for heart transplantation (HT) with the objective of evaluating the presence of PH (class of recommendation: I, level of evidence: B);[8]
- Every 3 to 6 months in patients listed for HT, especially in the presence of previous PH or worsening HF (class of recommendation: I, level of evidence: B);[18]
- Patients who are candidates for implantation of long-term left ventricular assist devices (VAD) with the objective of assessing right ventricular (RV) function and predicting RV failure after VAD implantation (class of recommendation: I, level of evidence: C);[7]
- Patients with refractory symptoms or cardiogenic shock, with the objective of assisting in hemodynamic optimization (class of recommendation: IIa, level of evidence: B).[8]

Practical aspects

Techniques for cardiopulmonary hemodynamic assessment

The standardization of techniques for correct assessment of the hemodynamic parameters obtained with PAC is essential to clinical and hemodynamic diagnosis, as well as to the implementation of appropriate treatment.

Table 3 summarizes the main practical aspects of techniques for assessing cardiopulmonary hemodynamics with right catheterization.[11]

The normal values of intravascular and cavity pressures and saturation are displayed in Table 4.

Table 1 – Classification of pulmonary hypertension

Group 1	Pulmonary arterial hypertension
Group 2	Pulmonary hypertension due to left heart disease
Group 3	Pulmonary hypertension due to lung disease and/or hypoxia
Group 4	Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
Group 5	Pulmonary hypertension with unclear multifactorial mechanisms

Table 2 – Classification of pulmonary hypertension in heart failure

Isolated post-capillary PH	mPAP > 20 mmHg
	PAOP > 15 mmHg
	PVR < 3 Woods
	TPG < 15 mmHg
Combined pre- and post-capillary PH	mPAP > 20 mmHg
	PAOP > 15 mmHg
	PVR ≥ 3 Woods
	TPG ≥ 15 mmHg

mPAP: mean pulmonary artery pressure; PAOP: pulmonary artery occlusion pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; TPG: transpulmonary gradient.

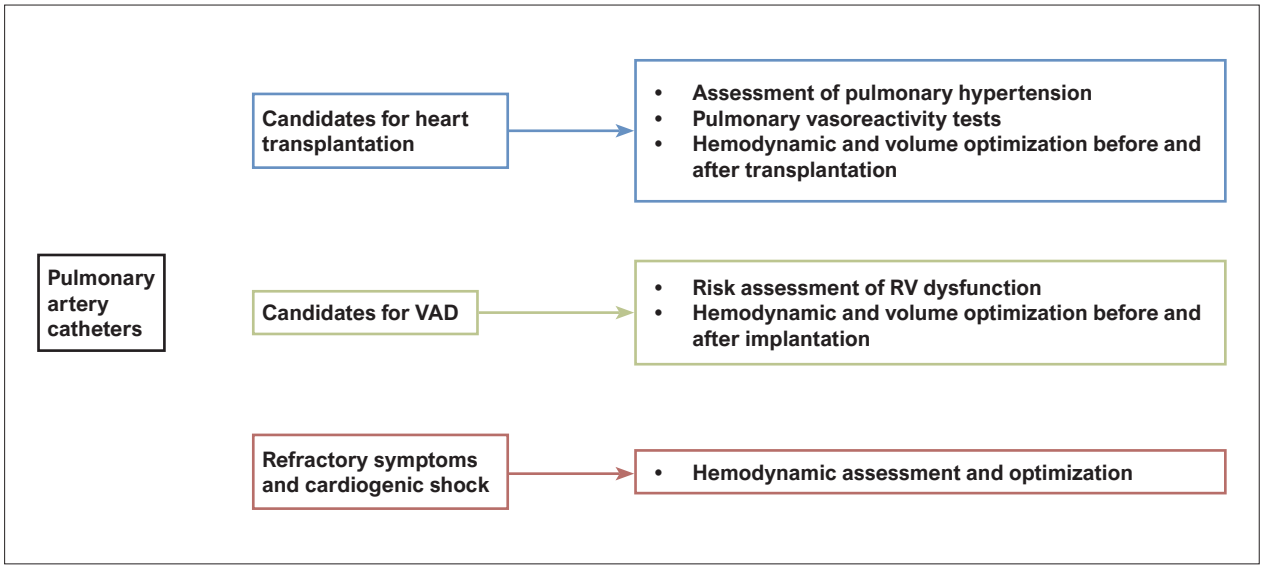

Figure 1 – *Indications for invasive cardiopulmonary hemodynamic assessment in patients with advanced heart failure. RV: right ventricle; VAD: ventricular assist device.*

Table 3 – Techniques for cardiopulmonary hemodynamic assessment

Preparation and positioning	Prior confirmation of catheter positioning (radiography or radioscopy)
	Full view of the hemodynamic monitor
	Patient in a supine position, with legs extended; avoid taking measurements while the patient is talking, coughing, or moving.
	Leveling of pressure transducers (RAP, PAP), which should be zeroed to atmospheric pressure at the level of the LA (mean distance between the patient's anterior sternum and back).
Quality assessment of tracings	Identify the presence of adequate pressure curves, without interference or artifacts.
	Aspiration of air bubbles from catheters and subsequent lavage can minimize artifacts.
Determination of right cardiac and pulmonary pressures	Pressure measurements should be performed during spontaneous breathing without performing the Valsalva maneuver.
	Measurements at the end of expiration are preferable.
	Measure right atrium, right ventricle and pulmonary artery pressures.
Measurement of pulmonary capillary pressure or PAOP	Measurement should be performed with an expiratory pause, without performing a Valsalva maneuver.
	If PAOP is very high and is questioned, correct confirmation of pulmonary artery occlusion can be achieved by measuring oxygen saturation > 90%.
	Mean PAOP pressure is generally correlated with LA pressure (and LVEDP).
	Presence of important MR, giant V wave, and AF may overestimate PAOP and should be reported.
Cardiac output measurements	Thermodilution measurements are preferable over indirect Fick calculation.

LA: left atrium; LVEDP: left ventricular end-diastolic pressure; MR: mitral regurgitation; PAOP: pulmonary artery occlusion pressure; PAP: pulmonary artery pressure; RAP: right atrial pressure.

Assessment of candidates for heart transplantation

The presence of PH with elevated PVR is classically associated with increased mortality after HT due to RV graft dysfunction, especially in individuals with PH with a pre-capillary component who do not show vasoreactivity in tests with pulmonary vasodilators.[18,19] The *Brazilian Guidelines for Cardiac Transplantation* consider this non-reactive (fixed) pre-capillary PH as a contraindication to HT.[20]

Thus, invasive cardiopulmonary hemodynamic assessment with a PAC is indicated for all patients who are candidates for HT.[20] In addition to identifying the presence of PH, it makes it possible to determine the hemodynamic factors that are possibly responsible and, in patients with PH with a pre-capillary component, to assess the reduction of pulmonary pressures with vasoreactivity tests. Invasive cardiopulmonary hemodynamic assessment

Table 4 – Normal values of intravascular and cavity pressures and saturation

	Systolic/diastolic pressure (mean) (mmHg)	Saturation (%)
Right atrium	(5-8)	70
Right ventricle	26/2	70
Pulmonary artery	26/8 (14)	70
Pulmonary occlusion	(8)	100
Left atrium	(8)	98
Left ventricle	120/8	98

also assists in hemodynamic optimization by adjusting blood volume, cardiac output, and pulmonary pressure before HT (Chart 1).

Patients with post-capillary PH generally do not need to undergo a pulmonary vasoreactivity test, given that the main hemodynamic components are hypervolemia and increased left ventricular filling pressures (increased systemic vascular resistance). Thus, diuretics and systemic vasodilators are the basis for volume and hemodynamic optimization and consequent reduction in pulmonary pressure (Chart 1).

Patients with PH with combined pre- and post-capillary components should undergo a pulmonary vasoreactivity test with the objective of identifying a component that is reactive to vasodilators (pulmonary vascular vasoconstriction). In these cases, the drop in pulmonary pressure and normalization of TPG and PVR with the pulmonary vasoreactivity test allow candidacy for HT (Chart 1).

In patients whose pulmonary pressure does not reduce or whose PVR does not normalize, treatment for hemodynamic optimization guided by invasive monitoring should be maintained for at least 24 to 48 hours, considering the use of diuretics (or even ultrafiltration), vasodilators, and inotropes. Left ventricular decompression strategies such as intra-aortic balloon can be considered, with the objective of reducing pulmonary pressures.[18]

The persistence of significant PH with high TPG and PVR, even after these strategies, is considered a contraindication for HT. In this scenario, VAD implantation as a bridge to later candidacy is a supportive option in selected patients. Left ventricular decompression obtained with the use of a VAD can lead to reduced pulmonary artery pressure and PVR in the medium term, making the patient a candidate for HT.[21-23] In patients with advanced HF and significant PH with a persistent pre-capillary component, heterotopic HT or combined heart-lung transplantation (in qualified centers), VAD implantation as a target therapy, and palliative care are options for treatment and support (Figure 2).

Some measurements during cardiopulmonary hemodynamic assessment may eventually be in disagreement with the patient's actual hemodynamics and lead to errors in interpretation. Table 5 describes some common errors and problems that occur during invasive cardiopulmonary assessment.

Chart 1 – Cardiopulmonary hemodynamic assessment in candidates for heart transplantation with pulmonary hypertension

	Hemodynamic assessment	PH classification	Suggested approach	New condition	Diagnosis	HT
PASP ≥ 50 mmHg	PAOP < 15 mmHg TPG ≥ 15 PVR ≥ 3 Woods	Pre-capillary PH	Pulmonary vasoreactivity Nitric oxide	PASP < 50 mmHg TPG < 15 PVR < 3 Woods	Reactive PH	✓
				PASP ≥ 50 mmHg TPG ≥ 15 PVR ≥ 3 Woods	Fixed PH	✘
	PAOP ≥ 15 mmHg TPG < 15 PVR < 3 Woods	Post-capillary PH	RAP > 12 mmHg: Diuretics SVR > 1200 $_{dynas/s/cm^5}$:SNP	PASP < 50 mmHg TPG < 15 PVR < 3 Woods		✓
	PAOP ≥ 15 mmHg TPG ≥ 15 PVR ≥ 3 Woods	Combined pre- and post-capillary PH	Pulmonary vasoreactivity SNP	PASP < 50 mmHg TPG < 15 PVR < 3 Woods	Reactive PH	✓
				PASP ≥ 50 mmHg TPG ≥ 15 PVR ≥ 3 Woods	Fixed PH	✘

HT: heart transplantation; PAOP: pulmonary artery occlusion pressure; PASP: pulmonary artery systolic pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; RAP: right atrial pressure; SNP: sodium nitroprusside; SVR: systemic vascular resistance; TPG: transpulmonary gradient.

Assessment of candidates for ventricular assist device implantation

RV dysfunction is one of the main causes of death and early morbidity after VAD implantation.[24,25] Accurate assessment of the risk of RV dysfunction during the early postoperative period after VAD implantation is important for planning eventual temporary circulatory support for the RV, which may attenuate the risk of postoperative mortality.[26-28]

Clinical, laboratory, echocardiographic, and hemodynamic assessment are part of the majority of scores that predict RV dysfunction after VAD implantation; however, these tools are still not totally reliable in correctly predicting RV dysfunction in this scenario,[29,30] making this assessment challenging.

Pulmonary hemodynamic assessment assists in prediction of RV dysfunction after VAD implantation.[25] The main hemodynamic parameters and their references for predicting RV dysfunction are described Table 6.

In addition to its role in pre-implantation assessment for VAD, cardiopulmonary hemodynamic assessment can assist in the management of some situations during the postoperative period after implantation, as follows:

- During the early postoperative period:[35]
  - Management of pulmonary hypertension and RV preload;
  - Left ventricular decompression (assisting in the decision to increase or decrease VAD rotations).
- Long-term follow-up:
  - Refractory patients with symptoms of HF: assessment of left ventricular decompression, RV function, and aortic regurgitation;[36]
  - Assessment of optimal VAD rotations (ramp test);[37]
  - Hemodynamic optimization with decoupling between diastolic pulmonary pressure and PAOP.[38]

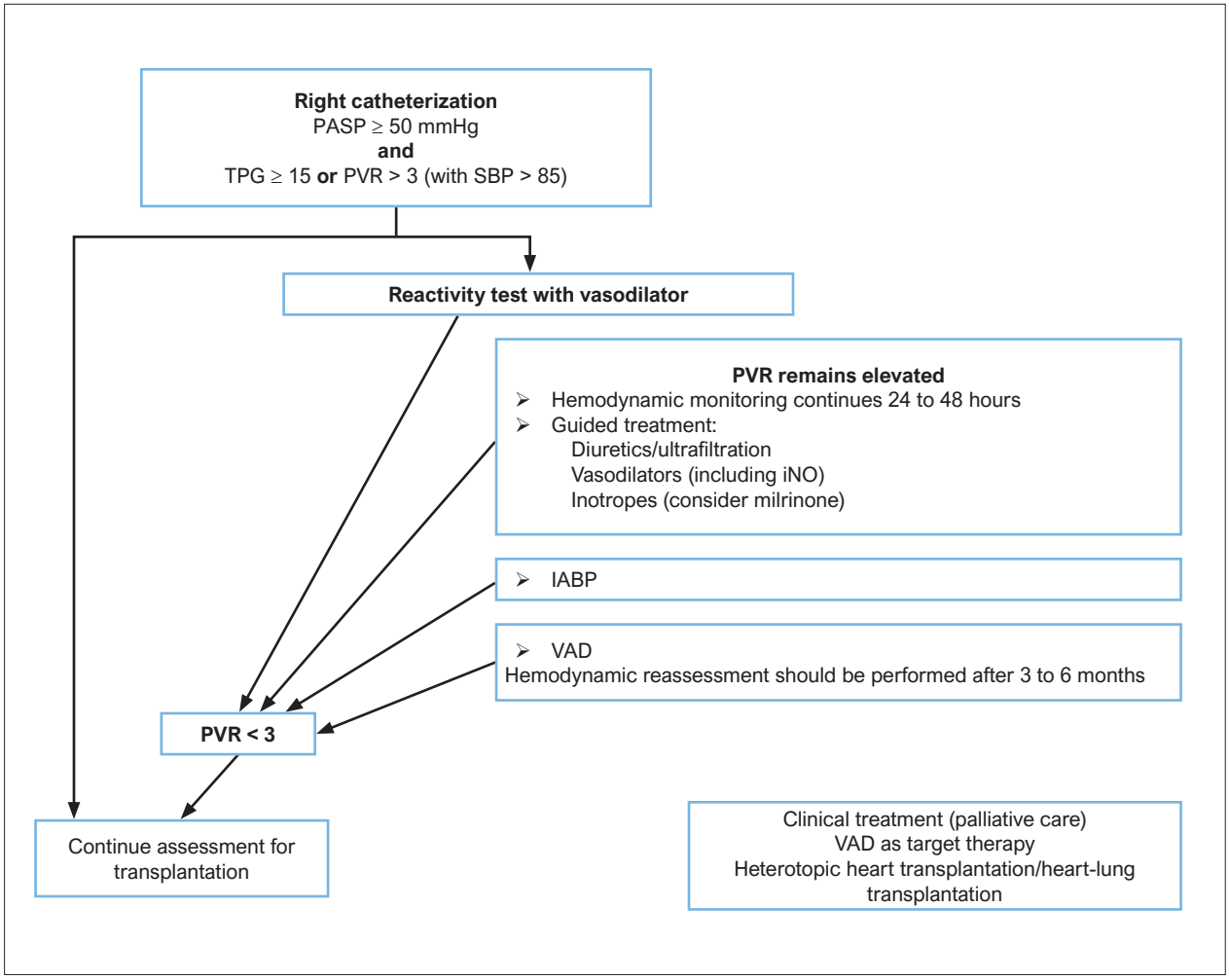

Figure 2 – *Assessment for heart transplantation in patients with advanced heart failure and pulmonary hypertension. IABP: intra-aortic balloon pump; iNO: inhaled nitric oxide; PADP: pulmonary artery diastolic pressure; PASP: pulmonary artery systolic pressure; PVR: pulmonary vascular resistance; SBP: (systemic) systolic blood pressure; TPG: transpulmonary gradient; VAD: ventricular assist device.*

Conclusion

Invasive cardiopulmonary hemodynamic assessment continues to be an important tool for assessing patients with advanced HF, especially in candidates for HT and VAD, as well as in the management of complex patients with unclear hemodynamics and cardiogenic shock.

Appropriate techniques for invasive hemodynamic assessment and correct interpretation of curves and pressures, in a systematic manner, are fundamental to understanding the mechanisms that involve cardiopulmonary hemodynamic changes. They allow guided hemodynamic optimization, thus promoting better clinical outcomes.

Author Contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Writing of the manuscript; Critical revision of the manuscript for intellectual content: Biselli B e Seguro LFBC.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Table 5 – Errors and problems in cardiopulmonary hemodynamic assessment

Situation	Comments
Contraindication of HT with a single isolated hemodynamic assessment	Identify hemodynamic component of PH and repeat new measurements after hemodynamic optimization and vasoreactivity tests.
Contraindication of HT with only 1 hemodynamic criterion altered	Always assess all cardiopulmonary hemodynamic variables together (pulmonary pressure, gradients, and PVR)
Disagreement between pulmonary pressure, PVR, and pulmonary gradients	
• Low PVR and elevated gradients	Possibly overestimated cardiac output (e.g., cardiac shunt, measurement error, obesity)
• Elevated PVR and low gradients	Possibly underestimated cardiac output (e.g., important RV dysfunction, severe TR)
• Elevated PVR and gradients, with low pulmonary pressures	Overestimated PAOP (e.g., severe MR) Check patient positioning, leveling, and correct execution of pressure.
Vasoreactivity test with iNO in patients with hypovolemia or very high PAOP	Risk of acute pulmonary edema

HT: heart transplantation; iNO: inhaled nitric oxide; MR: mitral regurgitation; PAOP: pulmonary artery occlusion pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; RV: right ventricle; TR: tricuspid regurgitation.

Table 6 – Cardiopulmonary hemodynamic assessment in candidates for long-term left ventricular assist devices

	Formula	Predictor of RV dysfunction
Pulmonary artery pulsatility index	PASP – PADP / RAP	< 2.0 [31]
CVP / PCP		> 0.63 [32]
RVSWI	[(CI / HR) × (MAP – PCP)] × 0.0136	≤ 5.0 g/m/m^2 [33]
RVSWI + PVR		RVSWI ≤ 5.0 g/m/m^2 PVR > 3.7 Woods [34]
Diastolic pulmonary gradient	PDAP – PCP	≥ 7 [34]

CI: cardiac index; CVP: central venous pressure; HR: heart rate; MAP: mean arterial pressure; PADP: pulmonary artery diastolic pressure; PASP: pulmonary artery systolic pressure; PCP: pulmonary capillary pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; RV: right ventricle; RVSWI: right ventricular stroke work index.

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Review Article

Treatment Strategies for Refractory Congestion

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Abstract

Worsening congestion is the main reason for hospitalization of most acute heart failure (AHF) patients. However, most patients are discharged with residual congestion, resulting in early readmissions that portend poor outcomes. Diuretics remain the mainstay of therapy. Nevertheless, these drugs stimulate the renin-angiotensin–aldosterone (RAA) axis and the sympathetic system and elicit adaptive responses in the nephron that may be counterproductive and lead to diuretic resistance. Renal failure and AHF are common and coexist in up to 40% of cases. Diuretic strategies that rely on combinations of diuretics are emphasized as a method to prevent resistance. If diuretic resistance does develop, higher-dose combination regimens, hypertonic saline solution, and mechanical ultrafiltration can be used to overcome diuretic adaptations and restore diuretic efficacy.

Introduction

Acute heart failure (AHF) accounts for 22.8% of admissions for cardiovascular causes in Brazil, according to the Ministry of Health hospital information system maintained by the Unified Health System (SUS - *Sistema Único de Saúde*). Despite the high cost of episodes of heart failure decompensation, rates of hospital readmission and death remain high. Intrahospital mortality from AHF in Brazil was 12.6%, according to data from the BREATHE study, which is much higher than rates in developed countries.[1]

Hypervolemia is one of the pathophysiologic pillars of AHF, whether because of fluid retention or because of volume redistribution. Congestion was observed in 90 and 93% of patients in the BREATHE and ADHERE (The Acute Decompensated HEart Failure National REgistry)[2] registers respectively.

Despite the near universal use of diuretics in hospitalized patients with AHF, many patients leave hospital without adequate decongestion. In the ADHERE registry, it was found that 33% of patients had lost a maximum of 2.5 kg at hospital discharge, while 20% had gained up to 5 kg while in hospital. This is even a common occurrence in clinical trials, which are situations that are far from representative of the "real world" of clinical practice. For example, 48% of participants in the classic studies DOSE-AHF (Diuretic Optimal Strategy Evaluation in Acute Heart Failure)[3] and CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure),[4] which will be covered in detail below, still had residual congestion at hospital discharge.[5] Concerns with worsening renal function associated with restoration of normovolemia are not justified, since it has been demonstrated that presence of congestion is a better predictor of mortality than creatinine elevation in patients discharged from hospital after AHF decompensation[6] (Figure 1). On the other hand, elevated creatinine in conjunction with persistent signs of congestion indicates poor prognosis, because it is often associated with diuretic resistance.

Diuretic resistance is defined as incapacity to achieve decongestion despite using diuretics at appropriate doses.[7] The lack of a consensus on specific criteria to define diuretic resistance means that its true prevalence is unknown. However, it is known to be an ominous complication of AHF that is predictive of mortality.[8]

The pathophysiology of resistance to diuretics is complex and has not yet been fully understood.[9] It involves a myriad of factors (Figure 2) that act in synergy to create and perpetuate the insufficient response to diuretics. Reabsorption of sodium in the distal tubules has emerged as one of its main determinants[10,11] and it is known that hypertrophy of distal tubule cells is present after even a few days of treatment with loop diuretics, which results in increased sodium resorption.[12] The "braking phenomenon" is already well known. This is a term used to designate the reduction in response after repeated doses of diuretics.[9] It is a homeostatic mechanism that strives to prevent excessive volume depletion during continual exposure to diuretics, but which is exacerbated in patients with AHF and contributes to diuretic resistance.[13]

The principal predictor of renal failure in patients with AHF is central venous pressure. The increased venous pressure is transmitted retrogradely to the renal vein, reducing glomerular filtration pressure and natriuresis capacity and setting up a vicious cycle that perpetuates congestion.[15] It is essential to identify patients with diuretic resistance early, so they can be given the appropriate treatment.

Treatment of congestion

Loop diuretics

Loop diuretics (furosemide, torsemide, and bumetanide) are essential medications in the management of hypervolemic patients, because they have greater natriuretic potential. The AHF treatment guidelines emphatically recommend use of diuretics to relieve the signs and symptoms of fluid overload.[16-18]

Keywords

Heart Failure; Diuretics; Ultrafiltration.

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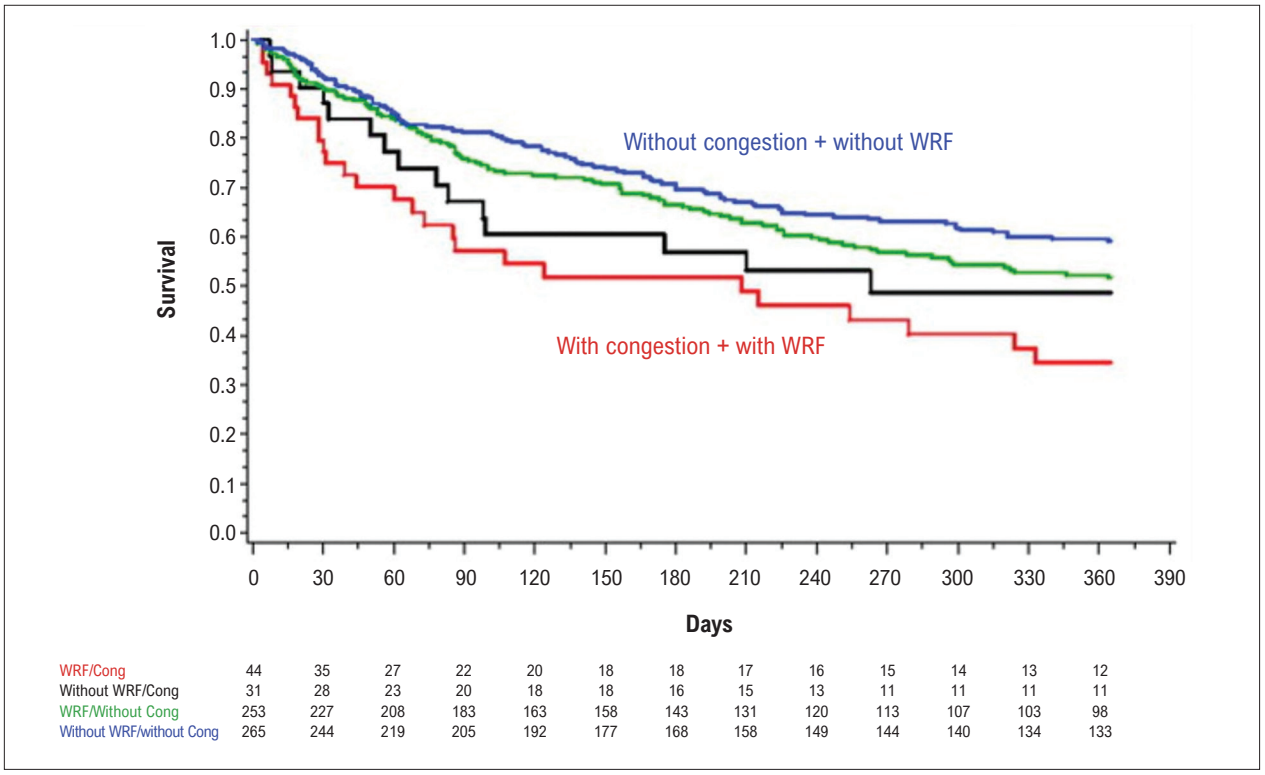


Figure 1 – *Survival curve according to presence of congestion and worsening renal function in acute heart failure patients discharged from hospital. Cong: congestion; WRF: worsening renal function. Adapted from Metra et al.*[6]

Adequate management of these medications requires knowledge of their pharmacokinetic and pharmacodynamic properties. In contrast with the other members of this drug class, the bioavailability of furosemide is variable (10 to 90%) and is even more erratic in the presence of AHF,[19] which generally involves loop edema. Next, furosemide is transported in the convoluted proximal tubule by the organic acids transport system and reaches Henle's loop, where it inhibits NKCC2 cotransporter in the thick ascending limb. It also inhibits the same symport in the apical membrane of macula densa cells, blocking chloride reabsorption and stimulating renin secretion. This neurohumoral activation can contribute to perpetuation of harmful effects in patients with AHF.[7]

Loop diuretic dose is chosen empirically and should be guided by urinary output and clinical status. Excessive use of diuretics activates reflex neuro-hormonal mechanisms and was linked with worse outcomes in the ESCAPE study (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness).[20] It should be remembered that patients who are chronic diuretic users will probably need higher doses. Diuretics have an S-shaped dose-response curve (Figure 3), and both AHF and renal failure shift the curve to the right, since higher doses are needed to achieve the maximum natriuretic response. In renal failure, furosemide and organic acids that accumulate in uremia compete for tubular secretion, in a situation analogous to what happens with administration of nonsteroidal anti-inflamatory drugs.[21]

Furosemide doses and administration strategies were compared in the DOSE multicenter study (Diuretic Optimization Strategies Evaluation), which is the largest clinical trial that has been conducted to date addressing this issue. The study enrolled 308 patients with AHF and used a factorial 2x2 design to assign them to intravenous administration of furosemide at a dose 2.5 times greater than their daily dose (high dose groups) or at the same dose as their oral dose (low dose groups) and to either receive intermittent doses (twice a day) or by continuous infusion for 72 hours. The patients were given an average of 260 mg or 120 mg of furosemide (high and low dose groups, respectively). There were no differences between groups in terms of overall symptoms assessment (primary outcome). However, the high dose group had greater relief of dyspnea, greater weight loss, and greater liquid loss (secondary outcomes). Worsening renal function by 72 hours (the other primary outcome) tended to occur more frequently in the high dose group. The authors also failed to detect any difference between the continuous infusion and intermittent dose diuretic administration strategies, which was possibly related to absence of a loading dose at the start of continuous infusion.

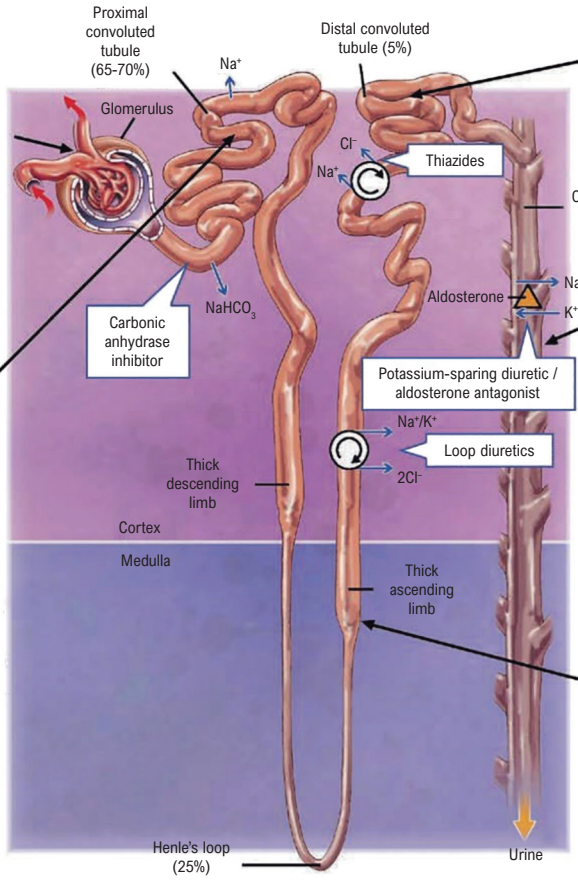
A post hoc analysis of the DOSE study data showed that an increase in creatinine concomitant with diuretic treatment was paradoxically associated with better outcomes.[22] This association was also observed by other authors[6,23] and probably reflects changes in glomerular hemodynamics, and not tubular injury.[24] To the extent that withdrawal, or even a decrease of the diuretic dose is not warranted in the event of renal dysfunction, if signs of hypervolemia are still present.

Reduced GFR:

Barriers	Possible solution
Glomerular hemodynamic changes	Withdrawal NSAIDS, consider withdrawing ACEi, ARB, and ARNI
Low cardiac output	Hemodynamic support
Chronic kidney disease or functional renal hypoperfusion	Increase loop diuretic dose

Proximal tubule hyperfunction:

Barriers	Possible solution
Neuro-hormonal activation	ACEi, ARB, or NARI
Sodium hyperavidity	Increase loop diuretic doses, acetazolamide
Post-diuretic effect	Multiple daily doses, continuous infusion of loop diuretics
Excessive daily sodium intake	Sodium restriction



Distal tubular hypertrophy:

Barriers	Possible solution
Rebound sodium retention	Sequential nephron blockade (combined diuretic treatment)

Distal nephron hyperfunction:

Barriers	Possible solution
Excessive aldosterone-mediated sodium retention	Aldosterone antagonist, potassium-sparing diuretic
Excessive vasopressin-mediated water retention	Vasopressin antagonist, free water restriction

Henle's loop hyperfunction:

Barriers	Possible solution
"Braking" effect	Higher loop diuretic doses

Figure 2 – *Mechanisms of diuretic resistance and proposed treatments. NSAIDs: non-steroidal anti-inflamatory drugs; ARB: angiotensin receptor blockers; ACEi: angiotensin-converting enzyme inhibitors; ARNI: angiotensin receptor and neprilysin inhibitors; GFR: glomerular filtration rate. Adapted from Jentzer et al.[14]*

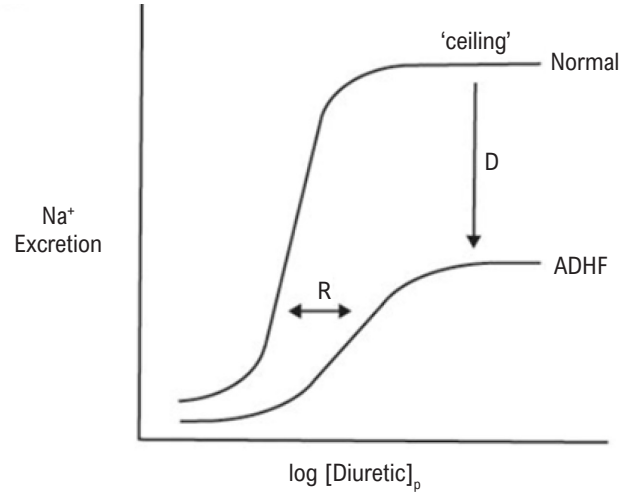


Figure 3 – *Relationship between natriuresis and loop diuretic concentration logarithmic scale. Adapted from Ellison DH[7]*

Thiazide diuretics

Thiazide diuretics (hydrochlorothiazide, chlorothiazide, and others) and "thiazide-like" diuretics (metolazone, chlorthalidone) block the sodium and potassium cotransporter in the distal convoluted tubule and can, at least partially, counterbalance the increased sodium resorption that is associated with chronic use of loop diuretics.[7] When used as monotherapy, they have a natriuretic effect equivalent to 30 to 40% of the effect of loop diuretics. Different members of the class basically differ in terms of their pharmacokinetic characteristics. In Brazil, only hydrochlorothiazide and chlorthalidone are available.

Combinations of thiazide and loop diuretics are often used to overcome diuretic resistance, although the evidence for doing so is not robust.[13] While there are more than 50 publications on the subject, just 300 patients with AHF were enrolled on small studies, many without control groups, and with primary focus on physiological variables, rather than clinical outcomes. There are two ongoing clinical trials that will provide more information about the magnitude of the effect of this combination (ClinicalTrials NCT0164793229 and ReBEC RBR-5qkn8h30).

Certain concepts that are used in clinical practice, but which have not been confirmed in clinical trials merit discussion. The first is that metolazone could be more effective for combined treatment with loop diuretics, possibly because of its inhibitory effect on the proximal tubule,[25] but there was no evidence of superiority in comparative studies.[26,27] The second concept is that thiazide should be administered 30 minutes before the loop diuretic, but this has not been assessed in studies of combination use of diuretics.[28]

Hydroelectrolytic disorders are more common with thiazide than with loop diuretics. The potential for caliuresis is greater because two to three potassium ions are lost for each sodium ion excreted. The combination of these two drug classes, in particular, greatly increases the predisposition to hypokalemia, which was present in almost two thirds of the patients in one clinical trial.[26] The North-American AHF guidelines recommend that the combination with thiazide should be reserved for cases that do not respond well to moderate to high doses of loop diuretics.

Mineralocorticoid receptor antagonists (MRA)

Sprinolactone is the only mineralocorticoid receptor antagonist (MRA) available in Brazil. It has been used as part of treatment to modify the disease in heart failure with reduced ejection fraction (HFrEF) because of its pleiotropic effects.[29] When used at high doses, it has diuretic properties.

Use of sprinolactone may be useful to counterbalance secondary hyperaldosteronism provoked by loop diuretics (30). High aldosterone levels have a harmful effect on the myocardium, contribute directly to diuretic resistance,[31] and have been associated with increased rates of mortality and readmission for AHF.[32]

These data were the basis for the ATHENA-HF study (Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure),[33] a double-blind clinical trial that compared addition of sprinolactone in high doses (100 mg) or usual doses (25 mg) to the standard treatment of 360 patients with AHF. The sample comprised patients with AHF, but without the criteria for diuretic resistance. Although this treatment was well-tolerated, administration of high doses of MRA did not result in any differences in the primary outcomes (plasma levels of N-terminal fragment of B-type natriuretic peptide [NT-proBNP]) or secondary outcomes (relief from congestive symptoms, dyspnea grade, urinary output, or weight loss). The short protocol duration (96 hours) is insufficient for the active metabolite of potassium canrenoate to accumulate and probably contributed to the null results, as did the fact that the study did not include patients with a very high severity profile.

Despite the results of ATHENA-HF, use of sprinolactone in high doses is one option for avoiding hypokalemia in patients taking large quantities of potassium wasting diuretics.

Carbonic anhydrase inhibitor

From a pathophysiologic point of view, strategies that target the proximal tubule could offer some benefil could offer some benefit for treatment of congestion. This segment is where the greatest quantity of sodium is reabsorbed, particularly in conditions such as AHF.

Acetazolamide blocks reabsortion of sodium bicarbonate in the proximal convoluted tubule by inhibiting the carbonic anhydrase enzyme. A greater quantity of sodium is therefore available for exchange at the level of Henle's loop, increasing the effect of loop diuretics, particularly in renal malperfusion states. Furthermore, the greater quantity of chloride available in the macula densa can inhibit renin secretion (reducing neurohumoral activation). When administered as monotherapy, acetazolamide has very poor natriuretic activity and so its use is restricted to combined therapy. It can be useful for treatment of metabolic alkalosis induced by loop diuretics.

Some small observational studies demonstrated that acetazolamide had a positive impact on natriuresis.[34,35] One of them showed that acetazolamide increased diuretic efficiency in patients with AHF, with additional excretion of 100 mmol of sodium for each 40 mg of furosemide equivalent administered. The second observed an increased diuretic response to addition of 250 mg of acetazolamide, similar to the response achieved by doubling the furosemide dose.

The ADVOR study (Acetazolamide in Decompensated Heart Failure With Volume OveRload)[36] (NCT03505788) is a double-blind randomized clinical trial that is ongoing in Belgium, with completion predicted for 2022. This study enrolled around 500 patients to test the effect of adding 500 mg of intravenous acetazolamide or placebo to a high dose loop diuretic regimen.

Tolvaptan

Arginine vasopressin antagonists (or vaptans) were developed to selectively block the V2 receptor (tolvaptan) in the collecting duct. The V2 receptors increase aquaporin-

mediated water reabsorption. Blocking it therefore increases excretion of electrolyte-free water, with no effect on excretion of electrolytes.[37] These drugs are therefore considered aquaretics.

Tolvaptan was tested in the ACTIV in CHF (Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure)[38] and EVEREST studies (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan).[39] In both studies, there were benefits for weight loss, dyspnea, and edema, and improvements in hyponatremia, without impact on mortality or rate of readmission for AHF.

Despite the neutral results for mortality and hospital admissions, tolvaptan demonstrated some favorable effects in patients with diuretic resistance in the EVEREST trial, such as greater weight loss, less dyspnea, and less edema. Notwithstanding this result, there is scant evidence to recommend tolvaptan for treatment of diuretic resistance. It is not currently approved by the Food and Drug Administration (FDA) for treatment of AHF, but it is approved for treatment of associated hyponatremia.

Ultrafiltration

Ultrafiltration (UF) is an alternative to diuretics for treatment of hypervolemia.[40] It consists of passing blood through hollow fibers surrounded by semipermeable membranes, subjected to a pressure gradient. The result is mechanical removal of fluid, termed the ultrafiltrate. Ultrafiltration removes sodium more effectively because whereas the ultrafiltrate is isonatremic in relation to plasma,[41] diuretics produce hypotonic urine, with around 60 to 80 mmol of sodium per liter. Moreover, it does not trigger neuro-hormonal responses or stimulate the macula densa. In other words, the process of decongestion is physiologically different.

To date, seven clinical trials have been published comparing UF with pharmacological treatment in patients with AHF, five of which examined clinical outcomes. The largest of these enrolled 224 patients, highlighting the difficulty of recruiting participants for studies evaluating invasive methods of treatment.

The first clinical trial was the RAPID-CHF (Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure),[42] with just 40 patients randomized to UF or pharmacological therapy. The study observed that UF improved symptoms and provoked greater loss of liquid, but with no differences in weight.

The first large study was published in 2007, randomizing 188 patients for a single UF session or standard treatment with diuretics within 24 hours of admission for AHF: the UNLOAD study (Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure).[43] The results were positive, since there was a 52% reduction in unplanned visits after hospital discharge, a 44% reduction in hospital admissions for AHF, and a 63% reduction in days in hospital after readmission. Some limitations of UNLOAD should be noted, such as that it was sponsored by industry and did not have an independent events committee.

The CARRESS-HF study was published next, enrolling 188 patients on a randomized clinical trial, funded by the National Heart, Lung, and Blood Institute. This study compared the effects of UF at a fixed velocity of 200 mL/h with goal-scaled drug treatment (loop diuretics, thiazide, vasodilators, and inotropics). No significant differences were observed in outcomes including weight loss (5.7 ± 3.9 vs. 5.5 ± 5.1 kg, respectively, $p = 0.58$), degree of dyspnea, and wellbeing rating, rated on a visual analog scale. There were no differences in mortality, emergency visits, or readmissions for heart failure by 60 days. However, the UF group had a higher rate of complications (7.2% vs. 5.7%, $p = 0.03$), represented by bleeding and dialysis catheter infection. Strangely, while the group on pharmacological treatment had a reduction in creatinine levels, the UF group had creatinine elevation of 0.23 mg/dL.

Certain details of the CARRESS-HF study merit mention because they could have contributed to the null result. First, the group on pharmacological treatment were given medication at doses titrated to maintain daily urinary output at 3 to 5 liters, whereas the UF group were given a fixed rate of 200 mL/hour of UF, which was not individualized. Second, the mean duration of intervention was much longer in the drug treatment group (92 hours) than in the UF group (40 hours). Another important limitation of this study was the high rate of cross-over, because 30% of the patients in the UF group were given diuretics after the end of the protocol and 10% of the patients allocated to UF did not receive it for a range of reasons. These results should therefore be treated with caution.

It should also be noted that the CARRESS-HF study cannot be considered a counterpoint to the UNLOAD study, since there were significant differences in the inclusion criteria and study protocols (Table 1).

The CUORE study (Continuous Ultrafiltration for Congestive Heart Failure)[44] was a smaller study that assessed UF and pharmacological treatment in 56 patients at two centers. As in the UNLOAD study, patients were also randomized within 24 h of admission to flexible UF strategies (rate and duration) or conventional unguided pharmacological therapy. In contrast with other trials, the UF group was also given pharmacological treatment. There was no difference in weight at hospital discharge between the two groups, but the UF group had a lower rate of readmission and mortality (combined) at 1 year.

The AVOID-HF study (Aquapheresis Versus. Intravenous Diuretics and Hospitalization for Heart Failure)[45] was designed to compare guided UF strategies and pharmacological treatment. It was designed to enroll 810 patients with AHF, but was unfortunately terminated early by the study sponsor, because of budget problems and slow recruitment. Although it did not achieve sufficient statistical power, analysis of the outcomes of the 224 patients recruited was favorable to UF, with a lower rate of occurrence of a first AHF-related event by 90 days (25% in the UF group vs. 35% in the pharmacological treatment group). The primary study outcome, time to first event, was longer in the UF group (62 days) than in the pharmacological treatment group (34 days), although without statistical significance ($p = 0.106$). At 30 days after

Table 1 – Comparison of the principal clinical trials assessing ultrafiltration in patients with acute heart failure

	UNLOAD	CARRESS-HF
Study design and protocol	Early UF, within 24 h of admission of patients with AHF	UF as salvage therapy in patients with AHF with worsening renal function
Prescription of UF	Flexible duration and rate of UF, to a maximum of 500 mL/h	UF duration and rate set at 200 mL/h
Drug treatment	No predefined algorithm	According to an algorithm for scaled diuretic doses

CARRESS-HF: Cardiorenal Rescue Study in Acute Decompensated Heart Failure; AHF: acute heart failure; UF: ultrafiltration; UNLOAD: Ultrafiltration Versus. Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure.

hospital discharge, fewer patients in the UF group had been readmitted for AHF (p = 0.034).

Due to the inconsistent results, the majority of centers reserve UF as a salvage strategy for patients whose hypervolemia cannot be resolved with pharmacological treatment. Figure 4 depicts a proposed algorithm for refractory congestion. Use of both methods (UF and pharmacological treatment) in synergy can also be considered..

The AHF treatment guidelines recommend UF in cases of refractory hypervolemia, but diverge on the degree of recommendation and level of evidence. According to the Brazilian guidelines, this indication is class I with level of evidence B, whereas the European guidelines give it a class IIb recommendation and level of evidence C. The recently-published American guidelines do not contain any specific recommendations on UF in patients with AHF.

Hypertonic saline solution

In the elegant work by Issa et al.,[46] the infusion of 7,5% HSS twice daily for three days prevented renal dysfunction in patients with decompensated heart failure. During the study protocol, the increase in serum creatinine (0,3mg/dl or above) occurred in 2 (10%) of the HSS arm and 6 (50%) of the placebo arm. (relative risk 0,3; confidence interval 0,09 a 0,98; p=0,01). Relative to baseline, serum creatinine and cystatin C levels were lower in HSS as compared to placebo.

Administration of hypertonic saline solution (HSS) has been used as a treatment option in cases of resistance to diuretics and refractory hypervolemia for more than two decades. Much of what is known about use of HSS comes from experimental models of hemorrhagic and septic shock.[47-49] Infusion of hypertonic NaCl solution results in a sudden increase in plasma osmolarity, immediately displacing fluid from the interstitium to the vascular space as a consequence of the increased tonicity, expanding plasma volume, and increasing renal flow. After infusion of HSS, a loop diuretic is administered in bolus. Over 20 years of experience, infusion of HSS has proven to be a safe and well-tolerated treatment.[50]

One of the first studies with HSS was observational, in a sample of 30 patients who were given 150 mL of NaCl solution (at 1.4 to 4.6%) administered twice a day, followed by furosemide (250-2,000 mg) over 6 to 12 days.[51] There were improvements in dyspnea, edema, and disease severity, according to functional class.

Later, the same authors conducted a single-blind randomized study that recruited 60 patients to compare furosemide (500-1,000 mg) combined with HSS (1.4 to 4.6% NaCl, depending on natremia) or placebo.[52] This study observed that the HSS group had greater urinary output and greater natriuresis and improvements in creatinine and New York Heart Association functional class.

Finally, a larger clinical trial with 107 patients tested the effect of HSS on rates of hospital readmission and mortality.[53] The same protocol as above was applied and resulted in a lower rate of hospital readmission in the HSS group (25 patients out of a total of 53) than in the placebo group (43 patients out of a total of 54) over the 31 ± 14 months of follow-up. Additionally, mortality was significantly lower in the HSS group (24 patients vs. 47, p < 0.001) than in the placebo group. Another large clinical trial (NCT05298098), with a double-blind and randomized design, is ongoing and will recruit 600 patients to test the effect of an even more concentrated solution (NaCl 10%), with results predicted for 2023.

The Brazilian guidelines recommend HSS in patients with refractory congestion (class IIa, level of evidence B). While the European guidelines do mention HSS, they do not make any specific recommendations.

Albumin

Loop diuretics are organic acids that circulate firmly bonded to albumin. Albumin increases secretion of furosemide in the proximal tubule and therefore hypoalbuminemia may reduce bioavailability of furosemide in Henle's loop. However, there are no studies of use of albumin in AHF and its role in the genesis of diuretic resistance may be irrelevant. There is a little evidence suggesting that infusion of albumin increases the natriuretic response, as long as serum albumin is above 2 mg/dL.[54] There is scant evidence on the role of albumin in AHF, limited to case reports and the experience of centers specialized in AHF.

Conclusions

Adequate management of congestion in patients with advanced AHF remains a challenge. Over the last two decades, several clinical trials in AHF patients have been published, but unfortunately without yielding significant advances in treatment for these patients. Better understanding

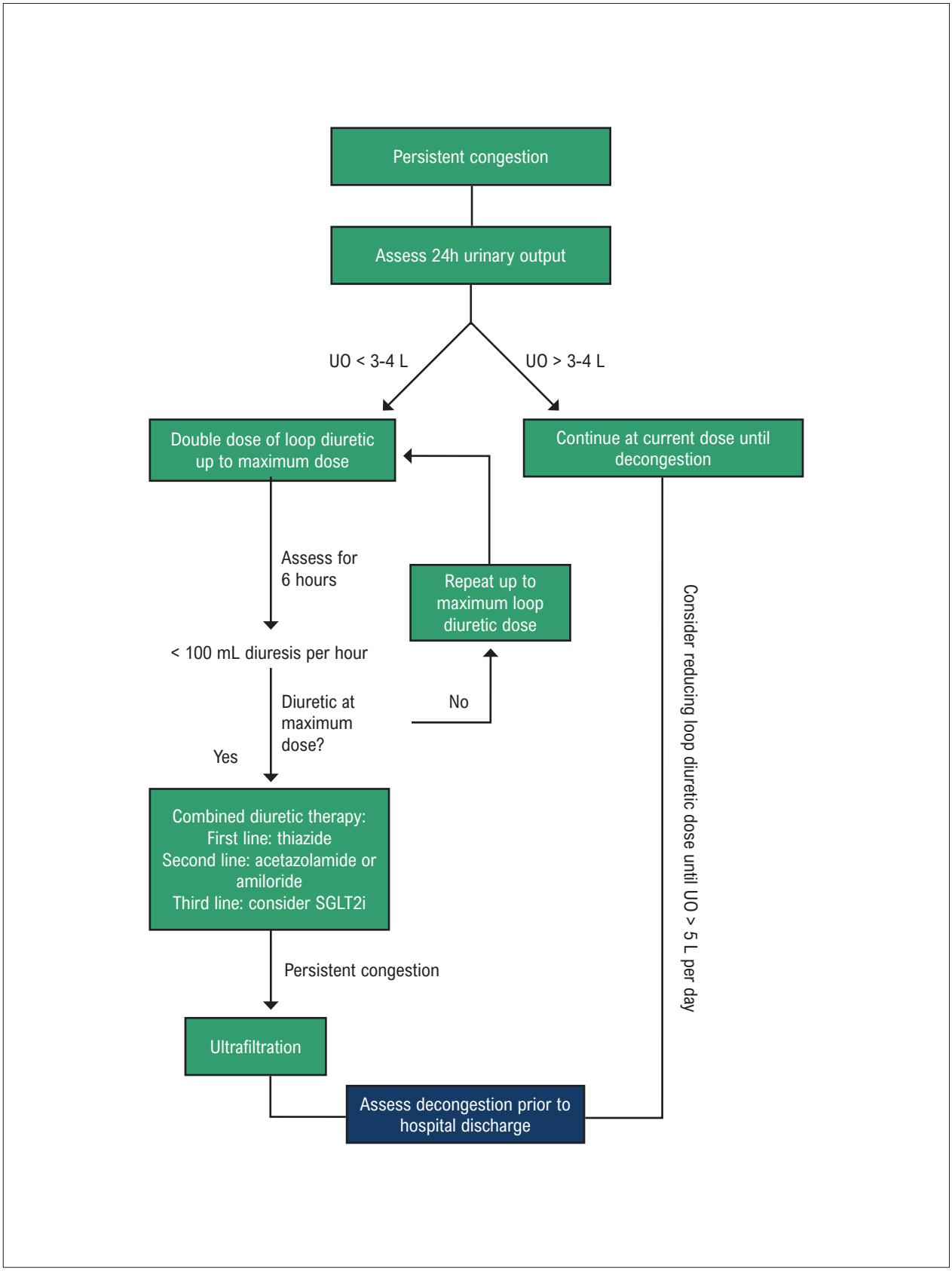


Figure 4 – *Therapeutic flow diagram illustrating treatment of congestion in acute heart failure. UO: urinary output; SGLT2i: sodium-glucose cotransporter 2 inhibitors. Adapted from Mullens et al.*[36]

of the mechanisms of diuretic resistance can contribute to appropriate treatment and better outcomes.

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Writing of the manuscript and Critical revision of the manuscript for intellectual content: Linhares GP, Souza-Neto JD.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Review Article

Long-Term Ventricular Assist Devices – Main Complications in Contemporary Clinical Practice

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Abstract

Advanced heart failure (HF) is associated with reduced quality of life and high hospitalization and mortality rates. Ventricular assist devices (VADs) promote an increase in cardiac output, and consequently improvements in body functions, functional capacity and patient survival. However, the use of VAD may be associated with complications and require systematic and specialized care. Ischemic and hemorrhagic stroke is among the most feared complications and its occurrence is related to thrombus formation in the pump. The connection between the driveline and the external power source is a potential source of infection that may extend to the mediastinum. Management of bleeding caused by anticoagulation therapy may be challenging, since discontinuation of the treatment may lead to thrombus formation. Aortic insufficiency and right ventricular dysfunction may occur, particularly in prolonged periods of support, requiring optimization of VAD parameters and clinical management. Although uncommon, mechanical failure of the VAD may occur and require replacement of the pump or even heart transplant. Thus, identification and management of the main complications of VAD in patients with advanced HF is needed, so that strategies for prevention and rigorous clinical follow-up can be implemented. This review aims to summarize the main adverse events in patients with long-term VAD.

Introduction

Stage D advanced heart failure (HF) is characterized by abnormalities in cardiac structure that lead to tissue hypoperfusion, target-organ damage, cachexia, and limiting symptoms.[1,2] It is estimated that 5-25% of patients with HF will develop the advanced stage of the disease, which is associated with high hospitalization and mortality rates, even among those under optimized drug therapy.[3-5] Also, a large number of patients will require advanced therapies.[6] In this context, heart transplant (HT) is usually the surgical treatment of choice; however, the feasibility of this treatment is limited by the low availability of organs and the potential clinical complications of the procedure.[7] Therefore, long-term ventricular assist devices (VADs) represent an important therapeutic alternative that allows patient to get back to daily life activities, promoting higher quality of life and survival.

VAD is a surgically implanted mechanical pump that provides circulatory support in patients with severe systolic dysfunction, restoring cardiac output and reducing left ventricular (LV) work.[8] The VAD has inflow cannulas positioned in the left ventricle, and a mechanical pump connected to the external power source. Today, VAD with two different technologies, named second- and third-generation devices are used. Second-generation axial-flow devices, like the HeartMate II (HMII; Abbott Labs), were widely used for about 15 years, but its use has decreased worldwide. Likely, the commercialization of the centrifugal-flow HeartWare Ventricular Assist Device (HVAD; Medtronic), which uses a combination of hydrodynamic and magnetic levitation, has been discontinued recently. The HeartMate III (HMIII; Abbott Labs) accounts for 77% of the implants today.[9,10] It consists of a magnetically levitated cardiac pump, with wider blood-flow paths and pulsatility and has been associated with better outcomes of stroke-free survival and reintervention due to malfunctioning of the pump.[11]

In the last decade, approximately 25 thousand patients have undergone VAD implantation.[10] In 2019, 3,198 VADs were implanted in the USA, which is the highest registered by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS).[10] VAD technology has improved substantially and its use for the treatment of advanced HF has increased tremendously.[12] Also, the 1- and 2-year survival between the years 2015 and 2019 has improved compared with 2010 to 2014 (82.3% in the first year and 73.1% in the second year *vs.* 80.5% in the first year and 69.1% in the second year).[10] Currently, median survival rate of patients with VADs is nearly five years.[9]

Despite advances in the VAD design and in clinical treatment, 30-day adverse events still occur in 31% of patients.[13] According to INTERMACS, 72% of patients are hospitalized at least once within 12 months after

Keywords

Heart Failure; Heart-Assist Devices; Ventricular Dysfunction, Left.

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implantation.[10] Thus, the use of VAD has been associated with complications that can increase morbidity and mortality and hence require a close follow-up for better outcomes of the intervention (Figure 1).[11,14]

Several measures should be taken to promote safety and minimize potential adverse treatment events for the patients using VADs.[15,16] This review aims to summarize the main adverse events in patients in long-term mechanical circulatory support.

Case report

Here we report a clinical case of a female patient, 54 years old, history of dilated cardiomyopathy and severe mitral insufficiency for Chagas disease, who underwent HMII implantation in 2018 due to inotrope dependence and immune hypersensitivity, which reduces the possibility of HT. The post-implantation was complicated with bleeding, sepsis, severe abdominal distension and difficult anticoagulation control. After about 10 months of follow-up, the patient developed sustained elevation of power and

Stroke
Anticoagulation
Thrombolytics (selected cases)
Endovascular therapy

Aortic insufficiency
Clinical management
Optimization of the VAD parameters (ramp study)
Valve replacement

Pump thrombosis
Clinical management
Intensification of anticoagulation
Thrombolytics (selected cases)
Device replacement or heart transplant

Right ventricular dysfunction
Clinical management
Optimization of the VAD parameters

Mechanical problems / alarms
Revision of the log files
Optimization of the VAD parameters
Device replacement

Infection
Antibiotics
Debridement
Device replacement

Bleeding
Management of anticoagulation and antithrombotics
Clinical management/transfusions
Endoscopic or surgical treatment (selected cases)

Figure 1 – *Main complications of the ventricular assist device and summary of treatments.*

important VAD flow variations, clinical signs of hemolysis – hemoglobinuria and hemoglobin fall, requiring blood transfusion, peak lactate dehydrogenase (LDH) of 2557 U/L and loss of renal function. The patient underwent replacement of the VAD pump, due to clinical suspicion of thrombosis, which was confirmed intraoperatively. After two years with a good clinical course, persistent low-flow VAD alarms occurred, and the patient developed progressive signs of HF and cardiogenic shock. Due to clinical suspicion of subocclusive thrombus in the outflow cannula and aortic insufficiency (AoI), the patient underwent another surgery. Surgical findings revealed dense fibrous tissue around the Dacron and polytetrafluoroethylene (PTFE) patch of the outflow cannula, and presence of inflammatory exudate within the cannula, causing extrinsic compression (Figure 2). The cannula was reimplanted after removal of the fibrous layer and aortic valve replacement was performed. This case illustrates some of the challenges faced in the follow-up of patients with VAD, related to bleeding monitoring, occurrence of hemolysis, and identification of mechanical changes in the cannulas and changes in valvular changes. Trained, multidisciplinary teams are essential for better outcomes.

We will now describe the main adverse events related to the use of VADs and a brief discussion of their management.

Main adverse events of long-term VAD

Stroke

Devastating neurological events such as ischemic (thromboembolic) or hemorrhagic stroke affect nearly 10% of patients with VAD within one year.[10] These events are the main cause of long-term mortality after VAD implantation. However, the growing number of centrifugal-flow HMIII device has caused a reduction in these events. In a two-year clinical follow-up, HMIII was associated with a lower incidence of any stroke, and an estimated two strokes could be prevented for every 10 patients who receive HMIII implant.[17]

The risk of stroke in patients with VADs is associated with several factors. Patient-related factors may be related to higher odds of cerebrovascular events, such as age, female sex, severity of HF, history of diabetes, hypertension, atrial fibrillation, hypercoagulability, and

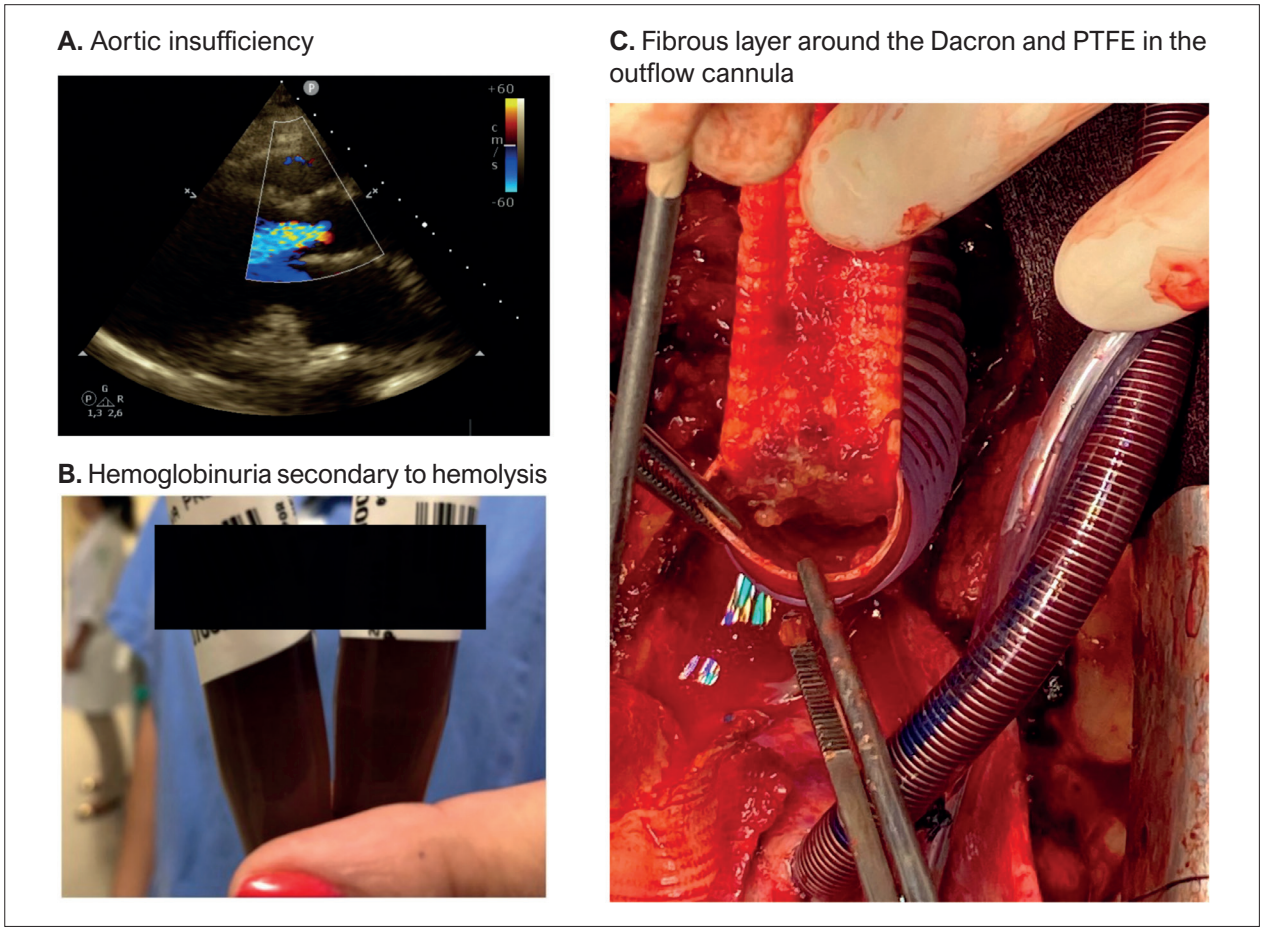

Figure 2 – *Complications in a patient using ventricular assist device. (A) Doppler echocardiography showing moderate-to-severe aortic insufficiency (B) Hemoglobinuria secondary to hemolysis caused by pump thrombosis. (C) Fibrous tissue layer around the Dacron and the polytetrafluoroethylene (PTFE) patch, causing extrinsic compression in the outflow cannula.*

infections unrelated to the implant. Besides, perioperative (aortic clamping and cardiac arrest with cardioplegia) and postoperative (duration of mechanical support, infection, subtherapeutic anticoagulation and hypertension following VAD implantation) factors, and those related to the VAD (infection, hemolysis and pump thrombosis) also influence the rate of stroke.[17,18]

During patient assessment, attention should be paid to the precise onset of neurologic manifestations and their course, using preferably the National Institute of Health and Stroke Scale (NIHSS),[19] and computed tomography angiography of the brain and intracranial vessels. Magnetic resonance is contraindicated due to the VAD metallic components, which can make difficult the early detection of ischemic events.

A previous imaging test and a careful clinical examination can help in the diagnostic and decision-making processes. VAD parameters should be analyzed for signs of the VAD malfunction or thrombosis.[17] Patients seen in hospitals without a circulatory support program should be followed by the VAD referring team, revising the therapeutic plan and determining the need for emergent transfer.[17] The most common events are the ischemic ones, caused mainly by embolism, whose management may be challenging depending on the extension of cerebral infarction. The balance between the risk of hemorrhagic transformation and the need of anticoagulation should be considered in the decision making. In the absence of hemorrhage, the selective use of thrombolytic agents and endovascular interventional neuroradiology should be considered in those with early presentation and clinical indication. However, it should be mentioned that these recommendations derive from clinical trials with patients without VAD.[20]

In cases where embolism is secondary to VAD thrombosis, systemic thrombolysis was shown to be safe in case reports.[17] However, a meta-analysis of observational studies did not show superiority of thrombolytic treatment over conventional pharmacological treatment, and the use of thrombolytics was associated with higher risk of major hemorrhage.[21] A randomized study is needed to evaluate whether the routine use of thrombolytics is beneficial in this condition. In hemorrhagic stroke, anticoagulation discontinuation or reversal with prothrombin complex concentrate is recommended for patients with INR ≤ 1.5. The time when anticoagulation should be resumed must be discussed with the neurovascular team.

Aortic insufficiency

Nearly 25% of patients that undergo VAD implantation develop severe-to-moderate AoI or aggravation of pre-existing AoI. This is a relatively high rate, considering that the prevalence of severe AoI prior to VAD implantation is 0.6%.[10]

Elevations in the pump flow lead to intermittent or permanent closure of the aortic valve and eventual commissural fusion.[9] This is the main risk factor for AoI, which is associated with high morbidity.[22] Also, the site and angle of the outlet graft anastomosis on the aortic wall contribute to AoI progression. AoI, in turn, causes a cascade of events – part of the cardiac output generated by the VAD returns to the left ventricle due to valvular incompetency, resulting in a fall in cardiac output and an increase in filling pressure.

The assessment of the aortic valve is essential for determining AoI severity and the planning of treatment.[23] Anatomic characteristics, such as the number of cuspids, remodeling degree, area of calcification and presence of aortic root dilation are also important, as well as the measurement of the regurgitation jet size.[23] Traditional echocardiographic parameters usually underestimate the severity of AoI; the regurgitant jet is present throughout the whole cardiac cycle since the left ventricle cannot compensate the flow during systole.[24] Therefore, even small regurgitant orifices can represent severe AoI.[23,24] Novel echocardiographic parameters have been used for grading AoI severity. Some of these include the systolic-to-diastolic velocity (S/D) ratio of the VAD outflow cannula, and the diastolic acceleration of the VAD outflow cannula, that are inversely and directly proportional to the AoI severity, respectively. A S/D ratio $<5 cm/s^2$ and a diastolic acceleration >49 cm/s^2 indicate moderate-to-severe regurgitation. However, these findings should be analyzed along with LV dilation, aortic valve remodeling and permanent closure, continuous regurgitant jet and aortic root dilation.[23] Such analysis requires an experienced professional and systematic reassessment. One of the strategies to prevent this complication is the flow velocity titration, guided by echocardiography, or maintenance of a pulsatile flow (native or generated by the device), allowing the intermittent opening of the aortic valve.[9] The benefit of this intervention, though, needs to be confirmed by clinical trial.[25]

The degree of AoI may not be reduced by clinical treatment and requires surgical intervention. Although there is still not a consensus on the best surgical approach, the Park stitch (a central coaptation stitch for leaflets) and the aortic valve replacement stand out. Both procedures can be performed either concomitantly or after the VAD implantation, in the presence of hemodynamically important AoI. Percutaneous aortic valve replacement for this indication has been noted in case reports, further studies are still needed.[9]

Right HF

Previous right ventricular (RV) dysfunction, associated with pulmonary hypertension and acute hemodynamic changes, facilitate the occurrence of right HF in the post-left VAD implantation in approximately 15-25% of patients.[26,27] Although its mechanism is still not clear, it is believed that changes in chamber geometry are caused by a sudden increase in LV outflow and RV preload. After the left VAD implantation, RV dysfunction is associated with impairments in body functions, longer hospital stays and higher mortality.[28]

The adequate screening for candidates for the VAD implantation by risk prediction is essential to identify those

patients with right HF that could benefit from a left VAD.[13] From the diagnostic point of view, electrocardiogram, echocardiogram, cardiac biomarkers, magnetic resonance, and right heart catheterization are complementary tests.[29] In the immediate post-operative period, patient monitoring using invasive parameters, such as the measurement of RV work, central venous pressure and serial echocardiograms is fundamental.[28]

Although most patients with RV dysfunction respond to inotropic therapy and optimization of VAD parameters, the early implementation of temporary RV circulatory support shows prognostic benefit.[30] New less invasive techniques for left VAD implantation seem to be associated with lower incidence of post-implantation RV dysfunction. However, late RV dysfunction may also occur, leading to a worse prognosis.[28] In these subacute and chronic contexts, increased pump velocity and flow can overload an already compromised right ventricle at any time after the transplantation. RV dysfunction may also occur secondary to ventricular arrythmias, pulmonary embolism, persistent pulmonary hypertension, and new or aggravated tricuspid regurgitation.[17,31]

Patients with right HF may develop hemodynamic deterioration, implantable cardioverter defibrillator, and even cardiac arrest with ventricular tachycardia or fibrillation caused by impaired filling and inadequate flow in the VAD. Echocardiography should be performed to exclude cardiac tamponade and to analyze ventricular filling and dimensions. Clinical treatment includes vasoactive therapy, diuretics and inotropic support, preferably with milrinone, and should be guided by invasive hemodynamic monitoring with pulmonary artery catheterization. In case of significant pulmonary hypertension, pulmonary vasodilator therapy should be considered, and percutaneous RV support may be less relevant.[17]

Pump thrombosis and cannula obstruction

Pump thrombosis has an incidence of 8% in the first year after VAD implantation and consists one of the main causes (up to 50%) of replacement of the device. According to the INTERMACS, pump thrombosis affects 5.5% of patients with HMII. In this regard, magnetic levitation devices, like the HMIII, provide a safer design, with an incidence of only 1% in a 24-month follow-up.[11]

Although the etiology of pump thrombosis has not been fully elucidated, it is known to be multifactorial and show variations depending on the device.[31] Associated factors include heat generated from the pump rotor, shear stress with platelet aggregation, thrombosis at cannulation site, impaction of the outflow cannula and migration or malposition of the inflow cannula. In addition, patient-related factors including a history of atrial or ventricular thrombus, atrial fibrillation, presence of left mechanical prosthetic valve, ventricular dysfunction degree and hypovolemia, and factors related to the management of the patient, like subtherapeutic anticoagulation, absence of antiplatelet therapy, low rotation, and control of infections.[31]

Patients with pump thrombosis usually present elevation in the pump speed and power, decreased flow, and different degrees of hemolysis and HF.[31] Fibrin deposition on the pump components causes flow delay, which requires compensation by an increase in the pump power to maintain the speed. The turbulent flow increases the shear stress, leading to hemolysis, which is manifested by hemoglobinuria, jaundice, increased serum LDH, free hemoglobin, total and indirect bilirubin, and decreased haptoglobin levels.[17] When this complication is suspected, the patient should be urgently transferred to a VAD-capable center. In patients with hemodynamic instability, intensive monitoring, anticoagulation and HF treatment should be immediately initated.[31]

Therapeutical strategies include anticoagulation and antiplatelet agents, thrombolysis and/or device replacement. The selection of the initial therapy is a complex decision, based on several factors, including patient clinical presentation. While pump replacement has been associated with an increase in perioperative mortality, clinical treatment is more likely to be unsuccessful, and to higher rates of recurrence or need for pump replacement or HT. Also, mortality is found to increase with every pump replacement.[31]

In case of improvement in clinical outcomes with unfractionated heparin and/or direct thrombin inhibitors, an increase in the antithrombotic regimen (AAS 200 mg or 325 mg/day and warfarin and target INR between 2.5 and 3.0), and eventually, dual antiplatelet therapy. If symptoms persist, aggressive antithrombotic therapy with direct thrombin inhibitors such as bivalirudin and argatroban should be considered, but data on their efficacy are still limited. Thrombolysis with recombinant tissue plasminogen activator (e.g. alteplase) should be considered only after cranial computed tomography to exclude eventual ischemic events and hemorrhagic transformation. It is important to mention that the evidence of the benefits of these therapies is still uncertain and based on case series, and the risk of severe hemorrhagic complications cannot be ruled out. For this reason, the therapies should be implemented with caution and be restricted to patients who are not candidates for surgical treatment.[31]

Surgical replacement of the pump for thrombosis is considered the definite (and gold-standard) treatment. Preoperative evaluation by computed tomography scan of the chest with contrast and echocardiography can be performed to detect possible anatomical causes of thrombosis. Suggestive findings of malpositioning of the inflow cannula and dynamic obstruction, kinking or compression of the outflow cannula are indications for the replacement of the VAD by median sternotomy due to limited access via the subcostal approach. The subcostal approach is the preferred route as it allows better access to the LV apex for manipulation of the pump and inflow connection. It can be performed with extracorporeal circulation (ECC) via peripheral cannulation or without ECC, depending on the ventricular reserve and hemodynamic stability of the patient. Good results have been reported with the subcostal approach in experienced

centers, with a 30-day mortality of 6.5% in patients with HMII.[31]

Emergency HT is a therapeutical option for patients without contraindications, considering that the estimated waiting time is not long, the management of the HF is feasible, and that hemolysis does not have important repercussions, such as the need for multiple transfusions or severe renal insufficiency. Favorable results of the management of outflow cannula stenosis with percutaneous stent implantation and intravascular ultrasound to distinguish between thrombosis from external compression have been reported.[9] Explantation of the VAD is usually the treatment of choice for patients with recovery of ventricular function.[31]

Bleeding

Although changes in the VAD design have caused a reduction in the incidence of bleeding, this is still one of the most common complications. The contemporary rate of bleeding is 1.4 events per patient-year within 90 days after the implantation, and 0.3 events per patient-year in the late follow-up period. According to INTERMACS, only 67% of patients are free from major bleeding in the first year of therapy. In addition, severe bleeding is the cause of 2% of deaths in patients with VADs.[10] In a two-year clinical follow-up, patients with HMIII showed lower rates of bleeding in comparison with patients with HMII, probably due to the pump design that promotes a lower interaction between VAD and blood.[11,32]

Perioperative bleeding is the most common immediate complication after VAD implantation, affecting up to 80% of patients. Besides the sternum, the most common site of bleeding is the outflow cannula anastomosis. Its preoperative prevention includes nutritional and hemodynamic optimization (especially for reversal of hepatic and renal dysfunction and related coagulopathies), suspension of anticoagulant and antiplatelet therapy. The risk of bleeding may be reduced by improvements of surgical techniques, appropriate reversal of heparin anticoagulation, and use of pro-hemostatic agents and factor concentrates as appropriate.[31]

In the postoperative period, gastrointestinal bleeding is the most prevalent, especially in elderly patients with a history of this condition.[9,10] Although its pathophysiology remains unclear, factors like low pulsatility, acquired von Willebrand disease secondary to shear stress, angiodysplasia (abnormal small blood vessels) in the gastrointestinal tract and anticoagulation therapy seem to be related.[9,33] The most common sources of bleeding are arteriovenous malformations in the stomach and duodenum, and inflammatory changes and ulcerous lesions in the digestive tract.[17] However, in many cases, the origin of bleeding cannot be identified. Endoscopic and colonoscopic evaluations are recommended to identify the bleeding source; it is worth pointing out, though, that the site of bleeding may be in the small bowel, which would reduce the diagnostic value of these procedures.[31]

The treatment of gastrointestinal bleeding includes volemic resuscitation, proton pump inhibitors and endoscopic approach. Either suspension or reversal of anticoagulation therapy yields modest benefits, with a recurrence rate of up to 9%, besides increasing the risk of severe thromboembolic events. Blood component transfusions may be required, but should be considered cautiously, as they add risk of immune hypersensitivity in candidates for HT.[9,31]

Epistaxis is the second most common hemorrhagic complication in patients with VAD. Its initial management consists of local vasoconstriction, cautery and tamponade. Percutaneous intervention including arterial embolization should be needed in severe cases, and evaluation by an otorhinolaryngologist is recommended.[31]

Infections

Infection is a common complication and an independent predictor of mortality in patients with VADs.[10] Risk factors include trauma in the driveline, obesity, duration of support, aging, diabetes, renal insufficiency, and malnutrition.[34] In 2011, a work group of the International Society for Heart and Lung Transplantation worked on the standardization of definitions of these infections and classified them as VAD-specific infections, VAD-related infections, and non-VAD-related infections.[35]

VAD-specific infections may occur in the pump, cannulas, pump pocket or driveline. An early identification and an aggressive treatment are essential in the infection control, which may require the removal of the device.[35] VAD-related infections refer to those that may also occur in patients who do not have VADs, but may have different characteristics or require specific care in patients with VADs, as in cases of infectious endocarditis and mediastinitis. Non-VAD infections are not affected by the presence of the VAD, such as pneumonia and urinary tract infection. In the INTERMACS registry, 42% of patients using VAD developed an infection at a median of 69 (interquartile range 12 to 272) days. Most were non-VAD infections (49%), followed by VAD-related (26%) and VAD-specific infections (25%).[36]

Gram-positive cocci, especially *Staphylococcus aureus* and coagulase-negative staphylococcus account for more than 50% of infections. Gram-negative bacilli may also be present, particularly *Pseudomonas aeruginosa*.[37] Fungal infections are less common but have a significantly worse prognosis; most infections are caused by *Candida spp*.[38] The identification of the causal agent is extremely important. Blood culture collection prior to antibiotic therapy and analysis of samples collected from exudates are essential in the assessment of patients with suspected or confirmed infection in any segment of the VAD.

Due to the smaller size and surface of contact, continuous-flow VADs are associated with lower rates of infection than pulsatile-flow VADs (e.g., 0.38 versus 0.62 driveline infections per patient-year with HMII and HeartMate XVE, respectively).[39] However, driveline infections remain a significant problem after the

device insertion, particularly in the first 30 days after implantation.[36] Its clinical manifestations include general malaise, fever may occur, and when so, are usually associated with higher impairment in functional capacity and abscess formation.[39-41]

Regarding laboratory data, VAD infections are marked by high white blood cell counts, and increased C-reactive protein levels.[42] In case of suspicion, echography and computed tomography of the abdomen and abdominal wall can detect from thickening of adjacent tissues to formation of organized collections.[42,43]

Controlling the source of the infection should be made whenever possible and includes drainage and debridement. Local debridement of the driveline exit site may be needed in the presence of fluctuant, hard, or necrotic tissue, and eventually, the driveline is relocated to another site, distant far from the infection. In patients with deep infection, surgical drainage and vacuum-assisted closure should be considered.[44,45] The benefits of negative-pressure wound therapy include removal of debris, edema reduction, improvement of blood, and granulation tissue formation.[42] Other local interventions with potential benefits are the use of antibiotic beads and omental or muscular transposition flaps.[46,47]

Infections of the surgical cavity refer to those in the pump pocket which, similar to the driveline infections, occur in the long term. First- and second-generation VADs required a large cavity between the abdominal wall or pericardium and the diaphragm and were more prone to therapeutic failure because of poor vascularization.[37] Modern devices are usually placed in the intrathoracic or preperitoneal space, and some of them do not require a surgical pocket.[44,45]

Bloodstream infections affect up to 30% of patients using VADs, especially in the first three months after the implant surgery.[48,49] These infections are normally related to the driveline, pump pocket or the pump, but other sources of infection (e.g. implantable cardioverter defibrillator and infectious endocarditis) should be investigated and controlled.[17] In most cases, a prolonged treatment with oral antibiotics is required.[45]

Mechanical failure

Mechanical dysfunction of the VAD occurs in up to 6% of patients in the first year.[10] Although the literature has focused on the pump failure, its incidence is on 13% only, and may be related to thrombosis, as previously discussed in this article. Other device components are potentially subject to malfunctioning, such as the controller (30%), driveline (14%) and battery (19%), with fatal and non-fatal repercussions.[50] Yet, the incidence of deaths due to device malfunctions has decreased from 3.9% to 1.4%,[10] and obesity was considered an independent predictor of mechanical dysfunction of the pump.[50] In 2021, after extensive use, the HVAD was removed from commercial distribution by the manufacturers because of events of delay or failure to restart after elective or accidental discontinuation of pump operation.[51]

The *short to shield* phenomenon occurs when stresses applied to the driveline with repeated stretching, bending, or twisting beyond the limits of robustness of the driveline causes fracture of the internal ground shielding, which can damage power data transmission, leading to pump stoppage.[50] Driveline failure frequently requires external repair or pump replacement in cases when the portion of the driveline that fails is close to the skin exit site or at its junction with the VAD. In the HMIII, the external segment of the driveline that connects the controller was improved with the addition of another connector that allows the non-surgical driveline replacement in case of damages. Also, failure of other external components may occur when the patient inappropriately connects the drivelines, damaging the connecters. Failure of the VAD controller may be caused by software issues, exposure to water or fluids, and damage from dropping, which reinforces the importance of always keeping a spare controller available. The inadequate use of the device and traumas can damage the battery damage, which reduces its expected life and affects its full recharge.[50]

Periodic VAD interrogation is essential for identification of failures. Registries of critical alarms and flow changes, pulsatility index and peak circulatory power should be recorded. A member of the VAD team should send log files for analysis by clinical engineers whenever appropriate.[17] VAD auscultation is not a reliable method to detect malfunctioning due to its low specificity.[31] In addition to the signs and symptoms of HF, physical examination of the patients should provide hints about the VAD malfunctioning. In most patients using VADs, peripheral pulse cannot be palpated due to reduced pulse pressure. Thus, mechanical dysfunction should be considered in patients with a palpable radial pulse. Examination of the sclera for icterus and the conjunctiva for small hemorrhages can also add information on hemolysis.[31]

Standardized preclinical tests and medical device engineering have been developed to prevent these failures. Patients, caregivers and health care professionals should receive systematic instructions about how to care for the VADs. However, there are challenges in real life that cannot be predicted by laboratory tests, and devices may be less robust in the long term for reasons not necessarily related to lack of care.[50]

Final considerations

In a relatively short time, VADs have become a well-established treatment for advanced HF, with an increasing number of adults being supported with VADs as destiny therapy, bridge to transplant, bridge to transplant eligibility and, less frequently, as bridge to recovery. Although the risks of adverse events are still significant, improvements in survival rates and reduction in morbidity tend to progress with advances in technology and patient selection and follow-up. Besides, there is a growing number of studies evaluating strategies for prevention, diagnosis and management of complications, despite the observational design in most of them. The continuous review of adverse events of VADs and the identification of unique aspects of their diagnosis and management become paramount as novel devices are developed and implemented in the clinical practice.

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Is There Room for Sacubitril-Valsartan in the Treatment of Advanced Heart Failure?

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PARADIGM-HF, published in 2014, was a landmark in the modern pharmacological treatment of heart failure (HF).[1] After several years and numerous clinical trials with disappointing results,[2-5] a new class of drugs was able to produce concrete results in clinically relevant outcomes. In this pivotal study,[1] sacubitril-valsartan, a molecule consisting of a neprilysin inhibitor and an angiotensin-receptor blocker (ARB), drastically reduced hospitalizations for HF, cardiovascular mortality, and overall mortality. The study included more than 8,000 outpatients, mostly New York Heart Association (NYHA) class II or III. Because of its differential mechanism, aimed at amplifying the natriuretic response and the effect of other vasoactive molecules, sacubitril-valsartan could induce pronounced vasodilation, natriuresis and inhibition of cystic fibrosis. These clinical benefits could potentially be extended to the whole spectrum of HF, including more advanced stages of the disease.

Although national and international guidelines have recommended the use of sacubitril-valsartan for HF patients with reduced ejection fraction (HFrEF) and NYHA class ≥II, it is worth mentioning that <1% of patients had NYHA class IV symptoms at randomization in PRADIGM-HF. In addition, only patients who had received and tolerated a single-blind treatment with a stable dose of ARB or angiotensin-converting-enzyme (ACE) inhibitor (run-in periods) and had a systolic blood pressure > 100 mmHg at screening were enrolled. Nearly 20% of patients screened for the trial did not complete the two run-in periods for presenting, among others, low blood pressure and low glomerular filtration rate, both characteristics of advanced HF. Similarly, the PIONEER-HF trial, that tested sacubitril-valsartan in patients with acute congestive HF, also included few patients with NYHA class IV.[6]

Due to the lack of evidence on the clinical benefits of sacubitril-valsartan in patients with chronic HFrEF and severe symptoms, the LIFE trial[7] was proposed, to test the hypothesis that this therapeutic approach would improve the levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) as compared with valsartan alone in patients with advanced HFrEF and NYHA functional class IV.[7] The LIFE study was a randomized, double-blind clinical trial with 335 patients with advanced HF, initiated in March 2017 and interrupted due to the COVID-19 pandemic. Patients were randomized to receive sacubitril-valsartan (target dose 200 mg twice daily) or valsartan (target dose 160 mg twice daily), in addition to the standard therapy for HF. The primary endpoint was the proportional change from baseline in the area under the curve (AUC) for NT-proBNP levels measured over 24 weeks of therapy. From patients included in the analysis, 245 were men (73%); men age was 59.4 (±13.5) years; 72 (18%) could not tolerate sacubitril-valsartan 100 mg/day during the run-in period, and 49 (29%) discontinued the drug during the study period. Median NT-proBNP AUC was 1.19 (IQR, 0.91-1.64) in the valsartan treatment arm (n = 168), whereas the AUC for the sacubitril/valsartan treatment arm (n = 167) was 1.08 (IQR, 0.75-1.60). The estimated proportional change in the NT-proBNP AUC was 0.95 (95% CI 0.84-1.08; p = 0.45). Compared with valsartan, treatment with sacubitril-valsartan did not improve the clinical outcome of number of days alive out of hospital and free from HF events (103.2 vs. 111.2 days; p = 0.45). The authors concluded that, in patients with HFrEF, there was no statistically significant difference between sacubitril-valsartan and valsartan with respect to reducing NT-proBNP levels.

Although the LIFE trial has produced neutral results, some important characteristics of this study should be considered. The primary endpoint was changes in NT-proBNP levels, an important biomarker in the context of HF. However, the sample did not have sufficient statistical power to either confirm or refute benefits in hard clinical endpoints. Besides, the protocol had a clinical follow-up was of 24 weeks, which is a short period to detect a significant number of major cardiovascular events. Also, the study was interrupted due to the pandemic of COVID-19, and the *a priori* defined sample was not achieved. Finally, except for the CONSENSUS clinical trial, published in 1987, that evaluated patients without any previous treatment for HF, all other studies that proposed to evaluate patients with advanced HF (Table 1) had markedly larger samples and follow-up periods. For example, the sample size in the CIBIS-II trial,[9] which tested bisoprolol in advanced HF patients in NYHA III-IV, was 10 times greater than that in the LIFE study, allowing a more precise evaluation of the clinical benefits of the intervention.

Pharmacological treatment of advanced HF is challenging. The tolerability for drugs is usually limited by borderline blood pressure levels and renal function. Yet, we must keep on trying to implement therapeutical strategies that can potentially

Keywords

Heart Failure; Treatment; Sacubitril-Valsartan

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improve the natural history of this syndrome. The results of the LIFE trial may have been disappointing, but they do not completely refute the possible clinical benefits of sacubitril-valsartan in more advanced stages of HF. Besides, the definition of the stages of this condition is always a dynamic process. A patient initially classified as advanced HF, for example, can gradually improve with the implementation of therapeutical strategies and become eligible for the four pillars of HF contemporary pharmacological therapy. Thus, the establishment of pharmacological treatments in advanced HF is a continuous process in clinical practice, and the cardiologist should try as many alternatives as possible for the improvement of quality and quantity of life before opting for more advanced and definitive strategies like cardiac transplant or ventricular assist device.

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Table 1 – Comparison of the main pharmacological studies on patients with advanced heart failure

	DRUGS	N	INCLUSION CRITERIA	NYHA	MAIN RESULTS
ACE inhibitors					
CONSENSUS (1987)[10]	Enalapril vs placebo	253	NYHA IV; congestive HF, cardiomegaly at chest X-ray; without ACE inhibitors	IV (100%)	Enalapril reduced overall mortality by 40% within 6 months (26% vs 44%, p = 0.002) and by 31% in one year (52% vs 36%, p = 0.001)
Beta-blockers					
CIBIS-II (1999)[9]	Bisoprolol vs placebo	2647	18-80 years; NYHA III–IV; LVEF ≤ 35%; chronic HF; treatment with ACE inhibitors and diuretics	III–IV (100%)	Bisoprolol reduced overall mortality by 34% (12% vs 17%, p < 0.001) in NYHA III and IV patients
COPERNICUS (2001)[11]	Carvedilol vs placebo	2289	NYHA III–IV for > 2 months; LVEF < 25%; clinically euvolemic	III–IV (100%)	Carvedilol reduced overall mortality by 35% (11% vs 17%, p < 0.001); in patients < 70 or > 70 years old and LVEF < 20 or > 20%
Mineralocorticoid receptor antagonists					
RALES (1999)[12]	Spironolactone vs placebo	1663	NYHA III–IV; FEVE ≤ 35% in the last 6 months; treatment with ACE inhibitors and diuretics	III–IV (100%)	Spironolactone reduced overall mortality by 30% (35% vs 46%, p < 0.001); in patients < 67 or > 67 years old and LVEF < 26 or > 26%, NYHA III or IV
Neprilysin inhibitors and angiotensin II receptor blockers					
LIFE (2021)[8]	Sacubitril-valsartan vs Valsartan	335	NYHA IV in the last 3 months; standard treatment for HF; (LVEF) ≤35%; BNP ≥250 pg/mL or NT-proBNP ≥800 pg/mL	IV (100%)	The estimated proportional change in the NT-proBNP AUC was 0.95 (95% CI 0.84-1.08; p = 0.45). Days alive out of hospital and free from HF events: 103.2 vs. 111.2 days (p = 0.45).
Hydralazine and isosorbide dinitrate					
A-HEFT (2004)[13]	Hydralazine + isosorbide dinitrate vs placebo	1050	≥ 18 years old; NYHA III–IV for 3 months; self-reported African American; standard treatment for 3 months.	III–IV (100%)	Hydralazine + isosorbide dinitrate reduced overall mortality by 43% (6% vs 10%, p = 0.02) and hospitalizations for HF by 33% (16% vs 24%, p = 0.001) and improved quality of life scores (p = 0.02)

ACE: angiotensin converting enzyme; LVEF: left ventricular ejection fraction; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal pro-B-type natriuretic peptide (BNP); NYHA: New York Heart Association.

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Is There Room for New Drugs in the Treatment of Advanced Heart Failure: SGLT2i?

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Over the last years, we have witnessed the inclusion of the use of sodium-glucose cotransporter 2 inhibitors (SGLT2i) for the treatment of patients with heart failure. Drugs in this group share the fact that they are able to inhibit glucose transport in the proximal tubule and thus promote glycosuria and blood glucose reduction in patients with diabetes. Other effects of these medications include increasing diuresis and natriuresis, lowering blood pressure, stimulating erythropoiesis, improving cardiac energy metabolism, reducing inflammation, inhibiting the sympathetic nervous system, preventing cardiac remodeling, preventing ischemia-reperfusion injury, inhibiting the Na+/H+ exchanger, reducing hyperuricemia, increasing autophagy and lysosomal degradation, decreasing epicardial fat, increasing erythropoietin levels, increasing circulating vascular progenitor cells, decreasing oxidative stress, and improving vascular function.[1]

SGLT2i were initially tested for glycemic control in patients with diabetes mellitus,[2-4] and it was quickly noted that, in addition to their antidiabetic effect, these drugs were able to significantly reduce cardiovascular events, especially episodes of decompensated heart failure. Based on these results, the natural sequence was to evaluate SGLT2i in patients with heart failure. The initial results obtained were among patients with heart failure with reduced ejection fraction, with the DAPA-HF (evaluating dapagliflozin) and EMPEROR-Reduced (evaluating empagliflozin) studies, which showed that inhibition of sodium-glucose cotransporter 2 (SGLT2) reduced the combined risk of cardiovascular death or hospitalization due to heart failure in patients with heart failure with reduced ejection fraction, with or without diabetes.[5] More recently, we have seen positive results in the context of heart failure with preserved ejection fraction, although the effects of medication have mainly focused on the group of patients with slightly reduced ejection fraction.[6]

Taken together, these results indicate that SGLT2i are safe and beneficial for a wide range of patients with heart failure. Nevertheless, it is noteworthy that certain patients are underrepresented in these clinical trials, such as patients with advanced heart failure. This group is known to be more severe, with higher presence of comorbidities and lower tolerance to medications, especially in the context of polypharmacy. Even though there have not been any clinical trials testing the use of SGLT2i in this specific population, some interesting data allow us to delve deeper into this topic.[7]

In relation to the presence of comorbidities, perhaps no other condition has the same prevalence and relevance in the context of heart failure as renal dysfunction, a recognized marker of worse prognosis in patients with advanced heart failure. In this regard, a meta-analysis of 7 clinical trials involving 14,113 patients with heart failure identified that the use of SGLT2i was associated with a lower risk of progression of renal dysfunction (risk ratio 0.673; 95% confidence interval 0.549 to 0.825; $p < 0.001$; $I^2 = 17.7\%$), notwithstanding a higher risk of volume depletion (risk ratio 1.177; 95% confidence interval 1.040 to 1.333; $p = 0.010$; $I^2 = 0.0\%$). This finding has significant prognostic and therapeutic implications.[8]

From a clinical and hemodynamic point of view, data from a single-center cohort of 17 patients with advanced heart failure who had received a CardioMEMS system, which allows continuous monitoring of pulmonary artery pressure, showed that pulmonary pressures fell after initiation of SGLT2i, without any change in the dosage of diuretics (Figure 1).[9] While it is recognized that this is an initial experience, these results indicate relevant clinical and hemodynamic effects in this patient population.

From a clinical and prognostic point of view, it is known that the occurrence of arrhythmias is a frequent event in patients with advanced heart failure and a relevant cause of death. Accordingly, a *post hoc* analysis of the DAPA-HF study[10] aimed to identify the effect of dapaglifozin specifically on the occurrence of ventricular arrhythmias and sudden death in patients with heart failure with reduced ejection fraction. The study found that, among the participants who received dapagliflozin, the composite outcome (ventricular arrhythmia, resuscitated cardiac arrest, or sudden death) occurred in 140/2373 patients (5.9%), compared to 175/2371 patients (7.4%) in the placebo group (hazard ratio 0.79; 95% confidence interval 0.63 to 0.99, $p = 0.037$), and this effect was consistent for each component of the composite outcome taken alone.

The recently published EMPULSE trial[11] aimed to evaluate the effect of empagliflozin, initiated during hospital stay in patients admitted for decompensated heart failure, regardless of ejection fraction. The study included 530 patients who were followed for up to 90 days after discharge, and empaglifozin was found to be well tolerated. It also showed what the authors termed the greatest clinical benefit, defined as a hierarchical composite of death from any cause, number of heart failure events, and time to first heart failure event, or a difference of 5 points or more in change from baseline Kansas City Cardiomyopathy Questionnaire, with total symptom score at 90 days (Figure 2).

Keywords

Heart Failure; Prognosis; Blood Vessels

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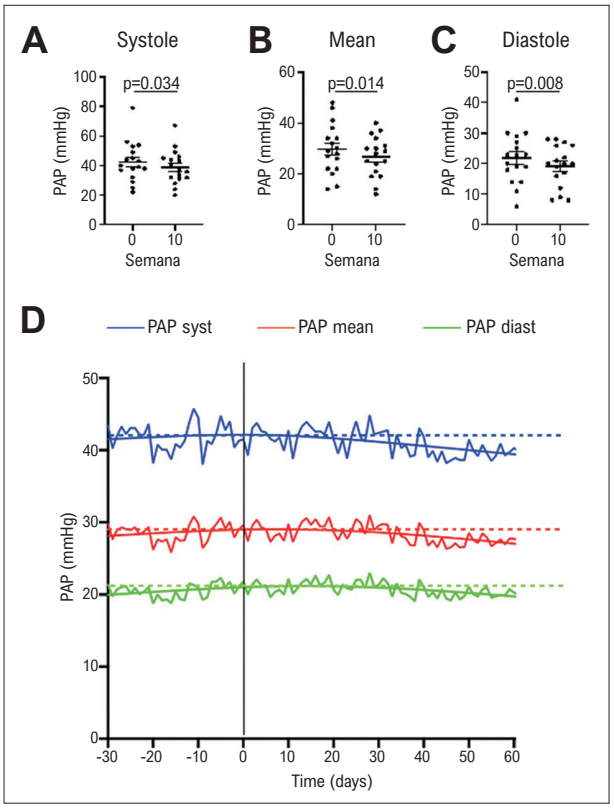

Figure 1 – *Systolic (A), mean (B), and diastolic (C) pulmonary artery pressures at baseline and 10 weeks after initiation of SGLT2i. (D) Pulmonary artery pressure evolution from 30 days prior to initiation of SGLT2i until 70 days after initiation of SGLT2i.[9] PAP: pulmonary artery pressure.*

Taken together, the current data indicate that SGLT2i are safe medications for use in patients with advanced heart failure, with a potential impact on prognosis. Will clinical trials in this specific population, however, be able not only to evaluate their effectiveness, but also to identify subgroups with greater risks or benefits?

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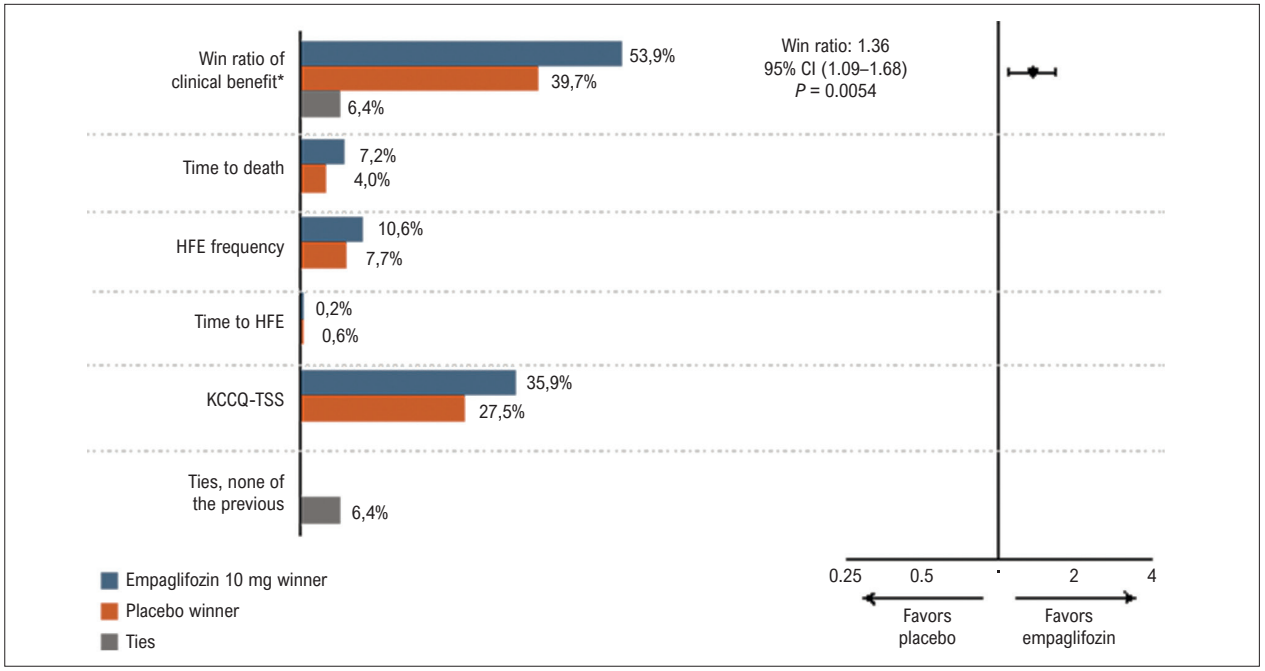

Figure 2 – *Stratified win ratio calculated using a non-parametric generalized pairwise comparison within heart failure status strata.[11] CI: confidence interval; HFE: heart failure event; KCCQ-TSS: Kansas City Cardiomyopathy Questionnaire, total symptom score.*

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Dobutamine vs Milrinone in Heart Failure with Preserved Ejection Fraction: How do We Choose?

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Heart failure (HF) occurs when the heart cannot pump sufficient blood to meet tissue needs and/or does so at the expense of high filling pressures, clinically manifesting itself through signs and symptoms of congestion and/or low cardiac output.

Decompensation is frequently observed in the condition's natural history. Approximately 20% of HF exacerbations occur in low cardiac output syndrome, with cardiogenic shock being the most severe presentation. When there is evidence of poor organ perfusion, inotropes are fundamental pharmacological support, with dobutamine and milrinone being the most commonly used drugs.

Dobutamine is a synthetic catecholamine that acts as a β1 and β2 receptor agonist, while milrinone is a phosphodiesterase 3 inhibitor that acts as an inotropic and vasodilator.[1] Although there are important pharmacokinetic and pharmacodynamic differences between these medications, there is little evidence in the literature about which is best in HF with reduced ejection fraction (HFrEF).

The hemodynamic effect of milrinone was compared to that of dobutamine in 14 patients with severe HF and low cardiac output (defined as pulmonary capillary pressure > 15 mmHg and cardiac index < 2.5 l/min/m^2). The drugs produced a similar increase in cardiac index and right ventricular (RV) ejection, with a reduction in RV end-systolic volume. However, the improved RV performance in the milrinone group can be partially explained by reduced pulmonary artery pressure (RV afterload reduction), which did not appear to be an important mechanism in the dobutamine contractility response.[2] Thus, it would seem that milrinone is a better choice in patients with significant RV afterload (pulmonary hypertension).

In the OPTIME-CHF study, 949 patients admitted for decompensated HF were randomized to placebo or milrinone for 48 to 72 hours. Among patients with ischemic etiology, milrinone increased the rate of death or prolonged hospitalization and/or re-hospitalization for HF within 60 days compared to placebo. The opposite was observed in patients with non-ischemic HF.[3] However, these results are subject to criticism since there was no standardized definition of ischemic vs non-ischemic HF, inotropes were prescribed without pre-established criteria, the ischemic HF group had worse results than the non-ischemic group (denoting greater severity and worse prognosis in this etiology), no comparison was made with another inotropic agent in the ischemic group (eg, dobutamine), and the results were derived from post hoc analysis. Although this study showed that inotropes may be associated with increased mortality, especially in ischemic etiology, this effect cannot be attributed exclusively to milrinone.

A 2001 retrospective analysis of 329 patients with advanced HF seen at the Cleveland Clinic (Cleveland, OH, USA), 82% of whom received dobutamine and 18% of whom received milrinone, found no significant in-hospital mortality differences between the groups, although nitroprusside was needed less often for clinical compensation in the milrinone group (40% vs 18%, p < 0.01). On the other hand, cost analysis showed that dobutamine was less expensive per patient than milrinone: USD 45 (standard deviation [SD], USD 10) vs USD 1855 (SD, USD 350)(p < 0.0001).[4] These results plus the cost-effectiveness analysis favor the choice of dobutamine, since there was no disadvantage in terms of mortality.

While waiting for a transplant, inotropes are often needed for long periods. In such a setting, there are conflicting results between dobutamine and milrinone. One study found no difference in hemodynamic changes, death, the need for additional vasodilators/inotropes, or the need for mechanical circulatory assistance before transplantation.[5] However, another study found that patients who received milrinone less frequently needed mechanical ventricular assistance or an intra-aortic balloon as a bridge to transplantation, although they found no difference in mortality between the groups.[6] In other studies, milrinone was associated with a higher survival rate among patients on the waiting list for heart transplantation.[7] This wait is often long and covers a group of patients with advanced HF in Interagency Registry for Mechanically Assisted Circulatory Support profiles 2 and 3. A number of factors must be considered in this patient profile. First, since dobutamine is associated with an increased chance of tachyphylaxis and eosinophilic myocarditis, milrinone should be preferred. Second, the hemodynamic profile is variable, comprising patients with: a) pulmonary hypertension and RV dysfunction, for whom milrinone can be a compensation strategy until transplantation, since reducing pulmonary hypertension

Keywords

Insuficiência Cardíaca; Dobutamina; Milrinona

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minimizes the chance of postoperative RV dysfunction; b) arterial hypotension and vasopressor use, for whom dobutamine is the drug of choice due to its lower potential for vasodilation and arterial hypotension. Third, since the waiting time can last for months, for prolonged hospitalizations, in which drug costs can be a relevant factor, dobutamine would seem best. Finally, in patients with advanced HF, there is a progressive downregulation of beta-adrenergic receptors that can compromise the response to beta-adrenergic drugs,[8] making inotropes that act through other pathways interesting alternatives.

For initial cardiogenic shock treatment, neither dobutamine nor milrinone was found superior. However, there were significant differences in side effects, including a higher incidence of hypotension with milrinone and arrhythmias with dobutamine.[9] Thus, rather than efficacy, tolerance to adverse effects may be the deciding factor in selecting an inotropic agent.

In 2019, a meta-analysis was conducted of 11 studies published between 2001 and 2016 (23,056 patients) that compared dobutamine and milrinone. No significant differences were found between the groups regarding all-cause mortality, length of hospital stay, or significant arrhythmias in patients with decompensated HF and low output and/or cardiogenic shock. A major limitation in the interpretation of these results is that most of the included studies were observational cohorts, with only one randomized trial (36 patients).[10]

A recent double-blind randomized study, called DOREMI, compared dobutamine and milrinone in 192 patients with cardiogenic shock. The primary composite outcome of in-hospital all-cause mortality, resuscitated cardiac arrest, heart transplantation, ventricular assist devices, nonfatal acute myocardial infarction, stroke, or transient ischemic attack, and the need for renal replacement therapy did not differ significantly between the groups.[11]

Thus, most of the available scientific evidence does not support the use of one drug over another. Hence, the choice of inotropic agent must be based on the patient's clinical characteristics in conjunction with the peculiarities of each drug's action and the side effects that the patient can tolerate. A summary of the differences is provided in Table 1.

Although an association of the inotropes has been little studied, it is practiced in some clinical scenarios. Patients with low cardiac output who cannot regain organic perfusion with a single inotrope and who have not yet received mechanical circulatory assistance may benefit from an association of milrinone and dobutamine. Since these drugs act through different pathways and receptors, together they may have greater power to increase cardiac output and reduce filling pressures, as has been previously indicated.[12] This association is also frequently used following heart transplantation until complete recovery of myocardial contractility is achieved, especially in recipients with primary graft dysfunction.

Most evidence in the literature is from mechanistic studies describing hemodynamic parameters[2,13] or retrospective cohorts. Randomized controlled trials comparing these two inotropes in different settings are scarce. In general, for patients with low output there seems to be little difference between inotropic drugs. Thus, the best inotrope may be determined through consideration of the patient's hemodynamic parameters.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Bonatto MG.

Table 1 – Comparison between dobutamine and milrinone

Characteristics	Dobutamine	Milrinone
Mechanism of action	β1 and β2 receptor agonist	Phosphodiesterase 3 inhibitor
Dose	2.5-20 µg/kg/min	0.375-0.75 µg/kg/min
Inotropic effect (increased cardiac output)	Equal	Equal
Vasodilation (SVR reduction)	Lower	Higher
Reduction of pulmonary artery pressure (PVR reduction)	Lower	Higher
0_2 consumption	Higher	Lower
Tachycardia/arrhythmia	Higher	Lower
Hypotension	Lower	Higher
Influenced by beta-blockers or downregulation of beta receptors	Yes	No
Tachyphylaxis	Yes	No
Cost	Lower	Higher

SVR: systemic vascular resistance; PVR: pulmonary vascular resistance.

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Shock Teams: A Call to Action for the Brazilian Cardiology Community

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Introduction

Despite advances in diagnosis and treatment over the last 30 years, especially in myocardial reperfusion therapies, mortality from cardiogenic shock remains high worldwide, with 50% of cases resulting in adverse outcomes.[1,2] In particular, there has been an increase in the incidence of non-ischemic cardiogenic shock (ie, associated with acute and/or advanced chronic heart failure), which has led to a shift with less patients hospitalized due to acute ischemic syndromes in critical cardiology units..[3,4]

In the last decade, due to persistently high mortality and the complexity of presentation and treatment involved in cardiogenic shock, especially of non-ischemic etiology, some institutions, particularly in the United States, developed process of care to improve outcomes for these patients, resulting in "shock teams", which were based on other successful initiatives to manage critical situations through multidisciplinary teams acting according to systematized protocols, such as rapid response teams, trauma teams, and stroke teams.[5,6]

In Brazil, however, data on cardiogenic shock are scarce and there are no reports of initiatives involving shock teams.[2] The shock team concept which uses a standardized treatment algorithm including team activation criteria and mechanical circulatory support (MCS) based on hemodynamic variables, was studied by Tehrani et al in Virginia, USA.[7] In this study, implementation of this system led to a significant increase in the 30-day survival of cardiogenic shock patients compared to the previous year. The main elements for successful shock teams are early recognition and rapid and coordinated movement by a team that includes interventional cardiologists, advanced heart failure specialists, cardiac surgeons and intensivists.[7,8] The team should focus on quickly classifying the stage of cardiogenic shock and taking appropriate measures to minimize onset of the multiorgan damage spiral over the next few hours. This team requires a recognized leader (referred to in a recent editorial as the "shock doc") who coordinates the team's activities, outlines the treatment goals, and determines the the checkpoints at which the results should be assessed.[9] The shock doc, the first person to be activated when there is a trigger, is responsible for coordinating the other team members and ensuring that treatment is implemented according to protocol, such as scheduling MCS and additional etiologic and prognostic assessments, allocating intensive care beds, and coordinating systematic reassessment of treatment (Central illustration).[9]

In our viewpoint, the first step toward structuring a shock team is the institutional perception of the topic's relevance and prioritize cardiogenic shock care institutionally. Institutional leadership must endorse the allocation of staff, time, and resources necessary to implement this initiative. This represents a *sine qua non* condition for subsequent development of a treatment algorithm that defines the role of each of each agent in the process of care. In order to achieve better outcomes, it is critical that team members are willing to work in a patient-centered strategy.[10]

In the shock team's algorithm, certain basic assumptions should be clear and prioritized: rapid identification and stratification of shock, mandatory hemodynamic monitoring, minimized use of vasopressors, and early use of MCS.[7] Easy-to-understand outcome definitions should be determined. Simple and uniform language for cardiogenic shock staging can help determine goals and standardize scientific communication. Recently, the Society for Cardiovascular Angiography and Interventions suggested a 5-stage classification system for cardiogenic shock (A-E) that has been increasingly used and has high prognostic impact.[11]

Hemodynamic monitoring in cardiogenic shock

In contemporary cardiogenic shock treatment, it is essential to recognize the role of invasive hemodynamic monitoring, which provides data to support bedside decision-making. In fact, routine early invasive hemodynamic monitoring in cardiogenic shock with a pulmonary artery catheter can help the team identify early cardiogenic shock, classify myocardial dysfunction as uni- or biventricular, adjust therapy according to the predominant hemodynamic profile, objectively assess the hemodynamic response to treatment, and escalate or de-escalate MCS levels.[12] The increasing use of this tool in cardiogenic shock seems associated with the increasing use of MCS, although its relevance as a prognostic tool has also been reinforced by measuring variables indicative of left and/or right ventricular dysfunction.[13,14]

Mechanical circulatory support in cardiogenic shock

The early use of MCS devices, such as intra-aortic balloon pump, extracorporeal membrane oxygenation (ECMO), and Impella devices, has been associated with better outcomes in cardiogenic shock.[7] However, best results depend on quick proactive decision-making, in which the shock team plays a fundamental role. Institutions must go beyond the basic training necessary to use MCS and develop expertise with

Keywords

Cardiogenic Shock; Myocardial Reperfusion; Heart Failure

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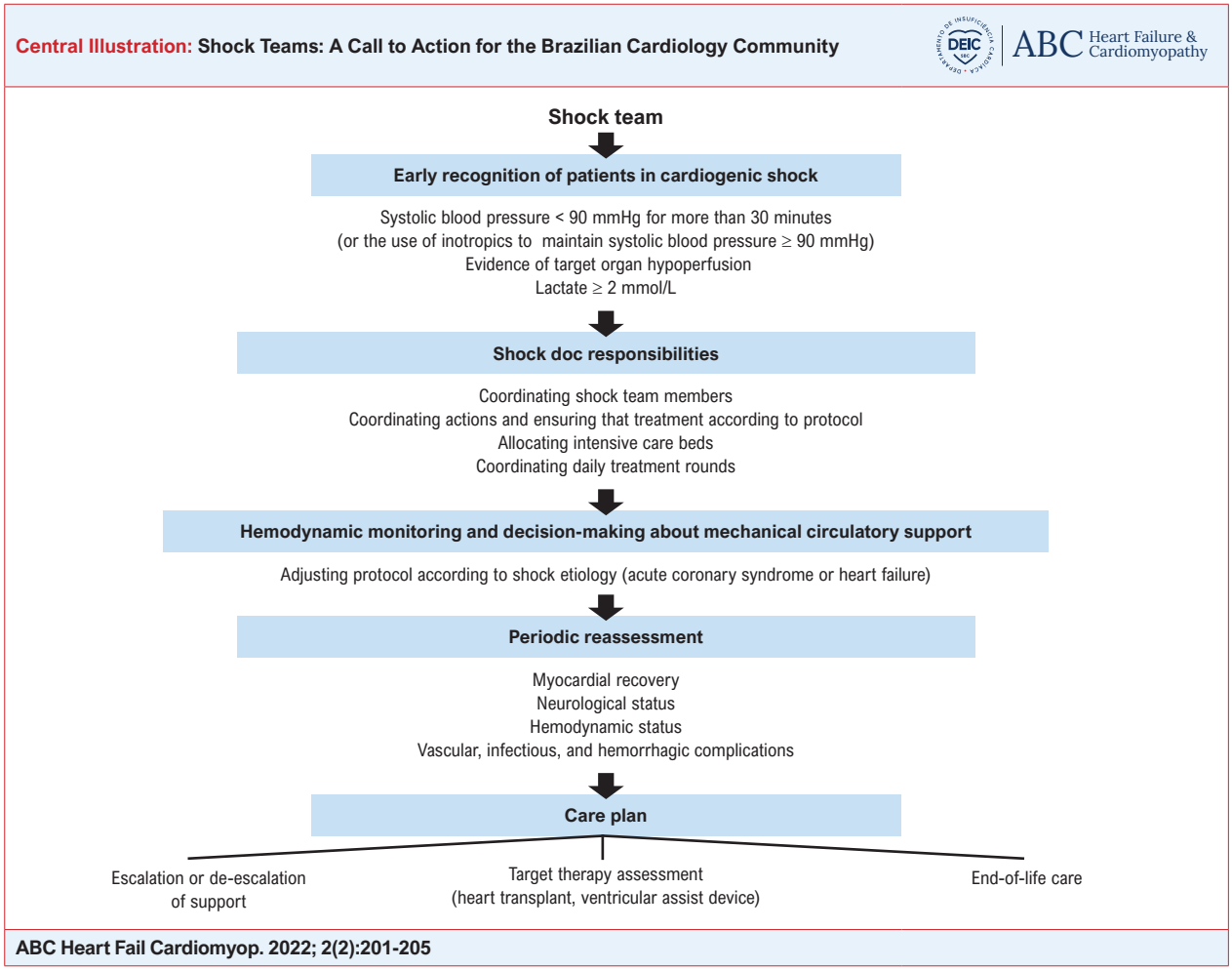

Central illustration – *A shock team based strategy to manage cardiogenic shock.*

these technologies. In Brazil, not many centers have different circulatory devices on the shelf, with the only one available in the Brazilian Unified Health System being the intra-aortic balloon pump. However, centers in different parts of the world have led initiatives to reduce cardiogenic shock mortality through veno-arterial ECMO (VA-ECMO) and Impella devices, especially the latter in cases of shock associated with acute myocardial infarction.[15]

In Brazil, few reports have been published on experiences with VA-ECMO and Impella in the context of cardiogenic shock, which might reflect the difficulties that both public and private institutions have in obtaining this technology. The most recent data on cardiogenic shock in our country came from a multicenter prospective cohort funded by a philanthropic project that provided training and implementation of MCS in the public sector. This study evaluated 49 patients treated with MCS, either ECMO (71%) or Impella (29 %), between 2018 and 2020.[2] The main causes of cardiogenic shock were acute myocardial infarction (45%) and decompensated heart failure (20%), with an overall mortality of 61%. Despite the high rate of deaths and complications, there was a progressive improvement in outcomes over the two years of study (83% vs 40% mortality, $p = 0.002$), which suggests that improvement in MCS results involves a learning curve.[2]

Experience with cardiogenic shock teams

Key studies have been published recently by centers that implemented shock teams (Table 1). Although none of these were clinical trials, the data demonstrated that working in a team led to better outcomes in patients with cardiogenic shock, regardless of ischemic or non-ischemic etiology.[7,16-19]

Challenges to implementing a cardiogenic shock team

Among the numerous challenges to implement a cardiogenic shock team, the first one is to make it clear that systematized shock management remains an unmet need. After this, creating a team requires recruiting personnel with expertise in critical cardiac patients who are full-time available, either virtually or in person. It is equally important to ensure periodic training and protocol review, especially at institutions that have a low volume of patients with cardiogenic shock. Naturally, these training sessions should include other relevant personnel, eg, intensive care unit nurses and nurse

technicians, perfusionists, and respiratory therapists. In Brazil, teams working in cardiac intensive care units must be restructured according to the growing new profile of critical cardiac patients, uniting these professionals to jointly define action strategies and recognize the shock doc as the central figure in this process.[10] Finally, it would be desirable to plan shock care as a hub-and-spoke model in the health system network, with a resourse-hierarchy among institutions. Those with the infrastructure and trained personnel to implement MCS or other advanced therapies would be designated as hubs, receiving cases that were initially evaluated and treated at spokes, ie, institutions with fewer resources.[15] Such a strategy could save both material and human resources, leading to better outcomes.

Conclusions and outlook for Brazil

Improving cardiogenic shock outcomes is a common goal in many regions of the world. However, to move forward with such projects in Brazil, it is critical to have a broader and deeper knowledge of national cardiogenic shock data. As an initial step, it would be strategic for each large public or private institution to register its cases of cardiogenic shock, ideally discriminating between ischemic (post-infarction) and non-ischemic origin. Next, ongoing processes of cardiogenic shock treatment must be identified, including points for improvement, establishing an institutional protocol that can be implemented and monitored with universally accepted metrics. Successful creation of a cardiogenic shock team requires institutional support and recognition of the players involved. It can only happen after thorough planning based on data that accurately reflect the local conditions of each institution. As part of this design, there is a pressing need to expand access to advanced MCS technologies in order to align national policy with international best practice and achieve improvement in cardiogenic shock outcomes. Finally, a joint initiative involving the Brazilian Society of Cardiology's Department of Heart Failure to create a national cardiogenic shock registry would be most opportune, providing data to improve the entire care process for this serious and challenging clinical condition.

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Table 1 – Experience with cardiogenic shock teams in the literature

Authors, year, institution	N	Shock etiology	Mechanical circulatory support	Study design	Outcome
Basir et al., 2019[18] Multicentric	171	Only patients with AMI who underwent percutaneous revascularization	100%	Prospective	72% survival to hospital discharge in patients treated by shock protocol
Tehrani et al., 2019[7] INOVA Heart and Vascular Institute	204	40% secondary to AMI and 60% to other causes	64%	Observational, prospective	Mortality reduction after implementing structured protocol and shock team. 30-day survival: 43% vs. 57.9% pre- vs. post-implementation. 1-year survival: 76.6%.
Taleb et al., 2019[19] University of Utah	244	65% secondary to AMI and 35% to other causes	100%	Retrospective, prospective	30-day mortality reduction in patients treated by shock team (HR 0.61; 95% CI 0.41–0.93; p=0.02)
Lee et al., 2020[16] University of Ottawa Heart Institute	100	13% secondary to AMI and 87% to other causes	39%	Retrospective	Mortality reduction among patients treated by shock protocol in median follow-up of 240 days (HR 0.50; 95% CI, 0.28-0.99; p = 0.03)
Papolos et al., 2021[17] Multicentric[2]	1.242	27% secondary to AMI and 73% to other causes	40%	Retrospective	Mortality reduction among patients admitted to centers with shock team (OR 0.72 95%; CI 0.55-0.94; p = 0.016)

AMI: acute myocardial infarction; CI: confidence interval; HR: hazard ratio; OR: odds ratio. [1] American hospitals participating in the National Cardiogenic Shock Initiative*. [2] American hospitals participating in the Critical Care Cardiology Trials Network.*

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Use of Intra-Aortic Balloon Pump in Cardiogenic Shock Associated with Advanced Heart Failure: An Outdated Strategy?

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The use of an intra-aortic balloon pump (IABP) was first described in the 1960s.[1,2] It is a short-term circulatory assist device that uses helium gas for inflation of a balloon positioned in the descending aorta during diastole and active deflation during systole.[1] The most evident hemodynamic effects are increased coronary perfusion, reduced left ventricular afterload, and an increase in cardiac output by 0.5 to 1 L/min.[1,3] Due to its greater availability, lower cost, easy implantation, and low complication rates, IABP quickly became the most used percutaneous device in cardiogenic shock.[2] Nevertheless, in spite of the advantages described and the extensive clinical experience, there are still some controversies in relation to its use.

The randomized IABP-SHOCK II Trial evaluated the use of IABP versus clinical treatment in patients with post-acute myocardial infarction (AMI) cardiogenic shock.[4] In this study, the use of IABP did not reduce the primary endpoint of 30-day mortality or the relevant secondary outcomes,[4] and, from then on, the use of IABP in post-AMI cardiogenic shock started to be discouraged by guidelines, with class III, level of evidence B for routine use (not recommended).[5,6] It is, however, noteworthy that other devices that provide greater hemodynamic support compared to IABP have also not shown a benefit in increasing survival in post-AMI cardiogenic shock.[7]

We know that most of the evidence on cardiogenic shock comes from studies in patients in the context of acute coronary syndromes.[2] Nevertheless, cardiogenic shock has more recently been recognized as a heterogeneous clinical syndrome, with a broad spectrum of clinical phenotypes and different stages of organic dysfunction.[2,8,9] Accordingly, we can differentiate, for example, post-AMI cardiogenic shock from shock due to chronic heart failure (HF) decompensation. In the first case, an abrupt reduction occurs in cardiac output with rapid onset, generally in patients without previous ventricular dysfunction. In the second, a gradual reduction occurs in cardiac output in patients who already have ventricular dysfunction, which is often severe. Therefore, an incremental support of 0.5 to 1 L/min may be insufficient to stabilize a patient with post-AMI cardiogenic shock; however, it may be sufficient to stabilize a patient with chronic HF, who has already adapted to hemodynamic conditions with borderline cardiac output. From the pathophysiological point of view, we know that the inflammatory component is predominant in post-AMI cardiogenic shock, whereas, in chronic HF, peripheral vasoconstriction is predominant.[10] This difference corroborates the benefit of the effect of the reduced ventricular afterload of IABP in cardiogenic shock associated with decompensated chronic HF.

In patients with advanced HF, the outcome of reduced mortality is unlikely to be achieved with temporary ventricular assist devices (VAD). Therefore, the main objective is stabilization until definitive treatment, especially heart transplantation or implantation of long-term VAD. Accordingly, a series of studies has demonstrated the feasibility of using IABP as a bridge to transplantation or long-term VAD implantation.[2,3,11] In a single-center, observational, retrospective study, Fried et al. evaluated 132 patients with cardiogenic shock associated with chronic HF who received aortic counterpulsation therapy.[3] The 30-day survival was 84.1%, of which 70.4% underwent long-term VAD implantation, 8.2% underwent heart transplantation, and 21.4% were discharged without need for escalation of device support.[3] In another prospective observational study, conducted in Brazil, metabolic and hemodynamic variables were evaluated before and after IABP implantation in 223 patients.[11] After institution of aortic counterpulsation therapy, there was a reduction in serum lactate (32.9 versus 17.1 mg/dL, $p < 0.01$); increased central venous saturation (50.6% versus 66%, $p < 0.01$), and reduced vasopressor use (36.2% versus 25.5%, $p = 0.0036$).[11] In a recent case series from the Heart Institute of the University of São Paulo, 90% of patients were transplanted under priority status, and 50% of them were using IABP.[12] Similarly, in the United States, after the change in the organ allocation policy that prioritizes patients using short-term VAD, the use of IABP as a bridge to transplantation significantly increased, from 7% to 24.9%.[11] As a result, in patients using IABP, there was a decrease in waiting time and an increase in the probability of receiving a heart transplant.[13]

Although initially described in the 1960s, the use of IABP has recently been revisited in other scenarios and in different forms of use.[14–17] One of them is the use of IABP as an initial strategy for decompression of

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Intra-Aortic Balloon Pumping; Heart Transplantation; Heart Failure

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left heart chambers after the institution of peripheral venoarterial extracorporeal membrane oxygenation. In a meta-analysis, decompression strategies were related to greater success in weaning from extracorporeal membrane oxygenation, and the device that was most used for this purpose was IABP.[16] Techniques for implanting IABP via the subclavian or axillary artery have also sparked interest, enabling mobilization out of bed and preventing physical deconditioning and frailty.[2,15]

In conclusion, we believe that studies conducted in the context of acute coronary syndromes are inappropriate for evaluating the use of IABP in advanced HF. Furthermore, a series of studies has demonstrated its efficacy in this profile. In the current scenario, IABP should not be seen as an outdated strategy in advanced HF, but rather as a contemporary one with an impact on improved clinical and hemodynamic parameters, ventricular decompression associated with the use of peripheral venoarterial extracorporeal membrane oxygenation, and as a bridge to transplantation or long-term VAD.

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Viewpoint

Intra-Aortic Balloon Pump Placement in the Axillary Artery: Where are We?

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The prevalence of patients with heart failure (HF) in Brazil is high, with an increasing number of hospitalizations for advanced HF in tertiary care services. This suggests that patients' conditions are persistently more severe, with recurrent episodes of pulmonary congestion or low cardiac output requiring frequent hospitalization. Multidisciplinary clinical support and optimized medical therapy are fundamental in the treatment of these patients. However, in refractory cases, bridge or destination therapies such as circulatory or ventricular assist devices (VADs) and heart transplantation may be indicated.[1,2]

Patients with decompensated INTERMACS 2 or 1 HF may have an indication for mechanical circulatory support (MCS) during hospital stay. Devices currently available in Brazil include intra-aortic balloon pump (IABP), Impella CP, venoarterial extracorporeal membrane oxygenation, and Centrimag.[2] The IABP is the most used device in Brazil and worldwide due to easy access, cost-effectiveness, and simple implant procedure and management. Despite having a modest effect on cardiac output, the IABP has a significant impact on circulatory hemodynamics, is simpler to use, and has an equal or superior safety profile compared with more modern devices.[3-5]

Complete or partial patient immobilization is inherent in critical HF and in the use of MCS and thus may be required. The development of additional complications due to immobilization is a risk factor for worse in-hospital outcomes, and complications such as sarcopenia and cachexia are more frequent and often progressive.[6,7]

Aiming at reducing immobility and its consequences while still providing the necessary hemodynamic support, McBride et al. first described in 1989 a technique for surgical placement of an IABP through the axillary artery.[8] In the early 2000s, two case series were published. The first series described the outcomes of 13 patients over a 3-year period who had received IABP support for a mean duration of 37 days. Of these, 10 underwent a heart transplant.[9] The second series reported the outcomes of 4 patients with ischemic cardiomyopathy on the heart transplant waiting list. Support duration ranged from 12 to 70 days, and all patients underwent successful transplants.[10]

In 2012, a series of 18 patients surgically implanted with an axillary IABP between 2007 and 2010 was published. Median support duration was 19 days, and 72% of patients underwent a heart transplant. Three patients developed device-related complications, ie, IABP displacement, rupture, or kinking. These complications were not associated with worse outcomes. There were no vascular complications or stroke.[11]

The first series of patients treated with an axillary IABP using only percutaneous access was published in 2013. Fifty patients referred for heart transplantation or VAD evaluation received a left axillary IABP between 2007 and 2012. Mean support duration was 18 days, and 84% of patients underwent a heart transplant. Complications requiring intervention included one case of significant bleeding and two cases of left upper extremity ischemia. IABP repositioning was required in 44% of patients, whereas 20% of patients required IABP replacement due to malfunction. There were no IABP-related deaths, strokes, or infections.[12]

In 2020, the same group of researchers expanded on previous experience and published a series of 195 patients who had received an axillary IABP between 2007 and 2018. Patients were divided into two groups according to therapeutic success, which was defined as destination therapy. Success rate was 68%; 120 patients underwent a heart transplant, and 13 patients received a long-term VAD. Among the remaining 62 patients (31.8%), 16 (8%) died, 18 (9.2%) required support escalation, and 28 (14%) underwent IABP removal (22 due to complications and 6 due to contraindications to destination therapy). The 1-year survival rate was 87% for heart transplantation and 62% for VAD implantation. Median support duration was 19 days. IABP replacement or repositioning was common (37%), with a mean number of IABP exchanges per patient of 0.68. Left upper extremity ischemia occurred in 3.5% of patients, but no patient suffered limb loss. Stroke, mesenteric ischemia, and bacteremia rates were 2.5%, 3%, and 9.2%, respectively. Among patients who developed bacteremia, 16.6% required IABP removal due to infection. Implant site-related bleeding occurred in 2.5% of patients, whereas 96 (49%) patients required IABP repositioning at least once.[13]

More recently, another study described 38 patients treated percutaneously between 2017 and 2020. IABP failure or migration requiring replacement occurred in 21.4% of patients. There were no major complications, and 81.6% of patients

Keywords

Intra-Aortic Balloon Pumping; Heart Failure; Axillary Artery.

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received the intended therapy.[14] Nishida et al. reported their experience with 241 patients implanted with an IABP, of whom 58.9% underwent axillary insertion. Ambulation was possible in 90% of patients, and 86.7% received the intended therapy.[15] Vascular complications occurred in 3% of patients who underwent percutaneous IABP placement, and one third of these patients required surgical treatment.[16]

Some Brazilian hospitals perform percutaneous IABP placement in the left upper extremity, but data on MCS implantation and advanced HF treatment are scarce (Figures 1 and 2). Knowledge is essential to better understand the risk factors involved in complications and unfavorable outcomes, as well as to precisely define the role of axillary IABP in the current setting of MCS. Although these approaches have not been directly compared, the positive impact on adequate physical therapy and motor rehabilitation favors IABP placement via the axillary artery compared with the femoral artery. By allowing ambulation and greater mobility, the processes of sarcopenia and cachexia are also likely to be attenuated.

According to the available data, percutaneous axillary IABP placement is a viable and safe alternative for the implantation of an IABP in patients who require long-term support. The data suggest that placement via the axillary artery requires careful attention for correct device positioning, with increased rates of IABP repositioning and exchange compared with the femoral artery. Prospective and randomized clinical trials involving multidisciplinary teams are needed to provide hemodynamic support and comprehensive care according to the demands and risk profile of each patient in this complex setting of advanced HF.

Author Contributions

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This article does not contain any studies with human participants or animals performed by any of the authors.

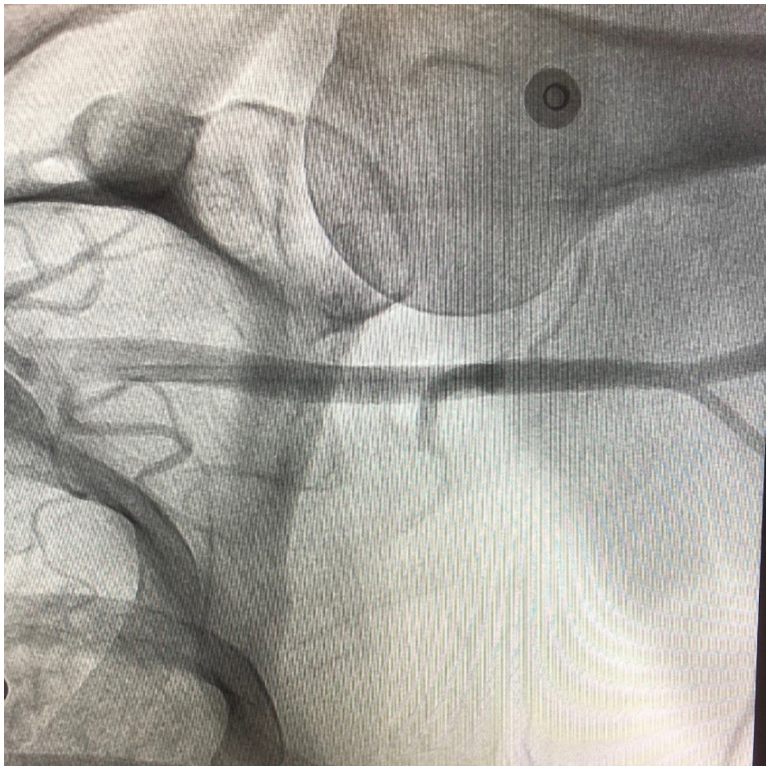

Figure 1 – *Arteriography performed with a 5F introducer to confirm puncture positioning.*

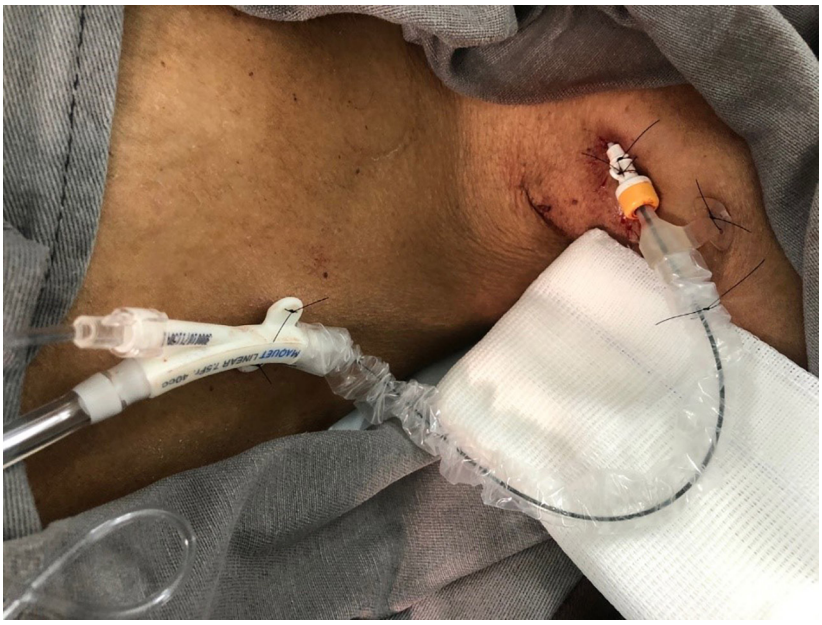

Figure 2 – *Final position of the intra-aortic balloon pump after percutaneous implantation.*

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Swan-Ganz Catheter and Lack of Evidence: Does it Reflect Clinical Practice?

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The physician is faced with a septuagenarian patient with chronic heart failure (HF) of severe ischemic etiology. She progresses with a major hemorrhagic complication after attempted percutaneous revascularization. In spite of volume compensation, she shows signs of respiratory infection, and, notwithstanding adequate antibiotic therapy, she continues to deteriorate clinically with signs of hypoperfusion, albeit with borderline blood pressure levels.

Would indication of invasive hemodynamic monitoring be scientifically associated with reduced clinical outcomes in this case? Acute clinical syndromes imply a greater degree of difficulty for conducting clinical trials, and some approaches applied in practice have not yet been tested in the ideal Cartesian model. The case described above seems to be a good justification for this discussion.

The first group to publish a prospective study on the effectiveness of the Swan-Ganz catheter was SUPPORT, where 10% of the population had congestive HF, showing an increase in mortality associated with the use of the catheter.[1] Subsequently, in 2005, the ESCAPE study[2] was published, analyzing 433 symptomatic patients with HF and ejection fraction (EF) < 30%, without criteria for cardiogenic shock (CS), showing no reduction in mortality; however, in the outcomes there was a benefit in relation to improved symptoms and functional capacity. In an analysis of the use of pulmonary artery catheterization (PAC) in HF with reduced and preserved EF, a decline was observed in use between 2005 and 2010, with a subsequent increase between 2010 and 2014 and a concomitant decline in mortality throughout the period, which is possibly associated with improvement in HF therapy.[3] The decline in use was also observed by Hernandez et al.,[4] who retrospectively analyzed 9,431,944 hospital admissions due to HF or CS, finding that the use of PAC in HF was associated with greater mortality, whereas patients with CS showed an association with lower mortality (34.9% versus 37%; odds ratio 0.91, confidence interval 0.87 to 0.97; p = 0.001) and cardiorespiratory arrest (14.9% versus 18.3%; odds ratio 0.77; confidence interval 0.74 to 0.81; p < 0.001). These outcomes continued even after propensity score matching.

The complexity of some patients with HF, whether due to the wide range of comorbidities and aggravating factors or even advanced heart disease, can confound the evaluation of clinical status. In corroboration with this, a prospective analysis of 97 patients with decompensated HF compared the accuracy of physical examination with invasive hemodynamic assessment, classified using Lee Stevenson's clinical-hemodynamic profiles, with subsequent reclassification by means of PAC.[5] There was an extremely low rate of clinical identification for the cold and wet subgroup, as well as volume status and cardiac output, even among experienced cardiologists, and the Swan-Ganz catheter altered decision making in the majority of cases. Taking into consideration these challenges as well as the fact that congestion in HF is associated with mortality,[6] PAC monitoring provides information that contributes to more accurate volume optimization and pharmacological action. In line with this, an analysis of data from the ESCAPE study evaluated the 141 patients with the primary objective of observing the association of PAC use with days to death, heart transplantation, and cardiac hospitalization at 6 months. They found that pulmonary artery occlusion pressure (PAOP) was associated with an increase in the recommended outcomes (hazard ratio 2.03; 95% confidence interval 1.31 to 3.15; p < 0.01), whereas cardiac index did not have the same association.[7]

The classification of CS proposed by the Society for Cardiovascular Angiography and Interventions,[8] based on stages, introduces the notion of risk of HF progression to tissue hypoperfusion and instability. Following this logic, PAC monitoring assists in the categorization of phenotypes, leading to more accurate assessment, given that the tenuous transition from acute HF to CS may not be clinically perceptible, especially in cases of isolated right ventricular dysfunction or shock with normal blood pressure levels.[9,10] Furthermore, parameters for the assessment of right ventricular dysfunction, such as the ratio between right atrial pressure and PAOP (RAP/PAOP > 0.8), the pulmonary artery pulsatility index (PAPi < 1.0), and the right ventricular stroke work index (RVSWI < 600 mmHg × mL/m^2) are essential for diagnosis and prognosis in these patients.[11]

Regarding the use of PAC in HF, the recommendations provided by the American College of Cardiology Foundation/American Heart Association,[12] the European Society of Cardiology,[13] and the Brazilian Society of

Keywords

Swan-Ganz Catheterization; Heart Failure; Functional Residual Capacity.

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Cardiology[14] are restricted to patients who are being considered for mechanical circulatory support or heart transplantation, especially for evaluation of the reversibility of pulmonary hypertension. In these cases, assessment of the fixed component of pulmonary hypertension assists in planning advanced therapies and post-transplantation prognosis.[15]

The available evidence favors the use of Swan-Ganz catheter in CS; however, the evidence does not favor its routine use in decompensated HF, and the specialist's experience plays a fundamental role. In spite of the unfavorable mortality outcomes, it is worth remembering that PAC is a diagnostic tool and not a therapeutic measure, and its effectiveness will depend on the clinical decisions made by the professionals involved.

Returning to the initial case, PAC monitoring was performed in the septuagenarian patient, providing evidence of a hemodynamic profile compatible with CS. The application of an inotrope was justified, and it led to clinical improvement in fewer than 24 hours, leading to discharge from the intensive care unit in 3 days.

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When to Suspect Advanced Heart Failure in Heart Failure with Preserved Ejection Fraction?

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Advanced heart failure (HF) accounts for almost 15% of patients with HF, and it has been defined as "the presence of progressive and/or persistent severe symptoms despite optimal guideline-directed management regardless of left ventricular ejection fraction (LVEF)."[1,2] Although patients with advanced HF are thought to usually present with severely reduced LVEF, it should be noted that the definition of advanced HF does not require low LVEF. Indeed, more than half of patients with advanced HF have LVEF above 40%, with all-cause mortality similar to those with LVEF below 40%.[2] Identifying patients with advanced HF is important in order to refer them to proper management, including heart transplantation, mechanical circulatory support, or palliative care. But when should we suspect advanced HF when the LVEF is preserved?

First, let's look at the current definition criteria for advanced HF (Table 1). Beyond LVEF below 30%, severe cardiac dysfunction includes severe congenital or valve disease or arrhythmogenic right ventricular cardiomyopathy. But these conditions have been excluded from HFpEF definitions in clinical trials and they are not mechanistically generally considered heart failure with preserved ejection fraction (HFpEF).[3-5] Advanced HFpEF requires the presence of severe diastolic dysfunction or left ventricular (LV) structural abnormalities accompanied by elevated natriuretic peptides.

Diastolic dysfunction is assessed by mitral flow velocities, mitral annular e' velocity, E/e' ratio, peak tricuspid regurgitation jet velocity, and maximum left atrial volume index. Although the American Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines provide grading criteria for diastolic dysfunction (grades I to III), there is no consensus on how severe diastolic dysfunction should be specifically defined to fulfill the criteria for advanced HFpEF.[6] In a recent epidemiological study of advanced HF in Olmsted County, United States, Dunlay et al defined severe diastolic dysfunction in patients with HF with mildly reduced ejection fraction or HFpEF as diastolic dysfunction grade 2 or greater. They also used other criteria that suggested elevated filling pressures, such as E/e' ratio above 9, to indicate severe diastolic dysfunction, but this was because diastolic dysfunction grading was missing in the administrative data.[2]

The definition of advanced HF also requires that diastolic dysfunction be accompanied by elevated natriuretic peptides, but it should be kept in mind that patients with advanced HFpEF display lower natriuretic peptide blood levels compared to patients with advanced heart failure with reduced ejection fraction (HFrEF).[2] Furthermore, comorbidities are more common in patients with HFpEF, and they can contribute to their functional impairment and worsen quality of life, which makes the diagnosis of advanced HFpEF more challenging.[2]

For the diagnosis of advanced HFpEF, severe symptoms, repeated hospitalizations for HF, and/or severe impairment in functional capacity should persist, despite optimal medical treatment. Differently from HFrEF, therapeutic options for HFpEF are limited. Guideline-based recommendations for treatment of HFpEF include treatment of cardiovascular and non-cardiovascular comorbidities, such as treating myocardial ischemia, reducing blood pressure in hypertension, and controlling heart rate in atrial fibrillation.[7] The guidelines also recommend using diuretics to alleviate congestion, as well as screening and treating specific etiologies, such as cardiac amyloidosis. An angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker/sacubitril-valsartan, a mineralocorticoid receptor antagonist, and a beta-blocker are not required for HFpEF, but they can be considered if tolerated for patients with LVEF below normal (i.e. HFmrEF) following results from sub-analysis of trials.[8-12] In addition, after the results of the first positive outcome-driven trial in HFpEF, empagliflozin should be considered as part of optimal treatment in HFpEF.[5] Patients with advanced HFpEF are those who remain severely symptomatic despite optimal clinical treatment, and they should be considered for advanced therapies.

The rational of advanced therapies in HFpEF relies upon our knowledge on the pathophysiology of the disease and underlying mechanisms of symptom development. HFpEF is characterized by increased LV and left atrial (LA) stiffness, which results in high LA pressure and pulmonary capillary wedge pressure, particularly during exercise. Patients with HFpEF tend to have exercise intolerance in early stages and to develop congestive signs/symptoms with the progression of the disease.[13]

Keywords

Heart Failure; Ejection Fraction; Advanced Heart Failure.

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Table 1 – Updated Heart Failure Association-European Society of Cardiology criteria for defining advanced heart failure

All the following criteria despite optimal guideline-directed treatment: 1. Severe and persistent symptoms of HF (NYHA III [advanced] or IV) 2. Severe cardiac dysfunction defined by either: - LVEF ≤ 30% - Isolated RV failure (e.g. ARVC) - Non-operable severe valve abnormalities or congenital abnormalities - Persistently high BNP or NT-proBNP values and data of severe diastolic dysfunction or LV structural abnormalities according to the European Society of Cardiology definition of HFpEF or HFmrEF. 3. Episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhytmias causing > 1 unplanned visit or hospitalization in the last 12 months. 4. Severe impairment of exercise capacity with inability to exercise or low 6MWTD (< 300 m) or pVO_2 (< 12 to 14 mL/kg/min), estimated to be of cardiac origin.
In addition to the above, extra-cardiac organ dysfunction due to HF (e.g. cardiac cachexia, liver, or kidney dysfunction) or type 2 pulmonary hypertension may be present, but are not required.
Criteria 1 and 4 can be met in patients who have cardiac dysfunction (as described in criterion number 2), but who also have substantial limitation due to other conditions (for instance, severe pulmonary disease, non-cardiac cirrhosis, or renal disease with mixed etiology). These patients still have limited quality of life and survival due to advanced disease and warrant the same intensity of evaluation as patients in whom the only disease is cardiac, but the therapeutic options for these patients are usually more limited.

ARVC: arrhythmogenic right ventricular cardiomyopathy; BNP: B-type natriuretic peptide; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; LV: left ventricular; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro b-type natriuretic peptide; NYHA: New York Heart Association; pVO2: peak exercise oxygen consumption; RV: right ventricular; 6MWTD: 6-minute walk test distance. Source: Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology.[1]

The management of congestion can be challenging in patients with advanced HFpEF. Treatment options are similar to those in HFrEF, namely, high doses of loop diuretics, concomitant use of thiazides, continuous intravenous infusion of diuretics, ultrafiltration, and peritoneal dialysis. Nevertheless, caution is advised since patients with HFpEF are sensitive to volume shifts due to high arterial and ventricular stiffness. They are more susceptible to intravascular volume depletion and may not tolerate "aggressive" decongestive therapies, such as intermittent high doses of loop diuretics and dialysis with high ultrafiltration rates. Alternatively, a combination of diuretics, continuous intravenous infusion, and low ultrafiltration rates may be better tolerated.[1]

Heart transplantation (HT) is the gold standard therapy for treating advanced HF, but most patients with HFpEF may not be suitable for HT due to older age and comorbidities. Many patients with advanced HFpEF referred for HT have a specific etiology for HF, such as hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM) or infiltrative cardiomyopathies.[12] These patients have faced more difficulties to receive HT compared to those with HFrEF. Due to preserved LVEF and narrow LV cavity, patients with HFpEF are not usually treated with inotropes or left ventricular assist devices (LVAD). They usually stay longer on the waiting list for HT, as they are not categorized in priority status for HT, which is the condition in which most patients undergo HT in Brazil. Recently, changes in the prioritization rules have helped mitigate this problem in some regions, such as the 2020 update to Transplant System allocation criteria in the state of Sao Paulo, where intravenous diuretics dependence for patients with HCM or RCM was included as a #3 condition in the priority criteria, equivalent to inotrope dependence.[14]

Although LVAD have shown to improve morbidity and mortality in patients with HFrEF, their use remains limited in patients with HFpEF. Due to small LV cavity and severe diastolic dysfunction, technical issues have occurred with LVAD in HFpEF.[13] The use of Heartmate II, a continuous flow axial LVAD, was reported in 8 patients with advanced HCM and RCM, showing the occurrence of suck-down events of the LA.[15] Simulation studies have been performed with LVAD in patients with HFpEF, and they appeared to result in beneficial hemodynamic effects, but these studies suggest avoiding a strategy with constant speed. Instead, they recommend using low pump speed at rest to prevent a suction event and high pump speed during exercise to prevent ineffective unloading.[16] Because of these technical issues, which are related to anatomical and pathophysiological features of patients with HFpEF, the use of LVAD is still limited in this population.

Left atrial assist devices (LAAD) have also been proposed. LAAD can be implanted in mitral position pumping blood from the LA to the LV. Another LAAD (PulseVAD) pumps from the LA to the descending aorta.[13] Although they are mechanistically interesting, clinical trials are needed to evaluate their roles in HFpEF.

The pathophysiology of advanced HFpEF also includes left atrium myopathy, and interatrial shunt devices (IASD) have been specifically developed to relieve symptoms by reducing LA pressure. A bare metal self-expanded device creating an 8-mm shunt, proven to be the optimal size to reduce LA pressure without overloading the right heart, was tested in a small randomized clinical trial, Reduced Elevated Left Atrial Pressure in Patients with HF (REDUCED-LAP-HF I).[17] In 43 patients with LVEF $\geq$ 40% and New York Heart Association functional class III/IV, the REDUCED-LAP-HF I trial showed a significant reduction in pulmonary capillary wedge pressure during exercise with IASD compared with the sham control group. This strategy is currently being tested in a larger multi-center randomized study, the REDUCED-

LAP-HF II. Two other promising IASD, namely, the V-WAVE[18] and the Atrial Flow Regulator,[19] are also being evaluated in large randomized clinical trials.

Treatment of advanced HFpEF is evolving and the first step in its management is to recognize this condition. From the practical point of view, the proposed acronym "I NEED HELP" remains useful to identify potential patients with advanced HFpEF, but we suggest a few modifications and observations that are detailed in Table 2.[12]

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Writing of the manuscript and Critical revision of the manuscript for intellectual content: Fernandes-Silva MM, Marcondes-Braga FG.

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Table 2 – Warning signs of advanced HFpEF

Acronym	Advanced HF alert	Comment for HFpEF
I	Intravenous inotrope dependence	Unusual in HFpEF
N	Persistent NYHA III/IV; persistent elevation in natriuretic peptides	Natriuretic peptides are less elevated in HFpEF
E	End-organ dysfunction	Particularly renal dysfunction
E	Elevated filling pressures; severe diastolic dysfunction	Replacing the original LVEF below 20%
D	Defibrillator shocks (recurring appropriate shock)	Less common, unless there is a specific etiology (e.g. HCM)
H	Recurring HF hospitalizations and emergency department visits in the last 12 months	
E	Persistent edema, refractory to escalating diuretics	Diuretic management can be difficult
L	Low systolic blood pressure, persistently below 90 mmHg	Augmented BP sensitivity to volume shifts
P	Progressive intolerance to optimized medical therapy	Fewer drug options, but most can be considered if LVEF is below normal

BP: blood pressure; HCM: hypertrophic cardiomyopathy; HFpEF: heart failure with preserved ejection fraction; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

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The Impact of Clonal Hematopoiesis of Indeterminate Potential on Advanced Heart Failure

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Introduction

The many processes that contribute to age-related diseases include Harman's free-radical[1] telomere shortening, inflammaging,[2] and Medewar's mutation accumulation theory,[3] especially in hematological malignancies.[4,5] As we age, hematopoietic stem cells may acquire mutations that modulate their function, proliferation, or survival, thus expanding the pool of mutated cells in blood, a process termed clonal hematopoiesis (CH).[6] With the addition of cooperating mutations, CH cells may progress to myelodysplastic syndrome and acute myeloid leukemia at rates ranging from 0.5 to 1% per year.[7] There are dozens of known CH-driver genes, a subset of the known leukemia driver genes, the most frequent of which are *DMNT3A*, *TET2*, *ASXL1*, and *JAK2*, which account for approximately 80% of all CH mutations.[8] CH increases with age: more than 2% of cells (Variant Allele Fraction [VAF]) will have these mutations in approximately 10% of individuals aged 70 years.[9] Indeed, new and highly sensitive targeted sequencing techniques have shown nearly ubiquitous CH mutations in adults over 30 years of age.[10]

Although the risk of developing a hematologic malignancy is more than 10-fold in individuals with CH, most will have no overt manifestation, hence the term: Clonal Hematopoiesis of Indeterminate Potential (CHIP).[7] Surprisingly, people with CHIP who carry leukocyte clones with mutated leukemia driver genes have a higher risk of developing and/or progressing to non-hematologic conditions of other age-related diseases, such as dementia,[11] osteoporosis,[12] stroke,[13] and cardiovascular diseases.[14] Various mechanisms linked with these diseases are associated with CHIP, including an excessive inflammatory response due to inflammasome activation and enhanced expression of inflammatory cytokines such as IL-1β and IL-6, increased thrombotic potential, and impaired DNA repair.[15-18]

Considering the increased risk of cardiovascular manifestation in carriers of CHIP mutations, independent of traditional risk factor (eg, high cholesterol), we discuss the implications of CHIP for heart diseases and progression to heart failure (HF). Assessment of such somatic mutations may provide a novel tool for personalized/precise cardiovascular medicine.

Cardiovascular impact of CHIP

Identifying cardiovascular risk factors, such as hypertension and diabetes, has enabled targeted treatments that have helped reduce cardiovascular mortality. In 2014, a landmark paper including more than 17,000 patients was the first to suggest an association between CHIP and increased adverse cardiovascular events.[14] To further investigate the risk of CHIP, this team performed a case-control study of coronary artery disease (CAD) patients.[15] They found that CHIP was associated with a 1.9-fold increase in CAD, a 4.0-fold increase in early-onset myocardial infarction (MI), and 3-fold increase in coronary artery calcification. CHIP was also associated with a 14% increase in ischemic stroke, as well as a 24% increase in hemorrhagic stroke in another study with more than 70,000 patients.[13]

Since age is a strong risk factor for CHIP and cardiovascular disease, CHIP could merely be indicative of older age rather than contribute causally to cardiovascular disease.[14] Some data have also suggested "reverse causation", ie, that atherosclerosis can increase CHIP. However, Mouse experiments have shown that loss of *TET2* function in myeloid cells, the second most mutated gene in CHIP, accelerates atherosclerosis.[15] These studies not only found larger atherosclerotic lesions in mice carrying CHIP mutations, but also the expression of several inflammatory cytokines and chemokines. On the clinical side, a small study including patients with severe degenerative aortic stenosis or chronic post-ischemic HF found higher expression of several inflammatory genes, such as IL-1β and IL-6, in individuals with CHIP mutations.[19] *TET2* mutation carriers with ischemic heart disease have shown higher levels of circulating IL-8.[15] These markers of increased inflammation reveal a pathway by which CHIP can affect cardiovascular risk.[16,19,20] A dose-response effect, crucial for determining causality, has also

Keywords

Cardiovascular Risk; Heart Failure; Clonal Hematopoiesis; CHIP; Inflammation; Mutations.

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been reported as a greater risk in those with larger clone size.[15,21] In mice, mutations in *TET2* and *DNMT3A* can promote cardiac function remodeling, including lower ejection fraction, increased left ventricular diameter, and myocardial fibrosis.[16,20]

In sum, abundant evidence supports CHIP as a newly recognized contributor to atherosclerosis and impaired ventricular function. Indeed, CHIP mutations are associated with a higher risk than hypertension, smoking status, and hypercholesterolemia, lower only than age and type 2 diabetes.[22]

Heart Failure and CHIP

Although CHIP was initially associated with increased risk of atherosclerotic diseases, including CAD and MI, recent sequencing studies have also revealed a connection between CHIP and HF.[15,21,23,24] Dorsheimer et al. studied the incidence and prognostic significance of CHIP in a cohort of 200 patients with chronic HF who underwent autologous bone marrow treatment for acute MI.[21] DNA from bone marrow–derived mononuclear cells was isolated and analyzed for the presence of CHIP, and 18.5% of participants were carriers of CHIP with VAF ≥ 2%. Over a median follow-up of 4.4 years, the survival analyses showed that CHIP carriers, particularly those with *DNMT3A* and *TET2* mutations, had worse clinical outcomes for death and death-plus-HF hospitalization than non-carriers. Remarkably, most deaths arose from worsening HF and emergent arrhythmia, with only one death due to subsequent MI. These results support the association of CHIP not only with the pathogenesis of atherosclerotic cardiovascular diseases but also with HF. There was also a significant dose-response association between %VAF and clinical outcomes, with VAF > 2% leading to worse outcomes.[21] Notably, the authors also found that halving the threshold to 1% VAF was still associated with poor outcomes, albeit to a lesser extent, further implying that CHIP has a "dose effect".[25] Moreover, CHIP mutation was associated with higher %VAF independently of other risk factors in a larger cohort of patients with previous MI and stable chronic HF.[26] Pascual-Figal et al. corroborated these findings, showing that clonal hematopoiesis due to *TET2* or *DNMT3A* mutations predicted worse outcomes in patients with HF, regardless of etiology.[23]

Subsequently, Yu et al. performed a meta-analysis of archived sequencing data to identify CHIP mutations among 56,597 individuals from 5 population-based cohorts in up to 20 years of follow-up to investigate the association between CHIP and incident HF.[24] CHIP was prospectively associated with a 25% increased risk of HF, which was comparable in individuals with and without CAD, regardless of traditional cardiovascular risk factors. These findings suggest a direct link between CHIP and HF, arguing against the possibility that this association only reflects a connection between CHIP and atherosclerosis. Interestingly, in single gene-specific analysis, *ASXL1*, *TET2*, and *JAK2* sequence variations were each associated with an increased risk of HF, whereas *DNMT3A* sequence variations were not associated with HF. This result may have biological significance since *ASXL1* and *JAK2* may provoke cardiovascular events through mechanisms that are distinct from *DNMT3A* or from *TET2*.[25]

CHIP may also contribute to the development and progression of HF with preserved ejection fraction; however, this hypothesis remains untested. Identifying CHIP in individuals with HF could provide diagnostic information and guide the development of therapeutic strategies that target the downstream consequences of specific mutations.

Future perspectives

CHIP is a newly recognized risk factor for cardiovascular disease that can help clarify the relationship between aging and CAD, MI, stroke, and HF.[15,21,23] According to clinical and experimental data, some CHIP mutations are associated with dysregulation of several inflammatory cytokines, indicating a new potential targeting strategy for cardiovascular disease treatments.[15,16,20] For example, in the Canakinumab Anti-Thrombotic Outcomes Study, individuals with TET2 mutations benefited more from administration of an anti-interleukin-I beta antibody. Moreover, probing the mechanistic links between specific CHIP mutations and cardiovascular diseases may help elucidate the pathophysiology of HF. Finally, such explorations may lead to new targeted treatments for HF orthogonal to current approaches focused on neurohormonal blockade or SGLT2 inhibition.

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Dr. Libby is an unpaid consultant to, or involved in clinical trials for Amgen, AstraZeneca, the Baim Institute, Beren Therapeutics, Esperion Therapeutics, Genentech, Kancera, Kowa Pharmaceuticals, Medimmune, Merck, Norvo Nordisk, Novartis, Pfizer, and Sanofi-Regeneron.

He is a member of the scientific advisory board for Amgen, Caristo Diagnostics, Cartesian Therapeutics, CSL Behring, DalCor Pharmaceuticals, Dewpoint Therapeutics, Kancera, Kowa Pharmaceuticals, Olatec Therapeutics, Medimmune, Novartis, PlaqueTec, TenSixteen Bio, and XBiotech, Inc. Dr. Libby is on the Board of Directors of XBiotech, Inc. and has a financial interest in Xbiotech, a company developing therapeutic human antibodies.

His interests were reviewed and are managed by Brigham and Women's Hospital and Partners HealthCare in accordance with their conflict-of-interest policies.

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The Heart-Gut Microbiome Intersection in Heart Failure

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The human body is co-inhabited by over a trillion microorganisms, including > 2000 species of bacteria, archaea, viruses, and single-celled eukaryotes that live symbiotically with their hosts.[1] The gut microbiota is a dynamic and complex ecological community in the gastrointestinal tract, an essentially anaerobic environment with abundant nutrients and ideal conditions for colonization; it acts as a virtual endocrine system that communicates with organs through metabolism-dependent pathways, releasing *de novo* products and transforming external nutrients and host metabolites into hormone-like signals.[2]

In addition to metabolic benefits, the gut microbiota provides essential capacities for regulating the intestinal epithelial barrier, immune homeostasis, optimal immune responses, and protection against pathogen colonization.[3-5] One of the most important roles of gut microbiota is to act in digestion and nutrient absorption, producing short-chain fatty acids that serve as energy substrate for intestinal epithelial cells. After short-chain fatty acids bind to their receptor, the enteroendocrine hormone peptide YY is released, which regulates host appetite and contributes to dietary energy availability.[6] Intestinal flora act to convert various dietary nutrients into trimethylamine, which is rapidly absorbed and oxidized in the liver to produce trimethylamine N-oxide (TMAO).[7] Some foods, like red meat, eggs, and fish, are rich in nutritional precursors that can be converted into trimethylamine through specific microbial enzymes; therefore, a change in microbiota composition can alter circulating TMAO levels.

Evidence indicates that the composition of gut microbiota changes throughout life via potentially modifiable factors, including medication use, diet, lifestyle, and oxidative stress. Such disruption of microbiota homeostasis results in an imbalance in the microbial community and is referred to as dysbiosis. Gut dysbiosis is associated with the pathogenesis and progression of heart failure (HF), has been linked to immune-mediated subtypes of cardiomyopathy, and has been associated with HF-related comorbidities, including atherosclerosis, hypertension, chronic kidney disease, insulin resistance, and cachexia.[4,8-12] Reduced cardiac output and elevated abdominal venous pressure can lead to intestinal hypoperfusion, mucosal ischemia, and gut barrier disruption (Figure 1). Such alterations have led to the gut hypothesis of HF, which posits that these structural changes contribute to increased intestinal permeability and subsequent bacterial translocation, resulting in elevated circulating endotoxins that correlate with HF severity.[13-16] Endotoxins, which are lipopolysaccharides found in the cell wall of Gram-negative bacilli, can induce the production of pro-inflammatory cytokines and impair endothelial function and peripheral blood flow, resulting in decreased ventricular contractility.[17,18] Likewise, endotoxin and inflammatory cytokines can also exacerbate intestinal permeability, promoting a loop of endotoxin translocation, systemic inflammation, and worsening HF.[19] Other potential mechanisms of the gut hypothesis have also been described, such as the upregulation of sodium-hydrogen exchanger 3 through hypoxia and acidosis in enterocytes, which promotes sodium and fluid retention.[20]

Several studies have supported the gut hypothesis of HF by showing different patterns in gut microbial composition and function between healthy individuals and patients with HF.[21-25] In healthy guts, *Firmicutes* (consisting mainly of *Lactobacillus, Bacillus, Clostridium, Enterococcus,* and *Ruminococcus*) and *Bacteroidetes* (consisting of *Bacteroides* and *Prevotella*) contribute to over 90% of the total bacterial species, also called alpha diversity.[26] Conversely, patients with HF have shifts in the alpha diversity, with an increased abundance of *Bacteroidetes* and a lower abundance of *Firmicutes*, resulting in a lower *Firmicutes*/*Bacteroidetes* ratio than healthy individuals.[21,24] Depletion of bacteria with anti-inflammatory properties, particularly *Firmicutes*, are associated with an increase in the number of pathogenic microbes, such as *Shigella*, *Salmonella,* and *Candida*.[4] The incidence of *Clostridium difficile* infection, which typically occurs after the use of antibiotics, is also higher in this population, as are the genera *Ruminococcus, Hungatella,* and *Succiclasticum*.[4,19,24,25] In advanced HF, an increase in *Pseudomonadota* (formerly *Proteobacteria*), has been demonstrated, a phylum that mainly includes pathogenic Gram-negative bacteria, whose abundance is considered a signature of dysbiosis.[21]

Investigations have indicated that not only does alpha diversity decrease with HF progression, but remains low in patients treated with a left ventricular assist device or heart transplantation,[9] a pattern in line with persistently elevated TMAO levels.[27] Studies of immunosuppression in heart transplantation have demonstrated that gut microbial diversity, inflammation, and oxidative stress are associated with tacrolimus dosing requirements early after engraftment,[28]

Keywords

Gastrointestinal Microbiome; Dysbiosis; Heart failure

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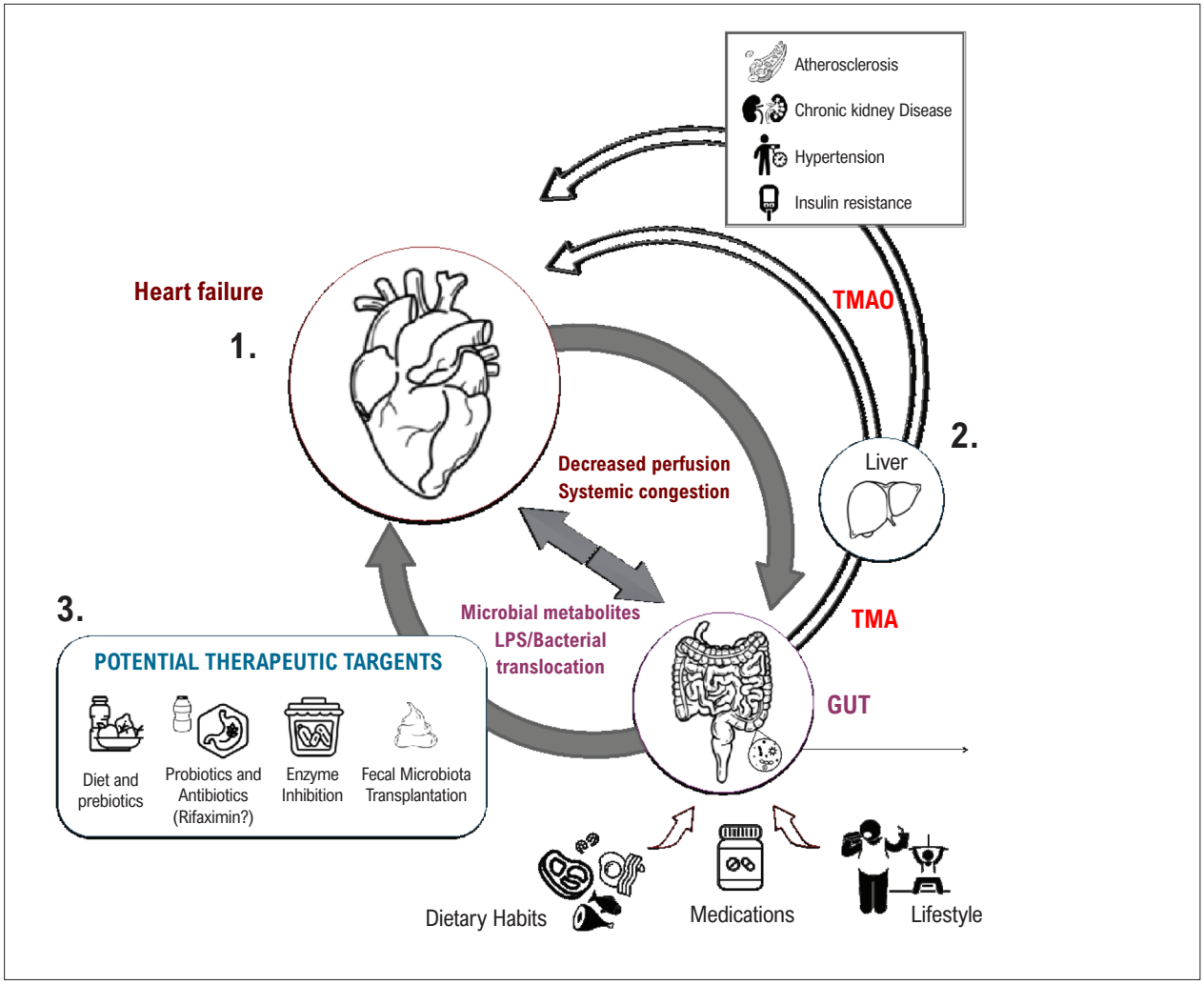

Figure 1 - *1) Reduced cardiac output and elevated abdominal venous pressure can lead to intestinal hypoperfusion, mucosal ischemia, and gut barrier disruption, with subsequent bacterial translocation and increased circulating endotoxins (lipopolysaccharides). Lipopolysaccharides induce the production of pro-inflammatory cytokines, resulting in decreased ventricular contractility. Likewise, endotoxin and inflammatory cytokines can also exacerbate intestinal permeability, promoting a loop of endotoxin translocation, systemic inflammation, and worsening heart failure. 2) Intestinal flora convert various dietary nutrients into trimethylamine, which is converted in the liver to trimethylamine N-oxide. Gut dysbiosis is associated with the pathogenesis and progression of heart failure and heart failure-related comorbidities, including atherosclerosis, hypertension, chronic kidney disease, insulin resistance, and cachexia. 3) Several potential therapeutic approaches have already been proposed, including dietary interventions, prebiotics, probiotics, trimethylamine N-oxide inhibitors, sodium-hydrogen exchanger 3 inhibitors, and fecal microbiota transplantation, as well as intestinal microenvironment modulators (Rifaximin).*

reinforcing the gut hypothesis at all stages of HF, from cardiac injury to end-stage HF and even after advanced therapies. Various HF phenotypes, such as preserved ejection fraction, require further study to understand the relationship between congestion and dysbiosis patterns. Pilot studies have revealed that the microbiota of patients with HF with preserved ejection fraction are imbalanced compared to healthy controls, with more *Enterococcus* and *Lactobacillus* and less *Butyricicoccus, Sutterella, Lachnospira*, and *Ruminiclostridium* at the genus level[29] and a non-significant decrease in the *Firmicutes*/*Bacteroidetes* ratio. How these alterations influence the observed pathobiology remains uncertain.

All of these changes in gut microbiota are linked to different physiological effects, such as cell cycle control, cell division, chromosome partitioning, ion transport, ribosomal structure, and amino acid metabolism. Identifying the composition of gut microbes is complex and requires sophisticated stool sample processing with 16S rRNA gene sequencing and whole metagenomic profiling. However, the use of surrogate circulating metabolites is less complicated and is readily available.[19,25] It has been discovered that certain microbial metabolites have recognized roles in HF pathophysiology, such as short-chain fatty acids, TMAO, amino acid metabolites, and bile acids; they may be promising therapeutic targets for gut dysbiosis in HF.[12] In fact, several therapeutic approaches have already been proposed, including dietary interventions, prebiotics, probiotics, TMAO inhibitors, sodium-hydrogen exchanger

3 inhibitors, and fecal microbiota transplantation, as well as intestinal microenvironment modulators (Rifaximin), but additional studies are still needed.[1] Further exploration of the heart-gut axis in the pathophysiology of HF may lead to advances in innovative individualized risk stratification and therapeutic interventions for patients with HF.

Author Contributions

Conception and design of the research: Vieira JL, Mehra MR; Acquisition of data and Critical revision of the manuscript for intellectual content: Vieira JL, Sidrim AFRR, Mehra MR; Analysis and interpretation of the data: Vieira JL, Sidrim AFRR; Writing of the manuscript: Vieira JL, Sidrim AFRR.

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Ethical and Legal Aspects of Palliative Care in Heart Failure in Brazil

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Introduction

Terminal heart failure (HF) poses numerous difficulties to clinical practice, with ethical, moral, and legal dilemmas.[1] Given that it is an advanced stage of incurable and progressive diseases, the few therapeutic possibilities that are available and tolerated aim to delay evolution, attempt to maintain the balance of organic functions, control symptoms, and offer comfort to patients. Generally, the clinical context is complex, involving interaction with other morbidities, low functionality, frailty, and high symptomatology.[2-4]

There is undoubtedly a high risk of death, in addition to a risk of suffering from the conditions caused by the disease or resulting from treatments. Decision making in terminal HF is a challenge, in the continuous search for adequate therapies that offer strategies that benefit the patient, without adding more risks or damages than are already inherent to their clinical condition.[5,6]

Palliative care (PC) is an approach that aims to provide quality of life, comfort, and dignity to patients suffering from serious or life-threatening diseases.[2,4,5,7-10] For good medical practice at the end of life, the focus of care must be patient-centered, with the understanding that the patient is a person with their own life story and values, as well as an individual way of thinking, living, and existing.[1] Therapeutic decisions must be proportional to the estimated disease prognosis, and they must consider patients' values, expectations, and preferences, respecting the dignity of the human being.[5,7,8] It is essential to be familiar with the legal, ethical, and sociocultural issues that involve patients.[4,5]

Legal opinion

PC is a philosophy and a concrete means of providing health assistance. Founded on multiprofessional action, it is directed at patients and their families, with the aim of promoting health through prevention and intervention in relation to physical, psychological, social, and spiritual symptoms.[5] Although it is an ancient practice, given that any action that seeks relief from suffering can be included in this definition, it has been given a more concrete format since the second half of the twentieth century, recognized by the World Health Organization and diverse international bodies and associations.[1,5,6] In Brazil, it is represented by the National Academy of Palliative Care, founded in 2005.[5] The Brazilian Society of Cardiology also recommends PC actions in its guidelines.[2,3]

In Brazil, there is not any federal law that regulates PC, but some of its guiding principles can be found in documents, such as the Brazilian Federal Constitution of 1988. Article 1 guarantees the dignity of human beings as one of the fundamental pillars of the Democratic State of Law. Article 5 covers the right to life and liberty; privacy, honor, and image are inviolable, with the guarantee that no person will be subjected to torture or inhuman or degrading treatment.[11] Based on these laws, guidelines have been derived to prohibit the practice of dysthanasia, with futility and therapeutic obstinacy that prolong the process of dying with suffering, which is divergent from the proposal of promoting comfort and dignity.[5,9]

In São Paulo, Law number 10.241 (known as the "Mário Covas law"), in 1999, was an important legal advance for end-of-life care, guaranteeing patients' rights, such as physical integrity, individuality, respect for ethical and cultural values, in addition to allowing patients to refuse painful and excessive treatments that attempt to prolong life (dysthanasia); they also have the right to choose their place of death.[12] In 2018, the Brazilian Official Journal of the Union, number 225 provided for guidelines for the establishment of the national PC policy, within the scope of the Unified Health System. Also in São Paulo, in 2020, Law Number 17.292 instituted the state's PC policy.[13]

Even with medical literature, laws, and resolutions, the recognition of the terminal phase and decision making at the end of life is not a simple task, nor one with an immediate response.[4,7] It is necessary for deliberation to take place within a well-founded framework of clinical information, assertive prognostic elaboration, and consideration of therapeutic measures, adapting them to the consequences and expected outcomes.[2] Deliberation should consider not only technical, clinical, and scientific data, but also personal aspects of the patient and family as well as ethical-legal issues.[1]

Patients in the terminal phase of progressive and incurable disease are close to their end of life and, consequently, to death, which is a natural and expected event that ends this process. With the exception of heart transplantation and ventricular assist devices, when possible,[3] therapeutic strategies at this stage of the disease are not very effective in saving lives, and it is very likely that the institution or maintenance of certain interventions are considered futile (meaning that they do not achieve the proposed objective) and potentially harmful. Measures are disproportionate when their purpose is dissociated from real prognostic expectations,

Keywords

Ethics; Jurisprudence; Heart Failure; Palliative Care; Terminal Care

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or when there is a high risk of causing harm faced with a low benefit. Dysthanasic practices are advised against, because they violate ethical principles of proportionality, non-maleficence, and prudence.[5]

Many professionals are insecure about not indicating, limiting, or suspending some procedures during terminal care due to concerns regarding being negligent or even blamed for the death. However, when considering that death is already an expected, natural, and proper event in the progression of the disease, if it becomes clear that the doctor could not or should not act to avoid the result, the death of a patient should not be understood as a result of on action or omission on the part of the doctor, but rather as inherent to the disease, with no professional penalty for the outcome.[5,10,14]

The Brazilian Federal Council of Medicine (CFM, acronym in Portuguese) published resolution 1805/2006, known as the "orthothanasia resolution", which states that physicians have permission to limit or suspend procedures and treatments that prolong the life of patients in the terminal phase of a serious and incurable disease, and they must continue to offer all necessary forms of PC.[5,15] Accordingly, the CFM is opposed to dysthanasia and objectively favors orthothanasia, recognizing the finitude of life and the need to allow death to occur in natural time, without prolonging it at the expense of additional suffering.

In the Brazilian Code of Medical Ethics, fundamental principle XXII, article 41, the CFM reinforces the need to respect the finitude of life in conditions of incurable, irreversible, or terminal diseases, and physicians must provide all necessary PC and limit diagnostic or therapeutic procedures that are unnecessary, useless, or obstinate.[5,16]

Article 41 also reiterates that doctors are prohibited from any form of abbreviation of life (euthanasia), which is considered homicide.[16] This practice differs from orthothanasia, because, in euthanasia, the medical action is directly responsible for death, and without this practice, death would not have occurred, and death is its final purpose. On the other hand, the objective of orthothanasia is care with comfort and respect for the natural time of the disease, death being a consequence of the disease and not of medical actions.[2,5,10]

Another relevant bioethical principle in patient-centered medicine is autonomy, which consists of giving voice and recognizing, in patients' expressed will, their values, desires, and preferences, so that medical conducts will be appropriate for them.[1,4,5,7-10]

The CFM validated advance healthcare directives with resolution 1995/2012,[5,17] wherein patients express the ways they would like, or not like to be treated and cared for at the end of life, making it possible to authorize a proxy to represent their will. The elaboration of directives is of great importance in order to better understand the adequacy of interventions and to assist in decision making during the terminal phase, and physicians should take them into account for greater alignment of conduct.[5,6,8] These manifestations must receive careful medical evaluation regarding their clinical relevance and ethical and legal adequacy.

Studies show that patients with advanced HF think about directives, but rarely express them to their physicians. Physicians, on the other hand, are generally unaware of their patients' directives, and they rarely advise patients to make them. Patients often complain about problems related to communication and express a desire for advanced life support measures based on unrealistic expectations of such treatments due to lack of information. Advanced HF patients are less likely to have PC discussions with their physicians than patients with cancer.[18]

With recognition of the terminal phase and prognostic evaluation, understanding the patient in question and mastering ethical and legal issues, there is a greater likelihood that complex decisions will be more assertive.[7] When actions in favor of survival become unlikely, given the prognosis imposed by therapeutic limitations or advanced disease stage, non-maleficence and respect for autonomy, which are also *prima facie* principles, take on greater relevance in the decision. With the individualization of care planning, at a time when comfort and dignity become the main focuses of care, therapies that had meaning and scientific evidence in earlier stages of the disease begin to lose value.[1,2,4,8,9]

Deciding not to refer patients with terminal HF to intensive care, not to indicate renal replacement therapy or vasopressors, not to proceed with cardiac resuscitation maneuvers or mechanical ventilation, to turn off the shock function on implantable defibrillators, to restrict antimicrobials or artificial diets, or to discontinue antiplatelet agents and statins are examples of legitimate and justifiable medical acts, applied to clinical practice in the condition of terminal and irreversible diseases, provided that the entire deliberation process has been respected.[2,4,5,8-10] It is essential for communication to be clear between all those involved, so that they are aware of the reasons and motivations that lead to the choice of a determined therapeutic plan, and this must be properly recorded in the medical records.[4,5,9,10]

Knowledge regarding the principles of PC is, therefore, fundamental and of great value in aiding the terminal phase of HF, and it should be incorporated into routine clinical practice in cardiology.

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VA-ECMO in Cardiogenic Shock as a Bridge to Heart Transplantation

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Introduction

The use of venoarterial extracorporeal membrane oxygenation (VA-ECMO) in cardiogenic shock as a direct bridge to heart transplantation is highly controversial. Most hospitals only use VA-ECMO as a bridge to decision, recovery, or other long-lasting devices.[1-3]

We report a successful case of VA-ECMO as a bridge to urgent heart transplantation in a patient in INTERMACS I cardiogenic shock. There was complete recovery of tissue oxygen and renal and liver functions, allowing for heart transplant in a patient with overall improved organ functions. In selected cases, VA-ECMO is a relatively low-cost alternative to mechanical circulatory support that could be more easily implemented in Brazilian hospitals.

Case Report

A 55-year-old male patient with no known comorbidities developed cough, edema, and dyspnea with progressive worsening approximately 2 months earlier. There were no viral or infectious prodromes. The patient was initially treated for pneumonia in another hospital with piperacillin-tazobactam and clarithromycin. A respiratory viral panel including influenza, respiratory syncytial virus, and SARS-CoV-2 was negative for all viruses.

An echocardiogram was performed during hospitalization and showed significant dilation of the cardiac chambers (left ventricle: 70 mm; right ventricle: 36 mm) with marked increase of the left atrium (left atrial volume index of 74 cm^2). The absence of tricuspid regurgitation did not allow for measurement of pulmonary artery systolic pressure.

After 4 weeks of hospitalization, the patient's clinical condition continued to deteriorate despite heart failure treatment. He developed systemic and pulmonary congestion resistant to diuretics, progressive worsening of renal function, increased liver transaminases, hypotension, and clinical signs of low cardiac output. The patient was started on 10 mcg/kg/min dobutamine and referred to our hospital for evaluation by the heart transplant team.

Keywords

ECMO; Cardiogenic Shock; Transplant

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The patient arrived in our hospital in INTERMARCS II cardiogenic shock and sinus tachycardia, with a heart rate of 122. He also had low blood pressure, poor peripheral perfusion, anuria, and anasarca, requiring immediate continuous hemodialysis. The use of a Swan-Ganz catheter identified the following: cardiac index 1.4 L/min/m^2, PAP 32/23 mm Hg, PAOP 21, CVP 12, SVR 1,066 dynes/seconds/cm^5, and PVR 148 dynes/seconds/cm^5 (Figure 1).

An intra-aortic balloon pump (IABP) was inserted, but there was poor clinical response. The patient became severely hypotensive, with a reduced level of consciousness, progressive increases in lactate levels, and signs of liver dysfunction despite the use of 20 mcg/kg/min dobutamine, 0.1 mcg/kg/min norepinephrine, and 1:1 IABP support. Orotracheal intubation was required.

Due to the patient's deterioration to INTERMACS I cardiogenic shock, we implanted a temporary mechanical circulatory assist device (peripheral VA-ECMO via the femoral artery). After clinical stabilization, an evaluation protocol for heart transplantation was initiated. The IABP was maintained to prevent LV hyperdistention, whereas continuous hemodialysis was maintained with the goal of aggressive negative fluid balance attainment (Figure 2).

After VA-ECMO implant, the patient progressed with rapid hemodynamic improvement and normalization of tissue perfusion and lactate levels and was extubated after 48 hours. There was also improvement of renal function, with discontinuation of renal replacement therapy after 7 days, and normalization of liver function and transaminases.

After 1 week on circulatory support, the patient was placed on the heart transplant waiting list with a priority status. After 14 days, the patient underwent a heart transplant, but there was severe right ventricular dysfunction during VA-ECMO weaning, thus we decided to maintain VA-ECMO until right ventricular function was recovered. On postoperative day 4, right ventricular function was completely stabilized, and the patient was successfully weaned off VA-ECMO. The patient was discharged from the intensive care unit on postoperative day 9 and from the hospital on postoperative 18 in good general condition for outpatient follow-up.

Pathological examination of the surgical specimen showed signs of lymphocytic myocarditis, dilated heart disease, and arterial thrombosis. Immunohistochemistry and viral investigation were not performed due to limitations in the pathology service.

Discussion

Despite several advances in recent years, cardiogenic shock remains a major challenge in critical care cardiology, with very high mortality rates and a scarcity of well-structured hospitals that can provide adequate care for this patient population.[4-6]

According to the Acute Heart Failure Guidelines, the use of mechanical circulatory assist devices is indicated in patients

Case Report

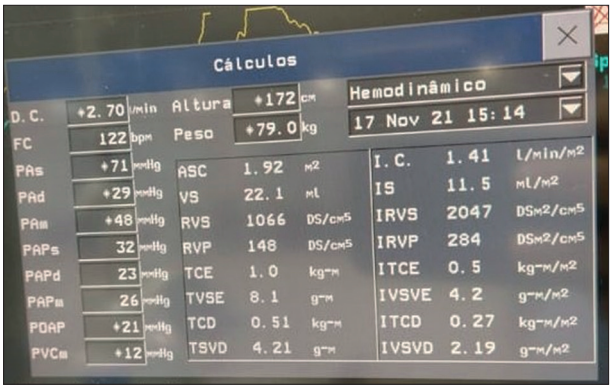

Figure 1 – *Swan-Ganz measurements immediately after patient admission.*

with INTERMACS II or I cardiogenic shock.[4,6] However, these devices are not available in most Brazilian hospitals.

Peripheral VA-ECMO is a short-term, relatively low-cost, easy-to-implement circulatory assist device. Considering how difficult it often is to provide medium-term devices for patients on the heart transplant waiting list, especially those with severe biventricular dysfunction who progress to INTERMACS II or I cardiogenic shock, peripheral VA-ECMO may be a viable and cost-effective alternative in selected cases and in hospitals with reduced waiting time for a heart transplant.[1]

In this case report, we showed that, although controversial, VA-ECMO can be successfully used as a direct bridge to transplantation in some hospitals in selected cases.[1-3] Author

Figure 2 – *Hemodynamic improvement after intra-aortic balloon pump and venoarterial extracorporeal membrane oxygenation implantation.*

Contributions

Conception and design of the research, Acquisition of data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Chaves RB, Ulhoa MB, Araújo MCCL; Analysis and interpretation of the data and Statistical analysis: Chaves RB, Ulhoa MB.

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Incessant Malignant Ventricular Arrhythmia in a Patient with Advanced Heart Failure: A Case Report

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Introduction

The occurrence of refractory ventricular arrhythmia in patients with heart failure (HF) is a therapeutic dilemma.[1] These patients, especially in the presence of advanced disease, may experience multiple triggering factors for ventricular arrhythmia, such as myocardial fibrosis, ischemia, hydroelectrolytic disorders, ventricular distention, the arrhythmogenic potential of drugs, and the underlying disease itself.[1–3] Conversely, sustained ventricular arrhythmias cause hemodynamic compromise, resulting in further ischemia and ventricular distension.[1] This can lead to a vicious cycle of hemodynamic worsening with an increasingly arrhythmogenic myocardium.[1] Usual treatment consists of direct current (DC) cardioversion, antiarrhythmic drugs, myocardial revascularization (when indicated), and catheter ablation. However, invasive procedures are always considered high risk in such cases. We report the case of a patient with incessant ventricular arrhythmia resistant to several types of treatment.

Case Report

A 53-year-old male patient was transferred to our hospital due to an episode of sustained ventricular tachycardia (VT) that had occurred 48 hours earlier and was initially treated in other hospital. The patient had been on the heart transplant waiting list for 2 years due to the presence of idiopathic dilated cardiomyopathy with a left ventricular ejection fraction (LVEF) of 26%. He underwent VT ablation 5 years ago and cardiac resynchronization therapy (CRT) device implantation 3 years ago. There was also a history of chronic atrial fibrillation (anticoagulated), hypertension, depression, and hypothyroidism. Before the event, the patient was in New York Heart Association (NYHA) functional class II. Immediately after admission, he had another episode of sustained VT with hemodynamic instability and underwent DC cardioversion. After the episode, the patient developed signs of low cardiac output and was started on dobutamine, sodium nitroprusside, and intravenous amiodarone. Electronic evaluation of the CRT device showed several episodes of sustained VT in the last 24 hours. Hydroelectrolytic disorders were also recognized and immediately corrected. Increased free T4 (2.04 ng/dL, reference value: 0.89-1.76 ng/dL) and normal thyrotropin levels were also identified. Amiodarone-induced thyroiditis was suspected and empirical treatment with corticosteroids was started. However, a new episode of sustained VT requiring DC cardioversion occurred in the next morning. During the afternoon, the patient had an episode of cardiac arrest with polymorphic VT rhythm (*torsades de pointes*) and underwent electrical defibrillation. Electrocardiogram showed a prolonged QT interval, thus the infused dobutamine dose was reduced and amiodarone infusion was changed to lidocaine. The patient had another episode of sustained VT requiring DC cardioversion on the following day, and amiodarone infusion was subsequently reinstated. An episode of supraventricular tachycardia occurred on the same day and rapidly progressed to acute pulmonary edema. Due to refractory ventricular arrhythmias and acute decompensated HF, the patient underwent intra-aortic balloon pumping (IABP) implantation on the following day (day 4 of hospitalization). After IABP, the patient was weaned off dobutamine and there was no recurrence of ventricular arrhythmias. However, the patient developed nosocomial pneumonia and required antibiotic therapy for 14 days (piperacillin-tazobactam, meropenem, and teicoplanin). Because the patient was dependent on mechanical circulatory support and the possibility of further VT ablation was excluded, his status on the transplant waiting list was reactivated and updated to urgent. On day 63 after IABP without arrhythmia recurrence, the patient underwent a heart transplant.

Discussion

The case described here shows the multifactorial mechanism of ventricular arrhythmia genesis in a patient with advanced HF. In addition to the arrhythmogenic substrate (idiopathic dilated cardiomyopathy which needed previous ablation), hydroelectrolytic disorders and amiodarone-induced thyroidopathy may have contributed to the onset of the condition. This leads to the vicious cycle of hemodynamic deterioration with perpetuation of the arrhythmic condition. The difficulty in clinical management is also evident: inotropic agents have the potential for hemodynamic stabilization at the expense of a proarrhythmic effect. Conversely, the occurrence of *torsades de pointes* due to QT prolongation exemplifies a known fact that antiarrhythmic agents may also cause proarrhythmic effects, although by different mechanisms. This issue was

Keywords

Heart Failure; Intra-Aortic Balloon Pumping; Tachycardia, Ventricular.

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resolved by using mechanical circulatory support through IABP for hemodynamic stabilization and ventricular arrhythmia control. IABP also allowed for dobutamine weaning, resulting in the removal of a proarrhythmic factor.

Some case reports and series describing the use of IABP with the primary objective of controlling ventricular arrhythmias have been published.[1,4–7] In one of the first cases described, IABP was able to control ventricular arrhythmias in the setting of post-infarction in a patient who received more than 120 electrical cardioversions.[7] Other reports have also demonstrated the use of IABP for refractory ventricular arrhythmia control in patients without coronary artery disease.[1,4,6] In a case series of 12 patients, IABP was effective in controlling ventricular arrhythmias in 18 cases.[1] Of these, 5 underwent a heart transplant, 12 became stable and were weaned off IAB support, and 3 were refractory to IABP.[1] One patient was diagnosed with cardiac amyloidosis and associated systemic involvement and was considered unsuitable for transplantation.[1] In this study, coronary artery disease (acute and chronic) was evident in 18 of 21 patients and all had ventricular dysfunction, with a mean LVEF of 29%.[1] Nineteen patients were discharged from hospital and followed up for 25.7 months, with a survival rate of 95%.[1]

Several mechanisms have been proposed to explain how IABP helps to control ventricular arrhythmias.[1,5] The primary mechanism is the increase in coronary perfusion by active insufflation during diastole, which may reduce ischemia as a precipitating factor in ventricular arrhythmia genesis.[5] However, IABP may also be effective in patients with no evidence of coronary artery disease.[4,6] In such cases, the support provided by IABP may allow sufficient time for anti-arrhythmic drugs to work and interrupt the vicious cycle of hemodynamic deterioration and arrhythmogenesis.[1] Finally, dilation and increased tension in the left ventricular wall have been shown to cause electrophysiological changes in the myocardium, creating an arrhythmogenic substrate.[1,3,8] This may be a particularly important mechanism in patients with advanced HF. In this case, IABP acts directly by reducing ventricular afterload, consequently decreasing tension in the left ventricular wall.[1,5]

The case described here emphasizes the complexity of managing incessant ventricular arrhythmias in a patient with advanced HF. It also shows the role of IABP in hemodynamic stabilization, interruption of the cycle of progressive arrhythmogenesis, and as a bridge to heart transplantation.

Author Contributions

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Case Report

Management of Patients with Advanced Heart Failure According to Hemodynamic Parameters

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Introduction

Heart failure (HF) is characterized by progressive functional or structural worsening of the myocardium. Despite significant therapeutic advances that have improved survival and quality of life, HF still has high morbidity and mortality rates. Patients with HF may progress with refractory disease, whose gold standard treatment is heart transplantation (HT).[1,2]

The assessment of pulmonary hemodynamics is indicated for HT candidates. The presence of fixed pulmonary hypertension (PH) is a contraindication for HT because it promotes right ventricular (RV) dysfunction in the graft, reducing post-HT survival. In addition, the assessment of hemodynamic parameters helps in bedside therapeutic management, including in the setting of PH, favoring HT indication.[1,2] We report a successful case of optimal bedside therapy guided by invasive hemodynamic parameters.

Case report

A 58-year-old man with diabetes, stage D HF secondary to idiopathic dilated cardiomyopathy, and recurrent hospitalizations despite optimal drug therapy was referred for outpatient HT evaluation, with evidence of reversible PH after vasodilator testing (Table 1). The patient required hospitalization due to disease progression, pulmonary congestion, and peripheral hypoperfusion. Echocardiogram showed a left ventricular ejection fraction of 25% with diffuse hypokinesia, left ventricular (LV) diastolic and systolic diameters of 68 x 64 mm, moderate RV hypokinesia (S' wave 6 cm/s; TAPSE 26 mm), and a pulmonary artery systolic pressure (PASP) of 55 mm Hg, with severe tricuspid regurgitation. Due to clinical severity, the patient was started on intravenous inotropic, diuretic, and vasodilator support. The patient underwent a new hemodynamic assessment with the use of a pulmonary artery catheter (PAC) in an intensive care setting, with evidence of PH (Table 2). Since the patient's clinical condition was a contraindication for HT, the implant of a long-term ventricular assist device (VAD) was considered but not conducted due to social reasons. The patient was placed on the HT waiting list for heterotopic transplantation, and therapeutic support was optimized with a combination of milrinone, circulatory support via intra-aortic balloon pumping (IABP), and inhaled nitric oxide.

After 4 months on the waiting list, a new invasive evaluation with a PAC identified significant reduction in pulmonary pressures (Table 2), supporting orthotopic transplantation. The patient underwent an HT 5 months after hospitalization with no complications.

Discussion

The case reported here illustrates the impact of optimal therapy on the improvement of hemodynamic parameters, assessed by serial invasive evaluation with a PAC, in a patient with decompensated HF and cardiogenic shock. PH associated with heart disease, called postcapillary pulmonary hypertension, is characterized by elevation in filling pressures, mean pulmonary blood pressure (mPBP), and pulmonary capillary wedge pressure (PCWP) and constitutes a marker of disease progression in HF with reduced ejection fraction. PH is characterized by an mPBP > 20 mm Hg and a pulmonary vascular resistance (PVR) ≥ 3 Wood;[3,4] if PCWP > 15 mm Hg, PH is considered postcapillary. In this case, the increase in pulmonary artery pressure occurs by retrograde transmission of increased hydrostatic pressure from the left atrium into the pulmonary veins and capillaries.[5]

Elevated central venous pressure resistant to drug therapy may be considered a contraindication for HT. In patients with evidence of PH, testing with intravenous vasodilators should be performed to demonstrate whether PH is reversible. Continuous 24-hour to 48-hour monitoring with full therapy consisting of diuretics, inotropes, and intravenous and inhaled vasodilators should be encouraged in cases of irreversible PH.[6]

Long-term VADs are a therapeutic option in patients that cannot undergo an HT as they may promote LV decompression, reduction in filling pressures, and, consequently, reduction in pulmonary pressures.[7] VAD indication in Brazil in the setting of public health is limited due to socioeconomic conditions. In this case, heterotopic transplantation may be an option with limited results.

In heterotopic HT, the graft is connected to the native heart, which is maintained in the patient's rib cage, and acts as a biological LVAD. This procedure may be considered in patients with obesity or increased PVR. However, the feasibility of the procedure remains uncertain.

Improvement in LV systolic volume causes increased RV preload, which may result in poor RV performance and compliance. Therefore, the presence of previous RV dysfunction

Keywords

Management; Advanced Heart Failure; Hemodynamics

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Table 1 – Right heart catheterization before hospitalization

	Before vasodilator testing	After vasodilator testing
CO	2.8 L/min	2.8 L/min
CVP	12 mm Hg	5 mm Hg
PBP	74 x 30 mm Hg	26 x 11 mm Hg
mPBP	44 mm Hg	17 mm Hg
PCWP	25 mm Hg	5 mm Hg
TPG	19	12
DPG	5 mm Hg	6 mm Hg
PVR	6.7 Wood	4.2 Wood
PAPP	44 mm Hg	15 mm Hg
PAPi	3.6	3.0

CO: cardiac output; CVP: central venous pressure; DPG: diastolic pulmonary gradient; mPBP: mean pulmonary blood pressure; PAPi: pulmonary artery pulsatility index; PAPP: pulmonary arterial pulse pressure; PBP: pulmonary blood pressure – diastolic and systolic; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; TPG: transpulmonary pressure gradient.

Table 2 – Progression of hemodynamic parameters during hospitalization and after 4 months of optimal guided therapy

	During hospitalization	After 4 months
CO	5.4 L/min	6.6 L/min
CVP	5 mm Hg	21 mm Hg
PBP	50 x 22 mm Hg	58 x 33 mm Hg
mPBP	30 mm Hg	41 mm Hg
PCWP	9 mm Hg	32 mm Hg
TPG	21	9
DPG	13 mm Hg	1 mm Hg
PVR	3.8 Wood	1.3 Wood
PAPP	28 mm Hg	25 mm Hg
PAPi	5.6	1.1

CO: cardiac output; CVP: central venous pressure; DPG: diastolic pulmonary gradient; mPBP: mean pulmonary blood pressure; PAPi: pulmonary artery pulsatility index; PAPP: pulmonary arterial pulse pressure; PBP: pulmonary blood pressure – diastolic and systolic; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; TPG: transpulmonary pressure gradient.

is a contraindication for both VAD implantation and heterotopic HT, which were not good options for our patient.[8]

Optimal therapy with parenteral and inhaled vasodilators promoted PASP and PCWP reduction, resulting in a decreased transpulmonary pressure gradient and increased cardiac output by reductions in RV afterload, LV preload, and, consequently, PVR. Hypervolemia reduction, on the other hand, promoted reduction in pulmonary pressures.[1] Dobutamine acts on the beta-1 adrenergic receptor increasing calcium influx and resulting in myocardial contractility. Milrinone is a phosphodiesterase-3 inhibitor that is involved in cyclic guanosine monophosphate degradation, leading to an increase in calcium influx and inotropism.[9] Due to phosphodiesterase inhibition, pulmonary vasodilation with a consequent reduction in PH and optimal RV afterload were observed.[7] The mechanism of action of IABP is aortic counterpulsation, aortic root diastolic pressure augmentation, afterload reduction, and, consequently, CO increase.[7,9]

The use of mechanical circulatory support should be considered in patients with a potentially reversible disease and pharmacologically irreversible PH. According to the International Society for Heart and Lung Transplantation, the use of mechanical circulatory support in the management of patients with HP is a class IIB recommendation.[6.]

The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) reported adverse events associated with the use of PACs, such as arrhythmias, sepsis, pulmonary artery perforation or rupture, and even death. Therefore, the risks of PACs outweigh the benefits, leading several guidelines to not indicate pulmonary artery catheterization.[10] However, if used with caution in combination with risk minimization techniques, PACs could help optimize patient support, as occurred in the case reported here.

Conclusion

The advanced stages of HF are challenging from a therapeutic perspective, especially when deciding on the optimal destination therapy. PH is a marker of advanced HF, and the use of invasive monitoring may be useful to optimize bedside therapy and to adjust hemodynamic parameters that allow for HT.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Statistical analysis, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Aragão CAS, Costa DM, Ávila MS.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

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Intermittent Inotrope Infusion Associated with Peritoneal Dialysis for Management of Advanced Heart Failure Secondary to Cardiac Amyloidosis

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Introduction

Advanced heart failure (HF) represents a therapeutic challenge, characterized by quality of life deterioration and multiple hospitalizations. When HF is secondary to cardiac amyloidosis, the recommended treatment for HF may have an unfavorable clinical course. In advanced HF cases, the clinical scenario is even more challenging.

Clinical Case

AOV, a 73-year-old, male patient with a 4-year HF onset along with 2 hospitalizations in the last year and a pacemaker due to atrioventricular block, was referred to a tertiary hospital due to worsening dyspnea within the last week. He was admitted with limiting dyspnea, orthopnea, lower limb edema, and abdominal discomfort. The patient was characterized as decompensated HF, with hemodynamic profile B, along with high-rate atrial fibrillation (AF). Initial exams showed NT-proBNP of 20,669 pg/mL, renal failure (creatinine: 2.1 mg/dL, urea: 68 mg/dL), electrocardiogram with AF, low QRS voltage, and advanced right bundle branch block. Chest radiography showed increased cardiac area, pulmonary congestion, and right pleural effusion. The echocardiogram revealed increased left atrial volume (43 ml/m^2); septum of 24 mm and posterior wall of 23 mm, and ejection fraction was 26% with grade III diastolic dysfunction (E/A = 3.1; E/e' = 14). Due to red flags, after light chain exclusion, the diagnosis of hereditary transthyretin amyloid cardiomyopathy was confirmed (pyrophosphate myocardial scintigraphy with grade 3 uptake and genetic testing showed the Val122Ie genotype). Shortly after discharge and a brief outpatient follow-up, the patient was readmitted to another service for 20 days, but this time due to a decompensated HF profile C, requiring dobutamine and high-doses of intravenous furosemide. Even though the patient was initially considered for heart transplantation, the procedure was discouraged due to comorbidities, age, and social profile. Although he was not eligible for transplantation, the patient presented a challenging scenario, namely, New York Heart Association functional class IV, INTERMACS profile 5, which brought up a discussion on palliative care. In addition to this severe clinical profile, after 2 recent subsequent hospitalizations, the patient required another hospitalization with inotropes that were weaned with levosimendan administration, and cardiorenal syndrome with refractory systemic congestion was managed with peritoneal dialysis. In spite of those treatments, the patient presented another HF decompensation with low output and arterial hypotension, requiring dobutamine infusion and levosimendan administration. Therefore, in order to avoid subsequent episodes of other severe hospitalizations, an outpatient inotropic infusion program was proposed, with the main goal of improving quality of life. Biweekly, the patient received a 6-hour infusion of levosimendan, on day hospital basis, with good safety profile. After this regimen was adopted, the patient did not have any new hospitalizations, and he reported significant improvements in appetite, symptoms, and nutritional aspects, as well as the return to usual activities, especially regarding social life. The patient remained in this biweekly outpatient inotropic infusion program for approximately 1 year without any major complications, until the outcome of sudden death at home.

Discussion

In this report, the HF-associated morbidity was well characterized, which is even more challenging in the scenario of cardiac amyloidosis. For these patients, quality of life should be prioritized throughout the patients' journey, as hospitalization is one of the main indicators of this worsening quality of life.[1]

The approach to advanced HF regarding control of congestive symptoms and management of reduced tissue perfusion has been increasingly discussed, including guidelines supporting both peritoneal dialysis and inotropic infusion as valid strategies for quality of life improvement.[2] A recent meta-analysis of 66 studies concluded that, although there is little evidence for its use in palliative care, inotropic infusion therapy can improve patients' functional capacity without worsening survival.[3]

Moreover, the use of levosimendan, which is an inotrope with hemodynamic (pulmonary and systemic) effects, may have a suitable application for patients, as a periodic outpatient infusion program. In previous studies, repeated use at fortnightly intervals was shown to be safe as well as effective in advanced HF cases, relieving symptoms, reducing hospitalizations, and improving quality of life.[4] In one of

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these studies, intermittent infusion of levosimendan showed a significant reduction in acute decompensation and death in the first and third month in the intervention group.[5] In another study, the use of the drug as a 6-hour infusion (0.2 mcg/kg/min), without bolus, every 2 weeks for 12 weeks, was associated with a lower hospitalization risk with similar adverse events when compared to placebo and, importantly, with savings for the health system.[6,7] Furthermore, repeated or intermittent infusion for patients with advanced HF was associated with a reduction in 3-month rehospitalizations; this strategy was considered safe and well tolerated in patients with HF who required inotropes, with remarkable improvements in quality of life and functional capacity.[8] Similarly, in another case report of a patient with wild-type transthyretin cardiac amyloidosis, an inotropic home infusion program was performed for 2 years, with positive impact on quality of life. In this case, the inotropic support strategy was a continuous home infusion of milrinone.[9]

In the reported case, the combined approach of peritoneal dialysis associated with outpatient inotropic infusion led to a significant improvement in the patient's quality of life, without new hospitalizations or safety concerns during the infusions.

Conclusion

The palliative approach to a patient with advanced HF due to cardiac amyloidosis is a therapeutic challenge. In this case, limiting symptoms and multiple hospitalizations were clearly linked to quality of life deterioration. The intermittent outpatient levosimendan infusion along with peritoneal dialysis was a safe and effective strategy, with a significant improvement in the quality of life and a reduction in the risk of hospitalizations without associated adverse events.

Author Contributions

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