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Invited Review Article

Cardiac replacement therapy: Critical issues and future perspectives of heart transplantation and artificial heart

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ABSTRACT

Diagnostic and therapeutic advances in the cardiovascular field have caused a progressive reduction in mortality from acute causes, with an ever-increasing chronicity of cardiovascular pathologies. In recent years, mechanical supports have played a fundamental role, allowing the patient to be stabilized in the most critical phase of acute heart failure (AHF) and acting as a "bridge" for definitive therapies. Heart transplantation (HTx) is the gold-standard treatment for end-stage HF, but it is burdened by a series of critical issues that limit its use, first of all the shortage of grafts. It also requires the patient to take immunosuppressive therapy for life, which exposes him to a greater risk of infectious and oncological diseases. For these reasons, in the last years, mechanical supports are increasingly used as "destination therapy", alternatively to HTx. However, also mechanical supports are not free from critical issues that limit their use. In this review we aim to analyze critical issues and future perspectives of advanced HF therapies.

Introduction

Heart failure (HF) is a clinical syndrome with signs and symptoms derived from the impaired cardiac function (both systolic and/or diastolic) which is no longer able to satisfy the metabolic needs of the body. It affects 64 million people worldwide,[1] and it is burden by high rate of mortality. It represents the final pathway of several cardiovascular disorders, mainly ischemic, but also cardiomyopathies, myocarditis and valvular diseases.[2-4]

In the end stages of HF symptoms (mainly dyspnea) are persistent, the quality of life (QoL) is compromised and hospitalizations are frequent. Medical therapy is no longer able to counteract the pathological mechanisms typical of HF (sympathetic and Renin-Angiotensin-Aldosterone System (RAAS) hyperactivation, fluid retention), and the prognosis is very bad.[5,6] Even device therapy (i.e. cardiac resynchronization therapy (CRT) or cardiac contractility modulation therapy (CCM)) is ineffective at these stages.[7,8]

Heart transplantation (HTx) is the best chance for these patients to improve survival and QoL,[9] although it's a very complex intervention with relevant risks and potential hard complications peri, postprocedural and for the rest of the patient's life. Although the numerous issues, HTx remains the gold standard treatment for end-stage HF, with a recommendation in class I provided in the most recent ESC guidelines.[10] Unfortunately, in addition to the technical issues related to the surgery, there are many issues also in the

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planning phase, related to the lack of donors and to the characteristics of recipients, which limit the applicability of HTx. For this reason, in recent years the use of mechanical circulatory support (MCS) devices has gained ground, both as a bridge to transplant or to recovery and as destination therapy. The artificial heart can be "partial" assisting only one ventricle, or "total" assisting the both ones. It has the advantage of bypassing the problem of lack of donors and avoiding immunosuppression in recipients, but it is still burdened by other critical issues that do not allow its widespread use as hoped. Therefore, patients who are not candidates for either HTx or artificial heart are referred to palliative care.

Heart transplantation

HTx is the gold standard treatment for end-stage HF: its most common indications are highly symptomatic HF, cardiogenic shock, uncontrolled ventricular arrhythmias and restrictive cardiomyopathies. In such patients with a very bad prognosis, it potentially provides a good life expectancy. Since the first human heart transplant was performed in 1967,[11] giant strides have been made both in surgical techniques and immunosuppressive therapies, that have led to the survival rate in recipients steadily increasing. Post-HTx mortality is high especially in the perioperative period, with a mortality rate of 15-20% in the first year.[12] Once this first critical phase has been overcome, the mortality rate drops to around 4% per year for the next 18 years, with a survival rate of 50% at 10 years and 15% at 20 years. Nowadays a heart transplant patient lives on average >15 years.[13] However, the use of this promising treatment is unfortunately limited by a number of factors, which we analyze below.

Donors/recipients ratio

First of all, there are far fewer heart grafts available than would be needed. In the last decades the number of brain deaths among young, potentially donor people have reduced in Europe, mainly due to the reduction in deaths from road accidents.[14] On the other hand, the number of patients on the waiting list has increased, in part due to the utilization of mechanical circulatory support (MCS) devices, such as intra-aortic balloon pump (IABP), ventricular assist devices (VAD) and extracorporeal membrane oxygenation (ECMO), that have reduced the acute mortality rate, by acting as "bridge to transplant".[15]

In Italy, from 2002 to 2021, 8933 registrations were placed on the waiting list for heart transplant,[16] 810 (9,5%) for pediatric patients and 7748 (90,5%) for adults, mainly males (79%). The most frequent diagnosis was Dilated Cardiomyopathy (DCM, 46%), followed by coronaropathy (33%). In 2021 only 226 patients in Italy received a heart transplant, of the 920 on the waiting list (25%), and 67 patients died while waiting (7%). The average waiting time for a heart transplant was of 13 months. From these data the need to expand the donor cohort as much as possible is evident and urgent. Consent to donation is collected differently in each country. In Italy, the principle of explicit consent or dissent applies.[17] The use of the electronic identity card throughout the national territory has certainly represented an advantage in this sense, as in conjunction with the renewal of this document the citizen has the possibility of expressing his will - be it positive or negative - on the topic of organ donation, and this will be then immediately transmitted electronically to the Transplant Information System. If the deceased has not left any testimony regarding his desire to donate, then it will be

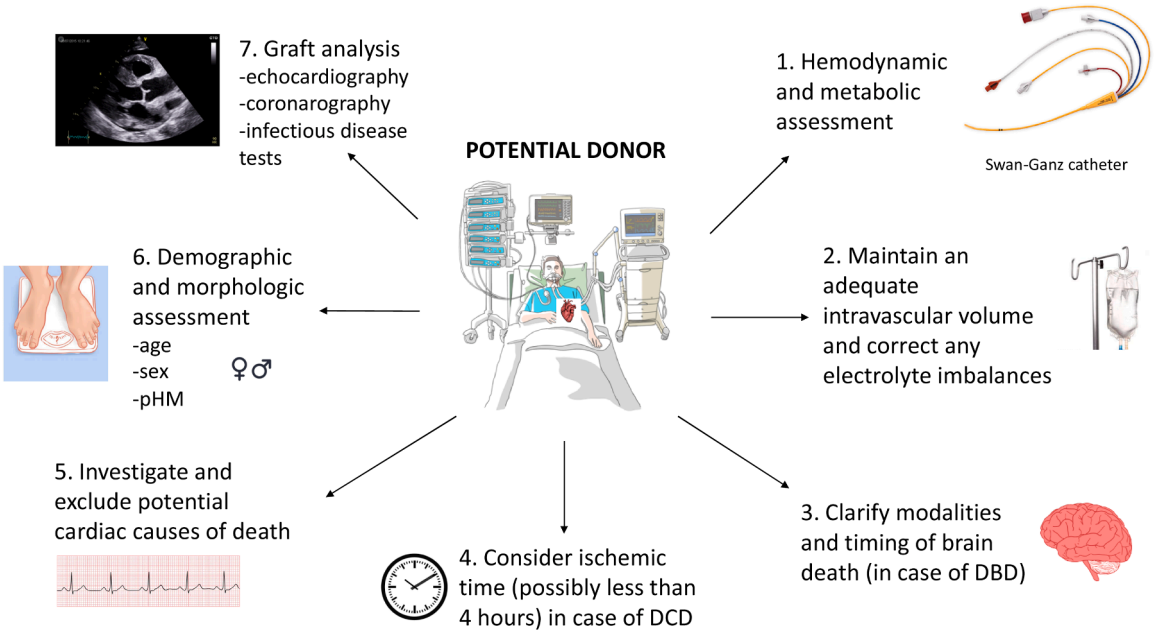

Fig. 1. Donor selection. A rapid but comprehensive evaluation of a potential donor should be performed as soon as possible. DBD: donation after brain death; DCD: donation after circulatory death; pHM: predicted heart mass.

up to the family members to decide to give consent. Therefore, it is essential to establish programs aimed at raising awareness among the population on the topic.

Donor selection

Once a potential donor has been identified, following a brain death, it is necessary to carry out a rapid but comprehensive assessment of the hemodynamic and metabolic conditions of the donor, taking into account the modalities and timing of brain death[18] (Fig. 1). Ideally the donor should remain hemodynamically stable with only low doses of norepinephrine (e.g., ≤0.1 μg/kg/min); in case of need for additional inotropes and/or vasopressors, the placement of a Swan-Ganz catheter should be considered, to precisely guide the medical therapy and therefore to increase the chances of using that graft.[19,20] Furthermore, it is essential to maintain an adequate intravascular volume and correct any electrolyte imbalances.[21] Modalities and timing of brain death are relevant to define eligibility for donation. For example, in case of carbon monoxide poisoning it is advisable to investigate carboxyhemoglobin levels, as well as cardiac troponin levels and any ischemic changes in the ECG, or ventricular dysfunction signs. If carboxyhemoglobin levels >40% or alterations of the other findings mentioned above are found, the subject ceases to be a good candidate for donation.[22,23] Subjects with explosive brain death (defined as traumatic brain death resulting from a gunshot wound, accidental head trauma, or severe intracranial hemorrhage[24]) may be considered potential donors for heart transplant, but it must be taken into account that a reduced long-term survival of recipients has been documented in these cases, likely due to a cardiac allograft vasculopathy-related mechanism.[24,25] There is a limited number of hearts available from donation after brain death (DBD). In order to meet the increased demand for grafts, in recent years HTx using donation after circulatory death (DCD) allografts has become increasingly common.[26] Some studies have shown that transplantation with a donor heart that had been reanimated and assessed with the use of extracorporeal non-ischemic perfusion after circulatory death, is safe and non-inferior to transplantation from a brain-dead donor heart.[26,27] Clearly, in case of unexplained cause of death, it is appropriate to investigate and exclude potential cardiac causes of death (i.e. hypertrophic cardiomyopathy (HCM), long-QT syndrome, Brugada syndrome, coronary anomalies), before considering heart transplant. A short ischemic time (possibly <4 hours) is important as well.[28]

After these initial evaluations, it is necessary to analyze the demographic and morphological data of the donor to find the perfect match with the recipient. Although there is currently no defined upper age limit for donors, the use of young donor hearts, possibly under the age of 45, is desirable and recommended.[29-33] Older donor hearts may be considered in elderly or highly sensitized recipients who would be less likely to be transplanted.[34,35] The "ADONHERS" protocol has been created to decrease shortage of donor hearts through the evaluation and possible use of hearts collected from donors over the age of 55 or under the age of 55 with cardiovascular risk factors. Recent data have shown no difference in survival of recipients transplanted with marginal donor (MD) hearts selected by dipyridamole stress echocardiography, compared to acceptable donor hearts.[36]

Another important topic is the match between donor and recipient size. Gender is important in itself but mainly because it is related to size.[37] It is quite common and safe to transplant a woman's heart into a thin male. What matters is that predicted heart mass (pHM) discrepancy between donor and recipient should not exceed 30%.[38] Male adults on the waiting list with a high body mass index (BMI) are less likely to be transplanted, due to the shortage of hearts from size-matched donors. The situation is even more problematic in case of pulmonary hypertension (PH), which could precipitate right cardiac dysfunction of the donor allograft. In these cases, choosing a larger donor heart may allow for better graft fit.[39]

The potential graft must be carefully analyzed, excluding the presence of pathological characteristics that could compromise the outcome in the recipient.[18] The donor heart is then subjected to a series of invasive and non-invasive tests (echocardiography, coronarography, infectious disease tests) aimed at proving its suitability. The ideal graft has no morphological defects (i.e. left ventricle hypertrophy (LVH), valvulopathies), is free from coronary atherosclerosis and has no infectious findings. The debate about using only optimal donors or broadening the organ acceptability criteria is long-standing but today more relevant than ever.[40] It is actually possible to transplant even imperfect organs, for example by performing Coronary Artery Bypass Graft (CABG) at the same time as the transplant in case of critical coronary atherosclerosis[41] or setting up antimicrobial therapy in case of latent infections. Clearly this approach allows us to increase the number of transplants, despite a risk that must be taken into account.

Screening of recipients

The evident discrepancy between the number of donors and recipients requires careful selection of the latter. Since not a single graft can go to waste, it is important to identify the patients who can most benefit from the transplant in terms of survival and QoL. Measures to identify patients eligible for HTx include:

- clinical indicators (i.e. previous or ongoing requirement for inotropes, >1 hospitalization for HF in the last 12 months, persisting fluid overload or NYHA class III or IV);
- HF prognosis score such as Seattle Heart Failure Model or The Heart Failure Survival Score;
- cardiopulmonary exercise test (CPET) with its parameters strongly prognostic, supporting transplant listing: maximal oxygen consumption (peak VO2) ≤ 12 ml/kg/min with respiratory exchange ratio (RER) > 1,05 in patients on beta-blocker, or peak VO2 ≤ 14 ml/kg/min with RER > 1,05 in patients off beta-blocker; VE/VCO2 slope > 35 especially if RER < 1,05; peak VO2 ≤ 50% predicted in women or in patients ≤ 50 years, are.[41]

Of importance, evaluation for HTx is recommended in patients aged ≤ 70, based on the assessment of comorbidities without

specific attention to age, while in patients over 70 years of age HTx may be considered in selected patients depending on comorbidities and functional status.[42]

Therefore, as soon as the therapeutic possibility of HTx is considered, it is advisable to subject the patient to a series of investigations aimed at confirming or rejecting his candidacy (Table 1).

- First of all, it is important to investigate if the patient carries antibodies directed against human leukocyte antigens (HLA). HLA are proteins present on the membrane of all cells in the body, except red blood cells.[43] Exposure to transfusions, infections, pregnancies, abortions and previous organ and/or tissue transplants can lead to the development of antibodies "anti-HLA", strongly involved in acute transplant rejection.[44,45] Anti-HLA antibodies screening is always performed before listing and while listed every 3 to 6 months or 3 weeks after a potentially sensitizing event. There are several HLA antibody screening methods, which are used pre-transplant to assess for sensitization and risk of antibody-mediated rejection (AMR), post-transplant for monitoring donor specific antibodies (DSA), and for monitoring the efficacy of desensitization therapy. Thus, a patient with anti-HLA "hyperimmunization", who is at increased risk for suboptimal outcome post-transplant, is defined as having a panel reactive antibody (PRA) or calculated PRA (cPRA) > 10%, that is a percentage of actual incompatible donors in the population who will express HLA antigen to which the recipient has relevant quantities of pre-formed antibodies.[42,46]
- Heart transplant surgery requires the use of extracorporeal circulation and is burdened by the risk of neurological complications, both ischemic and hemorrhagic.[47] Screening for carotid artery stenosis is recommended in candidates with history of stroke or neurologic sign or symptoms concerning cerebrovascular disease with carotid ultrasonography; screening for peripheral arterial disease with ankle-brachial index (ABI) is recommended in patients with symptoms, risk factors or atherosclerotic disease, while further testing may be required.[42] Moreover, a preventive evaluation of brain anatomy (by angio-CT) is often used in some Centers before surgery.
- HTx candidates with severe obstructive ventilatory defects or severely reduced diffusion capacity for carbon monoxide, have an increased risk of post-transplant mortality and the benefit of HTx is uncertain. Thus, it is essential to evaluate candidates with pulmonary function testing as well as chest computed tomography (CT).[42]
- It is then important to exclude that the patient has infectious or oncological diseases. After the transplant, indeed, the patient will have to undergo immunosuppressive therapies for the rest of his life. That could reveal latent pathologies, which would then be difficult to treat. Therefore, the finding of an active infection or a tumor clearly constitutes a contraindication to being placed on the transplant list. For this reason, when planning a HTx, it would be appropriate to subject the patient to blood tests to investigate the presence of infectious diseases and tumor markers.
- All candidates should be screened for latent or chronic infection (such as Human immunodeficiency viral (HIV), Tuberculosis (TB), hepatitis B and C virus, Epstein-Barr virus, Cytomegalovirus, Toxoplasma), in order to resolve or suppress active infection and to develop a post-HTx prophylaxis and surveillance plan.[42] In particular, guidelines strongly recommend systematic testing and treatment of latent tuberculosis infection (LTBI) for 6-9 months in patients preparing for organ transplantation, i.e. by Mantoux test[48]; while in patients with HIV, guidelines recommend a consultation with specialist to ensure stable anti-retroviral regimen and exclude opportunistic infections, detectable HIV RNA and CD4 counts < 200 cells/microliter.[42]
- Furthermore, all candidates should be screened for solid organ tumors. In particular, imaging tests (abdominal ultrasound (US), chest CT and in selected case positron emission tomography (PET), even if its role of screening is not clear yet[42,49]), dermatological examination,[50] prostate-specific antigen (PSA) for patients aged > 50 years (if not at higher risk), screening mammogram for women aged > 45 years, HPV test for women aged > 25 years, and fecal occult blood test (FOBT),[51] eventually followed by gastroscopy and colonoscopy, are recommended as well, both as screening before transplantation and as periodic follow-up after surgery.[42] Actually, transplant patients have a higher risk of developing oncological pathologies than the general population,

Table 1
Check list recommended before HTx in potential recipient. *based on the individual risk profile.; ABI: ankle-brachial index; BMI: body mass index; CPET: cardiopulmonary test; DXA: dual X-ray absorptiometry; EGDS: esophagogastroduodenoscopy; eval.: evaluation; FOBT: fecal occult blood test; HF: heart failure; HLA: human leukocyte antigens; HRCT: high resolution computed tomography; HTx: heart transplantation; PET: positron emission tomography; RHC: right heart catheterization; US: ultrasound.

Patient eligibility for HTx	Compatibility tests	Oncological screening	Infectious disease screening	Other tests*
• Clinical indicators (i.e. requirement for inotropes, >1 hospitalization for HF in the last 12 months, persisting fluid overload or NYHA class III/IV) • CPET • RHC • HF prognostic scores • Age	• Blood group (AB0) • Anti-HLA antibodies	• Blood tumor markers • Dermatological examination • FOBT • EGDS, gastroscopy and coloscopy • Pulmunary HRCT • Abdominal US • Angio-CT total body • PET • PSA • Mammogram • HPV test	• Viral serology • Mantoux test • PET • HIV RNA and CD4 counts	• Carotid US • ABI • Brain angio-CT • Psychosocial assessment • Nephrological eval. • Hepatological eval. • Diabetological eval. • BMI • DXA scan • Dental eval. • Rheumatological eval.

mainly lung and skin cancer, again due to the long-lasting immunosuppressive therapy.[52-54] Therefore, it is advisable to subject transplant patients to periodic tests to identify and treat any new diseases early. Furthermore, in candidates with a history of malignancy, a shared decision with treating oncologists and a specific period of observation before transplant listing are recommended: malignancy-related survival must not impact post-HTx survival and the risk of recurrence must be low based on tumor type and response to therapy; in this context, new technologies (such as circulating tumor DNA) should be use to provide information on the status of a patient's malignancy in certain settings.[42]

- Right heart catheterization (RHC) is recommended in all HTx candidates to assess the presence of PH (mean pulmonary artery pressure $>$ 20 mmHg) that might contribute to a reduction of post-transplant survival: pulmonary artery systolic pressure (PASP) $>$ 50 mmHg and either transpulmonary gradient (TPG) $\geq$ 15 or pulmonary vascular resistance (PVR) $\geq$ 3 Wood units are potentially prohibitive thresholds; in this case an acute vasodilator challenge (i.e. nitroprusside) should be administered to document an appropriate reductions of PVR $\leq$ 2,5 Wood unit and of TPG $\leq$ 12, maintaining a systolic arterial blood pressure $>$ 85 mmHg.[42,55] After listing, it is indicated to perform surveillance RHC every 3 or 6 months to optimize medical therapy, define candidacy urgency and indicate a potential need for MCS.[42]
- Psychosocial assessment of candidates for HTx is also strongly recommended.[56] The transplant journey is long and complicated. As mentioned above, beyond the discomfort of the surgery, the recipient must continually undergo periodic tests and take medications for the rest of his life.[57,58] It is essential that the patient is aware of what this process entails, that he is highly motivated and has a consistent social support network. A psychological support program should be set up before the transplant and continue afterwards.[59] Actually, the risk of developing psychiatric conditions, particularly depression, is high in heart transplant patients.[60] Moreover, 6 months of abstinence from tobacco smoking, excessive alcohol use and drug use are recommended, while a psychosocial screening tools should be used to identify any evidence that cognitive status may compromise patient adherence and post-transplant outcomes.[42]
- Last but not least, pre-transplant evaluations should also include: a comprehensive assessment of kidney function in order to differentiate a dysfunction that may reverse with the hemodynamic optimization after HTx from a dysfunction that will not improve post-HTx, with an estimated glomerular filtration rate (eGFR) $<$ 30 ml/min/1,73 m^2 which recommends an evaluation for simultaneous heart-kidney transplantation; a comprehensive assessment of liver function; a multidisciplinary collaborations for candidates with connective tissue disorders or sarcoidosis, in order to evaluate the severity of these diseases; a BMI assessment to achieve a value $<$ 35 kg/m^2; a careful assessment of diabetic control and end-organ damage; a dual X-ray absorptiometry (DXA) scan to assess osteoporosis risk; a dental evaluation.[42]

During the evaluation, it is essential to determine the patient's blood group. An identical blood type match is generally sought, although AB blood type recipients appear to have no significant difference in survival after identical, rather than compatible, AB0 matching. Furthermore, some studies suggest better survival of young recipients with blood group AB transplanted with a group 0 donor heart.[61] On the other side, as expected, group 0 patients tend to be less likely to be transplanted and appear to have a higher rate of adverse events while on the waiting list.[62]

Mechanical circulatory supports

All the critical issues mentioned above considerably limit the applicability of HTx. For this reason, in the last years, considerable efforts have been made to improve the applicability and diffusion of mechanical supports, as an alternative to transplantation. Actually, the use of MCS bypasses various issues related to transplantation, such as graft availability and donor-recipient compatibility. Patients difficult to transplant (i.e. blood group 0, hyperimmunized, extremely large size), or who cannot undergo adequate immunosuppressive therapy (i.e. due to infective or oncological diseases) can be referred to MCS, both as "bridge to transplantation" ,[15,63] while waiting for the right graft or trying to resolve the current contraindications to transplantation, and as "destination therapy" ,[64-66] to improve patients' QoL and survival if compared with optimal medical therapy[67] (Table 2).

MCS are of various types, depending on the cardiac chamber that needs to be supported. In most cases a left ventricular assist device (LVAD) is implanted,[68] less frequently a right ventricular assist device (RVAD) or a total artificial heart (TAH), assisting both the ventricles. In the beginning these devices were largely extracardiac, with high infectious risk and poor QoL, since the patient could not be discharged.[69] Over time, clinical and technological progress have allowed the development of increasingly smaller pumps, up to the

Table 2
Patient characteristics influencing eligibility for advanced therapies of HF. HF: heart failure; MCS: mechanical circulatory support.

Patient characteristics	Heart transplantation	MCS
Young	✓	✓
Elder	X	✓
Hyperimmunization	X	✓
Latent infectious	X	✓
Oncological disease	X	✓
Coagulation disorders	✓	X
Extremely large size	X	✓
Poor compliance	X	X

current intrapericardial devices.[70-72] However, the batteries are not yet small enough to be implantable, so they are extracorporeal and connected to the devices by external transmission lines. The management of these lines is delicate and requires adequate training of the patient and caregiver, to avoid infections.[73-75]

LVAD

Left ventricular assist device consists of a pump that sucks blood from the apex of left ventricle and ejects it into the ascending aorta. It represents a valid therapeutic option in cases of inotrope-dependent HF patients with systolic dysfunction of the left ventricle only,[76] even achieving a 2-year event-free survival rate with new generation devices,[77] with median survival exceeding 5 years.[78,79] Survival benefit is less clear in hemodynamically stable patients with advanced HF. The main condition that a LVAD implantation requires, is that the right ventricle must be structurally and functionally adequate. Actually, LVAD increases the circulating volume, which passes from the left sections to the right ones. If the right ventricle is unable to cope with this change in hemodynamics, the support system will fail.[80] An exhaustive analysis of RV function has to be performed, possibly using the most recent techniques, such as RV free wall strain (FWS), to establish the candidacy to LVAD implantation.[81-83] Regarding LV assessment, it is important to evaluate the end-diastolic dimension (EDD): some studies reported worse outcomes in case of small LV dimensions, that is EDD $<$ 60 mm,[84] with decreased overall survival and increased postoperative stroke rate. Also indexing the value of EDD for the body surface area (BSA): smaller preoperative LV EDD index ($<$ 33.5 mm/m2) was associated with worse outcomes.[85] Another important condition to LVAD implant, is the absence of relevant aortic calcifications, that could preclude the adequate insertion of the outflow cannula.[86] For this reason, it is appropriate to perform a preoperative angio-CT to evaluate thoracic aorta. Furthermore, it is important to investigate the presence and the severity of aortic regurgitation (AR), prior to LVAD implant. AR assessment should be performed by TTE, eventually integrated with TEE if no conclusive.[87] Patients with moderate to severe AR require surgical intervention: aortic repair or replacement may be considered either prior or at the time of LVAD implantation.[88] An AR that is at least moderate and not suitable for correction constitutes a contraindication to LVAD implantation.[87] Actually, severe AR is associated with worsening hemodynamics, increased hospitalizations, and decreased survival in LVAD patients.[88]

Behind the structural cardiac examination, a complete assessment of the patient must be performed to verify his suitability for the treatment. A significant percentage of patients who are candidates to LVAD implantation, underwent previous cardiac surgery, which poses technical obstacles to the procedure.[89] However, adapting the standard LVAD implant technique to the specific clinical case has been showed to lead to similar outcomes in terms of reoperations for bleeding, perioperative RVAD support or survival to transplant.[89,90] Screening for coagulative disorders is also important: positive laboratory tests for hypercoagulability without positive clinical histories seem to have no impact on survival and freedom from thromboembolic complications after LVAD implantation. Therefore, hypercoagulability alone should not serve as a contraindication to LVAD implantation.[91] On the contrary, clinically manifest hematological diseases, such as systemic lupus erythematosus (SLE), contraindicate LVAD implantation, since recurrent and diffuse spontaneous bleeding after the procedure were described in this court of patients.[92]

LVAD implantation could also be contraindicated in irreversible severe chronic kidney disease (CKD): patients with CKD Stage IV and V are associated with increased morbidity and mortality in the postoperative period, hence they should be carefully selected for LVAD and an initial support with a temporary device to evaluate a potential renal recovery before implanting can be considered.[93,94] Other absolute contraindications include severe hepatic or neurological disease (i.e. recent stroke), systemic illness with a life expectancy of $<$2 years or malignancy within 5 years.[95]

Psychosocial assessment of candidates for LVAD, as for HTx, is strongly recommended.[96,97] The complete compliance of the patient

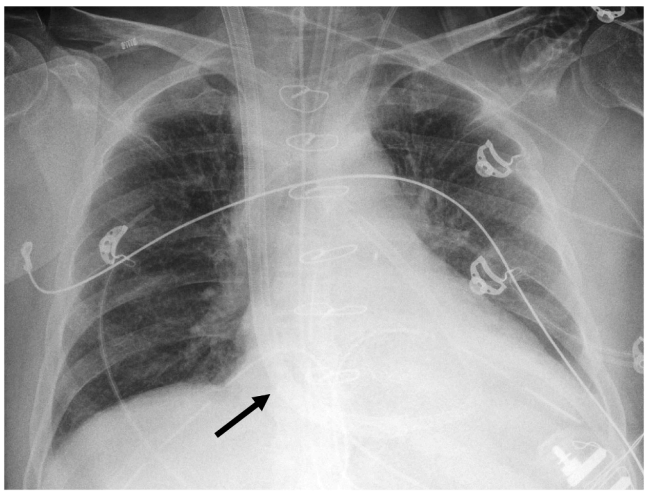

Fig. 2. X-ray showing a "Protek Duo" cannula, a right-side MCS. The dual-lumen ProtekDuo™ cannula (arrow) drains venous blood from the right atrium through the outer lumen and returns it in the pulmonary artery trunk from the tip of cannula through the inner lumen.

is essential, both for the physical management of the device and for the adherence at anticoagulation therapy.[98] Previous difficulties in obtaining adequate anticoagulation are a deterrent factor for LVAD implant.

Once eligibility has been established, it is extremely important to plan the LVAD implant with the right timing. Actually, deferring surgery could expose the patient to the risk of developing irreversible RV dysfunction or multiple organ failure (MOF) .[76,99,100]

RVAD

Right ventricular (RV) failure is another critical cause of morbidity and mortality, although for decades it has been considered less important than LV dysfunction. Actually, RV is more difficult to study, we only see pieces of it by ultrasound.[101] Nevertheless, over time the prognostic importance of RV failure has been recognized in various pathological fields, including myocardial infarction (MI), cardiogenic shock (CS), pulmonary embolism (PE), pulmonary hypertension (PH), chronic left heart disease, valvular disease, congenital heart disease, after LVAD implantation and in acute respiratory distress syndrome.[102-110] The clinical diagnosis of RV failure is made by considering various factors, from physical and laboratory data to imaging and RHC ones.[111] In case of RV failure refractory to medical therapy, MCS can help in promoting decongestion and improve survival.[112,113] In detail, a RAP/PAWP ratio $>$ 0.86 or PAPi $<$ 1.5 are suggestive of potential need for right-side MCS.[114]

Right-side MCSs support RV function, draining venous blood from the right atrium and returning it in the pulmonary artery trunk[115] (Fig. 2). Therefore, on the one hand these devices increase LV preload resulting in improved cardiac output (CO), on the other hand they help in decongestion of vital organs, thus improving their perfusion.[116] Nowadays, the use of right-side MCS is mainly temporary and intended for hospitalized patients.[116] Durable MCS dedicated to right sides are still under investigation. Meanwhile, some commercially available durable LVADs have been adapted to the right-side position to cope with isolated RV or biventricular failure.[117,118]

TAH

A total artificial heart (TAH) consists in two artificial ventricles that supply the function of the both original ones, linked to external batteries by percutaneous cables.

Nowadays, TAH is burdened by important issues (i.e. bulkiness, limited durability, poor biocompatibility, high complication rates and low QoL for the recipients) that limit its use as “bridge to transplantation”.[119] In this context, the CARMAT Aeson is the first TAH of proven biocompatible blood contact materials and an automatic patient adaptable control system, and that obtained its CE mark in 2020 as a bridge to transplant device in patients suffering from end-stage biventricular heart failure.[120] Other indications may be: severe organ dysfunction or rejection after HTx; recurrent arrhythmic storms; end-stage HF in patients with restrictive cardiomyopathy; failure to recover from veno-arterial ECMO.[121]

Certainly, in the near future we will see progress in research on this topic (for example through the future use of BiVACOR, an artificial heart powered by a magnetic levitation for very low wear of the device’s internal components[121]), but there is still a long way to go before TAH emerges as a real alternative to HTx.

Complications of MCS

Most complications of MCS devices concern infections or coagulation disorders.[73] As mention above, despite the technological progress these devices still have extracorporeal parts, which represent a constantly entry site for infections.[122] Actually, infections affect more than one-third of VAD recipients. PET appears to be a promising imaging modality to identify and characterize VAD infections, allowing timely treatment.[123] It is important to treat the patient at the slightest sign of infection without delay, otherwise the consequences could be fatal.

The other major group of complications related to MCS durable devices concerns coagulation disorders, both in terms of bleeding and thrombosis.[124] These devices have high thrombogenicity, therefore anticoagulant therapy is essential to avoid the risk of thrombosis which could cause both peripheral ischemia and device dysfunction.[125-127] On the other hand, anticoagulant therapy increases the risk of bleeding.[128] For this reason, it would be appropriated to screen the candidate for hematologic disorders and potential sources of bleeding prior to implantation.

In the end, psychological complications such as anxiety and depression are frequent in MCS recipients. A recent French study demonstrated an increased risk of attempted or completed suicide in LVAD recipients, significantly higher than in the general population or those with other chronic diseases.[129]

Conclusions

The prevalence of patients suffering from end-stage heart failure is ever-increasing, and with it the need for targeted treatments. Heart transplantation is the gold standard treatment for these patients, but it is limited by numerous issues, mainly the lack of donors and the need for long-term immunosuppressive therapy, which exposes the patient to a greater risk of infectious and oncological diseases. In patients who are not eligible for transplantation, mechanical supports have recently emerged as a valid alternative as “destination therapy”, with better outcomes than medical therapy alone. In the next years, we expect to see further advances in technologies, with increasingly smaller and biocompatible devices, up to complete intracorporeal ones.

Declaration of competing interest

The authors declare absence of conflict of interest.

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