TRANSPLANTATION AND REGENERATIVE MEDICINE

A scientific forum for advanced organ failure, organ transplantation and regeneration

Volume 1 • Number 1 • 2015

Transplantation and Regenerative Medicine

A scientific forum for advanced organ failure, organ transplantation and regeneration

The official publication of Advanced heart failure and transplantation programme and Transplantation center at University medical center Ljubljana

ISSN 2386-0944

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Organ transplantation and regeneration: a complementary approach

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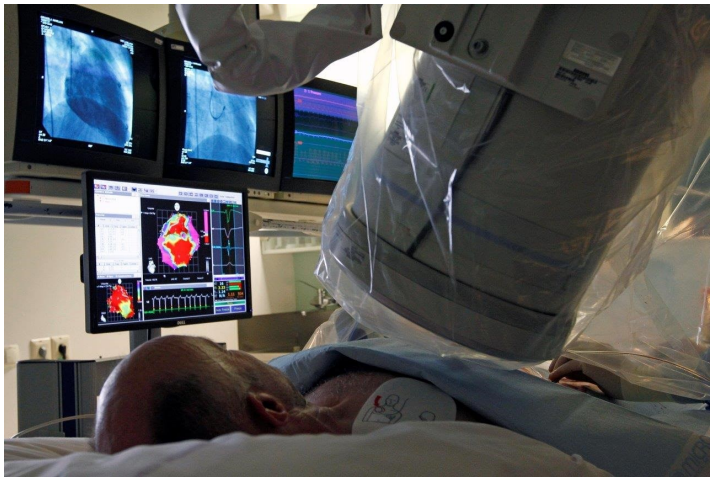
Chronic advanced organ failure is one of the main challenges in contemporary medicine. Already being highly prevalent, its incidence expected to grow further due to better results in acute care and aging of the population. Despite significant improvements in management of such patients, the disease often progresses, which can ultimately result in the need for replacement of the affected organ. As an alternative to organ transplantation, recent research is focusing on the concept of organ repair and regeneration, using either biological agents or mechanical support strategies.

In the field of heart disease, chronic heart failure represents the only entity with increasing incidence and prevalence, and thereby represents one of the most important healthcare issues worldwide. In attempt to improve the outcome of patients with advanced chronic heart failure, different groups have used a variety of treatment approaches, aiming to either replace the heart (heart transplantation, total artificial heart) or recover its function (mechanical circulatory support, stem cell therapy). Recently, the two treatment approaches appear to be merging, resulting in a common clinical platform that encompasses both the concept of 'replacement' and 'regeneration'. Therefore, it is reasonable to believe that modern treatment of heart failure should offer an integrated approach, tailored to the individual patient needs.

In accordance with this concept, the aim of journal 'Transplantation and Regenerative Medicine' is to offer insights into different perspectives of management of advanced organ failure and provide a platform for debate, ultimately leading to consensus documents aimed at improved patient care. With emphasis on recent clinical developments in transplantation, mechanical support and stem cell therapy, and in collaboration with world's leading experts and centers in the field, we are looking forward to the challenge ahead.



Organization of Transplantation centre in UMC Ljubljana

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The mission and the task of the Transplantation Center (TC) is interdisciplinary coordination of the transplant activity in University Medical Center Ljubljana in Ljubljana, Slovenia (UKCL). TC is an organization unit of the UKCL performing the tasks of planning, coordinating and monitoring the implementation of measures for ensuring availability and safety of biological materials for the purpose of medical treatment.

Establishment of the TC is fetching unification of the management of patients after organ transplantation and transfering that field to the appropriate interdisciplinary level based on an environment that allows adequate insulation against infections.

TC plans, prepares, coordinates and monitors the implementation of the Slovenian National Programme for transplantation of organs, tissues and cells in conjunction with the Public Agency of the Republic of Slovenia for Medicinal Products and Medical Devices (JAZMP) and Slovenia-transplant (ST) - the Slovenian national transplant institution. ST is responsible for development, optimization and rationalization of all donation and transplant activities. ST has been a member of Eurotransplant International Foundation since 2000.

In accordance with Directive 2004/23 / EC, adopted by the European Parliament, the provisions of the Slovenian legislation by the Law on the quality and safety of human tissues and cells intended to treat (Official Gazette of RS, no. 61/2007) and the subordinate regulations. The activity of human tissue and cells intended to treat, cover donation, procurement, processing, preservation, storage and distribution and allocation of human tissues and cells (including reproductive tissues and cells) and donor testing, as well as imports and exports of tissues and cells and their input and output including procedures of medically-assisted fertilization. Such activity may be carried out only in an institution authorized to perform activities of supply of human tissues and cells, issued by the JAZMP.

TC could streamline administrative procedures of the transplantation of organs, tissues and cells, establish and manage the information system, registries, central archive and standardize reporting to the JAZMP and ST.

TC ensures a 24-hour alarm and coordination system of the transplantation programme and monitoring and call-in of harmful events and events concerning blood, organs, tissues and cells, including risk assessment and proposals for corrective measures.
TC participates in the preparation of draft expert bases for the drawing up of strategic documents, laws and regulations from its scope of work, plans and participates in the preparation and implementation of projects and programmes in the field of organ, tissue and cell transplantation.

TC participates in the drawing up of strategic planning of the Ministry of Health, in defining strategic goals from its scope of work, determines possible risks, monitors the realization of set goals, follows success indicators, reports on their realization and other activities in pursuit of realizing the objective of its establishment, in accordance with the law, makes sure that each expenditure is justified by real need and verified in prior control.

TC is divided into two subunits: (1) Unit for organ transplantation and (2) Unit for tissue and cell transplantation.

Last but not least, co-ordination of research work in the field of organ, tissue and cell transplantation is also an extremely important area and this journal is an eloquent proof.

Therapeutic algorithms for outpatient management of chronic heart failure

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Heart failure (HF) is characterized by an increasing complexity of clinical management due to evolving diagnostic and therapeutic options, and its diverse etiology (heart failure is a possible end-stage of any cardiac disease), patophysiology (reduced vs. preserved ejection fraction - HFrEF vs. HFpEF), and clinical trajectory (acute, chronic and advanced). HF management therefore requires effective shared care between primary and HF specialist care. Also, rising incidence and prevalence of HF (mainly driven by HFpEF in the ageing population), detection of HF at earlier symptomatic stages, and limited hospital resources have yielded to a significant increase in number of HF patients that are safely and effectively managed in the outpatient setting.

Outpatient management of heart failure

HF managements requires special consideration - frequent follow-up visits, structured education, introduction and uptitration of evidence-based medication, management of co-morbidities, and timely referral for advanced diagnostic and therapeutic options, such as device and cardiac replacement therapy, cardiac rehabilitation, or paliative care, if indicated. Outpatient management can vary in form - due to organisational issues such as resources and national/local specifics, but usually involves a multidisciplinary team with specific knowledge and skills necessary to safely and effectively provide all interventions that are currently believed to modify the unfavourable natural course of HF.

Education of patients and their families/significant others aims at delivering information on causes, natural course and management of HF, while special consideration is dedicated to lifestyle intervention (including diet, tobacco and alcohol consumption, everyday activities and exercise), psychosocial support and self-management (including daily weighting, prompt recognition of heart failure worsening, and adjustment of diuretic dosing).

Pharmacologic management consists of symptomatic therapy with diuretics and disease modifying medication in patients with HFrEF. Neurohormonal blockade with angiotensin converting enzyme (ACE) inhibitors (or angiotensin receptor blockers, ARBs, in patients who do not tolerate ACE inhibitors), beta-blockers and mineralocorticoid receptor antagonists (MRA) has been shown to decrease morbidity and mortality in HFrEF. In patients with EF below 35% and sinus rhythm with heart rate above 75 bmp, addition of ivabradine should be considered. A new class of drugs - the aldosterone receptor/neprilysin inhibitors (ARNI) - has recently been shown to improve survival when compared to ACE inhibitors in patients with HFrEF, but has yet to been integrated in guideline-endorsed therapeutic algorithms.

Heart failure with preserved ejection fraction

Management of HFpEF is more elusive as no trial to date has inequivocabily demonstrated efficacy of medication to prevent mortality or hospitalisations in this large subset HF patients. Management therefore relies on clinical judgment, with focus on management of causes (eg. hypertension and myocardial ischemia), symptoms (eg. diuretics for congestion), and co-morbidities (eg. atrial fibrillation, anemia, diabetes etc.). As ACE inhibitors/ARBs, beta blockers and MRAs are indicated in various diseases leading to or associated with HFpEF (especially hypertension and ischemic heart disease), their use is still a feasible option advocated in guidelines and reflected in clinical practice.

Recommendations

At present, guidelines recommend uptitration of ACE inhibitors/ARBs, beta blockers and MRAs to maximum doses that have been proven effective in major clinical trials and/or doses that can be tolerated by the patient. Conversely, diuretic therapy should be minimised to doses that still allow maintenance of stable congestive symptoms. Both, neurohormonal blocking agents and diuretic therapy require frequent clinical follow-up and monitoring of renal function and electrolytes. Nurse-managed titration programs have been proven effective in terms of achieving target goals of medication.

Follow-up of patients is individually tailored to the patients' needs. Clinical trajectory is extremely diverse, and the same patient can experience asymptomatic, acute, chronic stable, or advanced stages (usually progressively, but sometimes also in reversed order) at different points in time. After diagnosis, frequent follow up visits (ie. every 2-4 weeks) are required in the initial education/ uptitration phase and in unstable/advanced HF patiens or patiens with significant cardiovascular co-morbidities.

In patients with persistent symptoms (NYHA III-IV) despite optimal pharmacological management, severe underlying cardiac dysfunction and poor exercise performance (eg. a VO2max below 14 ml/min on exercise test), advanced HF therapy options should be considered. Patients with severely reduced EF (<35%) should be considered for device therapy (an implantable defibrillator or, in case of a prolonged QRS on ECG, cardiac resynchronisation therapy). Also, early referral for cardiac replacement therapy (heart transplant or ventricular assist device therapy) should be considered (1-3). If advanced therapeutic options are contraindicated or have been exhausted, palliative care should be considered.

Shared care between the general practitioner (GP)/ family physician and the HF managing specialist is pivotal throughout the process. Especially in patients with HFpEF with limited cardiovascular therapeutic options, but a nonetheless unfavourable prognosis and with several co-morbidities, the role of share care is expected to grow along with new cases of HFpEF driving the ongoing HF epidemic. An initiative by the European Society of Cardiology is currently promoting shared training of dedicated GPs, HF specialists and nurses in local communities, while several ongoing projects are trying to establish a national framework of HF clinics in Slovenia, aimed at decreasing regional differences in patients' uptake, management protocols, patient education, training of personnel, inter-disciplinary shared care and communication, and prompt referral to tertiary therapeutic options for advanced HF.

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Anemia in chronic heart failure

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While advances in treatment strategies and pharmacotherapy have produced a dramatic reduction in the mortality of patients with heart failure during the past 15 years, there is still a major challenge to improve patient well being, reduce hospitalizations and reduce mortality further. Despite the significant successes of pharmacologic blockade of neurohormonal activation in chronic heart failure (CHF), it seems that we have reached a "ceiling of benefit" with regard to this approach. This has led to the search for novel mechanisms by which to address the persistent morbidity and mortality associated with CHF. Anemia has recently been demonstrated to be a common comorbid condition in patients with CHF, and multiple studies have demonstrated an independent association between lower hemoglobin and adverse clinical outcomes in this syndrome. Although these findings have generated substantial interest in anemia as a potentially important therapeutic target in patients with CHF, there is little discussion of assessment and treatment options for anemia in recent CHF clinical guidelines.

Treatment options

The consistent association of anemia with adverse clinical outcomes in HF has led to substantial interest in anemia as a potential therapeutic target. Potential treatments for anemia include the use of red blood cell transfusions, intravenous iron therapy and treatment with erythropoietin analogs to increase red blood cell production. The impact of red blood cell transfusion on cardiovascular disease is controversial. Although a "transfusion threshold" of maintaining the hematocrit >30% in patients with cardiovascular disease has been commonly accepted, this concept has been based primarily on expert opinion rather than on clinical trials. Blood transfusion may be associated with other adverse effects including immunosuppression with increased risk of infection, sensitization to HLA antigens, and iron overload. Given this profile of risks and benefits, transfusion may be considered as an acute treatment for severe anemia on an individualized basis but does not appear to be a viable therapeutic strategy for the long-term management of chronic anemia in CHF.

A number of different intravenous iron agents are commer-cially available with a low toxicity profile. Considerable variety exists with regard to the carbohydrate shell that surrounds the central iron molecule in each intravenous iron preparation. The anaphylactic reac-tions to iron preparations seen in the past were not related to iron itself, but rather related to the dextran in the shell. Hence, dextran-free preparations are a safer and preferred alternative. The first double-blind, randomized, placebo-controlled study was per-formed by Toblli et al using iron sucrose. A total of 40 ane-mic patients with iron deficiency were included and received 200 mg of intravenous iron sucrose or placebo weekly for 5 weeks. After 6 months, hemoglobin increased from 10.3 ± 0.6 g/dL to 11.8 ± 0.7 g/dL in the iron sucrose group, and NYHA class, left ventricular ejection fraction, N-ter-minal probrain natriuretic peptide, and 6-minute walking distance improved (all $P < 0.01$). However, no such propensities were noted in the placebo group. In the FERRIC-HF (Ferric Iron Sucrose in Heart Failure) study, a total of 35 patients were enrolled. According to their hemoglobin values at baseline, anemic (<12.5 g/dL) and nonanemic (12.5 –14.5 g/dL) patients were randomized into two groups in a 2:1 ratio to treatment group or control, respectively. This study demonstrated that treat-ment with iron sucrose resulted in an increase in transferrin saturation ($P < 0.0001$) and serum ferritin ($P<0.0001$). Interestingly, patients showed improvement in their clinical symptoms, independently of whether anemia was present or not. The improvements were more pronounced in anemic than in nonanemic patients. The FAIR-HF

(Ferinject®) Assessment in patients with Iron deficiency and chronic Heart Failure) trial is the largest study of intravenous iron published thus far, in patients with chronic heart failure. This study enrolled 459 patients with CHF NYHA functional class II and III with iron deficiency and a hemoglobin level of 9.5–13.5 g/dL. Patients were randomly assigned in a 2:1 ratio to receive 200 mg of intravenous iron (ferric carboxy-maltose) or saline (placebo). The primary end points were self-reported Patient Global Assessment and NYHA func-tional class, both at week 24. Secondary end points included distance walked in 6 minutes and health-related quality of life (69). Using the Patient Global Assessment, 50% of patients receiving ferric carboxymaltose reported being much or mod-erately improved, as compared with 28% of patients receiving placebo. At week 24, 47% of patients assigned to ferric carboxymaltose had an NYHA class I or II, as com-pared with 30% of patients in the placebo group. Strikingly, the results were similar in patients with and without anemia. Investigators also noted significant improvements with ferric carboxymaltose in the distance on the 6-minute walk test and quality of life assessments. The rates of death, adverse events, and serious adverse events were similar in the two study groups. It was concluded that treatment with intravenous ferric carboxymaltose in patients with CHF and iron deficiency, with or without anemia, improves symptoms, functional capacity, and quality of life together with an acceptable side effect profile. These studies indicate that intravenous iron therapy improves symptom status and quality of life in patients with chronic heart failure with and without anemia. In addition, they elucidated the importance of iron deficiency as a valid and independent therapeutic target.

The use of recombinant human erythropoietin (rHuEpo) in the treatment of chronic anemia was first applied on a large scale in patients with anemia resulting from end-stage renal disease. In anemic patients with end-stage renal disease on dialysis, erythropoietin therapy has been associated with regression of left ventricular hypertrophy and reduction in left ventricular end-diastolic volume. Comparable beneficial effects of erythropoietin therapy on cardiac remodeling has also been demonstrated in predialysis anemic patients with chronic renal disease and concomitant structural heart disease. The currently available erythropoietic agents for treatment of anemia are epoetin-a, epoetin -b, both of which are recombinant human erythropoetin (rHuEpo), and darbepoetin-a. Plasma half-life of rHuEpo after intravenous dosing is 6 to 8 hours. Approximately 25% of the administered dose is absorbed after subcutaneous dosing, but the plasma half-life is increased to >24 hours. The amount of subcutaneous rHuEpo needed to achieve hemoglobin targets in patients with chronic kidney disease is approximately 25% less than that needed for intravenous dosing. Darbepoetin-a is a long-acting, N-linked supersialylated analog of human erythropoietin. Compared with both native and recombinant erythropoietin, it has stronger affinity for erythropoietin receptor and longer plasma half-life of approximately 48 hours, with consequent longer dosing intervals of 1 to 2 weeks during maintenance therapy. Three small studies have been published directly examining the effect of rHuEPO therapy on clinical outcomes in patients with heart failure. In an uncontrolled study, Silverberg et al. demonstrated an improvement in ejection fraction, NYHA functional class, and hospitalization after treatment with erythropoietin and intravenous iron in a group of 26 patients with NYHA functional class III to IV HF. In this study, the dose of rHuEPO was adjusted to maintain a hemoglobin level of 12 g/dl. The same group subsequently conducted a small randomized trial of rHuEPO and intravenous iron in 32 patients with NYHA functional class III to IV heart failure. Treatment of anemia in this patient population resulted in improved functional class and a decrease in the need for hospitalization. Several features of these studies suggest the need for caution in the interpretation of these results. Both studies examined very small numbers of patients. The initial study was not randomized and had no control group. Additionally, the randomized trial was significantly limited by its lack of a placebo control and the fact that neither patients nor investigators were blinded to treatment assignment. Given the subjectivity of assessments of functional class and criteria for diuretic dosing or HF hospitalization, these end points

must be interpreted very cautiously in the setting of an unblinded study. Mancini and colleagues conducted a single-blinded, randomized, placebo-controlled trial of rHuEpo therapy in 26 patients with advanced CHF and anemia (hematocrit <35%). Patients received subcutaneous rHuEpo 5000 IU 3 times per week adjusted to raise hematocrit to >45% for up to 3 months or a single subcutaneous injection of saline. Supplemental oral iron and folate were also given to the patients who received rHuEpo therapy. Compared with the placebo group, rHuEpo therapy was associated with significant increases in hemoglobin (11.0±0.5 to 14.3±1.0 g/dL, P<0.05), peak oxygen uptake (11.0±1.8 to 12.7±2.8 mL/min per kilogram, P<0.05), and treadmill exercise duration (590±107 to 657±119 seconds, P<0.004). The increases in hemoglobin levels were linearly associated with the increase in peak oxygen uptake (r=0.53, P<0.02). Subjects with both hemodilution anemia and true anemia with reduced red blood cell volume appeared to derive comparable improvement in exercise capacity in response to rHuEpo therapy. In the hemodilution subgroup with expanded plasma volume, the rise in measured hematocrit in response to rHuEPO treatment was primarily due to a decrease in plasma volume. As diuretic dosing did not change during the study, this finding suggests that erythropoietin has direct or indirect effects on renal regulation of plasma volume. The effect of treatment with darbepoetin-a (0.7 μg/kg subcutaneously every 2 weeks for 26 weeks) on exercise tolerance in 41 anemic patients with congestive heart failure (hemoglobin 9 to 12 g/dL) was evaluated in a randomized placebo controlled trial. An abstract report of the study findings indicates favorable effects of darbepoetin-a on exercise duration and quality of life when compared with placebo.

Current guidelines from the National Kidney Foundation recommend use of intravenous iron to maintain serum ferritin level of 100 to 800 ng/mL and a transferrin saturation 20% to 50% to optimize the clinical response to erythropoietic agents.

Recommendations

As it was stated, there is little discussion of assessment and treatment options for anemia in recent CHF clinical guidelines. At present there is insufficient data to make a general recommendation for aggressive treatment of anemia in patients with CHF. A diagnostic evaluation for potentially reversible causes of anemia (such as iron deficiency or occult blood loss) and subsequent treatment, if identified, is appropriate in all patients. Preliminary studies indicate that erythropoietin therapy is well-tolerated and associated with short term clinical benefit in patient with CHF. The optimal target hematocrit, erythropoietin dosing regimen, and iron supplementation regimen for anemic patients with CHF remain to be determined. Treatment of mild anemia with erythropoietin analogs can, thus, not be considered a proven therapy for HF based on currently available data, and the results of larger, more carefully controlled clinical trials will be required before such treatment could be considered a viable therapy. For the subpopulation of patients with CHF with moderate-to-severe anemia (hemoglobin <11g/dL) and concomitant moderate to severe chronic kidney disease (estimated glomerular filtration rate <60 mL/min), former guidelines of the National Kidney Foundation recommend treatment with erythropoietic agents and supplemental iron to a target hemoglobin of 12 g/dL. It seems that current guidelines, which recommend target hemoglobin of 13 g/dL are not justified since more aggressive treatment of anemia is associated with increased risk, a likely increased cost, and no proven benefit.

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Diabetic cardiomyopathy

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among people with diabetes mellitus, who have a risk of cardiovascular mortality two to four times greater than that of people without diabetes. Diabetes is commonly associated with other cardiovascular risk factors, interacting with these to accelerate atherogenesis. Multifactorial interventions, such as those targeting hyperglycaemia, hypertension and hypercholesterolaemia, significantly reduce the risk of both fatal and non-fatal CVD. Over the past two decades, there has been a significant reduction in the incidence of diabetes-related complications. The greatest absolute decline was in the number of cases of acute myocardial infarction, likely reflecting a combination of enhanced awareness, detection and early management of risk factors.

Definition of diabetic cardiomyopathy

Diabetic cardiomyopathy (DCM) is defined as the presence of of abnormal myocardial performance or abnormal structure in the absence of epicardial CAD, hypertension and significant valvular disease. Clinical and experimental studies with diabetes have demonstrated that DCM was associated with cardiac structural and functional changes. To date, several pathophysiological mechanisms are responsible for this entity: hyperglycemia, non-enzymatic glycosylation of several proteins, reactive oxygen species formation, and fibrosis all lead to impairment of cardiac contractile functions. Impaired calcium handling, increased fatty acid oxidation, and increased neurohormonal activation also contribute to this process. Demonstration of left ventricular hypertrophy, early diastolic and late systolic dysfunction by sensitive techniques, help us to diagnose diabetic cardiomyopathy. Traditional treatment of heart failure is beneficial in diabetic cardiomyopathy, but specific strategies for prevention or treatment of cardiac dysfunction in diabetic patients has not been clarified yet.

Diagnosis of diabetic cardiomyopathy

There is no widely accepted method for the diagnosis of DCM. The best approach is detection of myocardial dysfunction, and exclusion of other heart diseases, which may cause myocardial structural and functional changes. Clinically, it may take several years for heart failure to develop in diabetic patients. So, it is very essential to demonstrate the abnormality before symptoms of heart failure begin. Studies have shown that heart failure is increased about 2-3 times in diabetic patients independent from the etiology. The prognosis of heart failure is much worse in diabetic patients. However, in the absence of hypertension and CAD, the mechanism of heart failure in diabetic patients is still not fully understood.

Cardiac dysfunction in asymptomatic diabetic patients can be detectable by various techniques. Echocardiography is a available, reliable and noninvasive imaging tool to demonstrate early fuctional changes of LV. Early diastolic and late systolic dysfunction can be shown by echocardiography. Normal echocardiographic findings at rest do not exclude the diagnosis of DCM.

LV dysfunction detectable by TDI, during exercise or stress, may also be the earliest sign of DCM. Other diagnostic methods such as computed tomography (CT), single photon emission CT, and MRI can be used for detection of myocardial dysfunction. Assesment of interstitial fibrosis and steatosis by using delayed gadolinium enhancement cardiac MRI is possible but its diagnostic value has not been established.

The role of hyperglicemia

Hyperglycemia is considered as a main factor for development of DCM. Hyperglycemia results in advance glycemic end-product formation, cardiac collagen accumulation and oxidative stress. A study by Kiencke et al. conducted in diabetic adults, without any evidence of structural heart disease, revealed that DCM was present in 48% of the patients who had an increased risk for functional deterioration, and possibly cardiovascular events, during follow-up. To date, it is unclear why certain diabetic patients develop cardiomyopathy. The possible explanation may be the severity of hyperglycemia and duration of DM, which well correlates with the presence of DCM.

Early diastolic and late systolic dysfunction correlate with glycemic status and duration of diabetes. It is imperative to make an early diagnosis and reduce disease progression. Therapeutic agents toward the specific metabolic and structural derangements of DCM are encouraging, but there is still no specific treatment strategy to manage DCM. Further clinical research focused on the mechanisms of DCM will clarify the therapeutic approach to the prevention and treatment of this entity.

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Hypertensive heart disease

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Aging of the population and prolongation of the lives of cardiac patients by modern therapeutic innovations has led to an increasing prevalence of heart failure (HF). Despite improvements in therapy, the mortality rate in patients with HF has remained unacceptably high, making early detection of susceptible persons who would benefit from preventive measures imperative.

Hypertension remains a major public health problem associated with considerable morbidity and mortality. Despite wide developed and choice of medical treatment only on average about 30% of people around the world have blood pressure controlled and even more there is high percent of people where hypertension is not detected. There is a problem with awareness and adherence which still need to be improved. Hypertension remains one the most important etiologic factor for HF development. It is today a hypertension-related complication, almost as common as stroke. Preventing heart failure is the largest benefit associated with BP-lowering drugs, including in the very elderly.

Epidemiology

The incidence of HF in hypertensive patients varies according to the population and duration of follow-up. As an example, approximately 2 percent of high-risk hypertensive patients in the ACCOMPLISH trial developed HF at three years. Among the high-risk hypertensive population enrolled into the ALLHAT trial, 1716 out of 32,804 (5.4 percent) participants developed HF during an average follow-up of nine years.

In contrast to the pattern seen in the general population, in which prognosis is poorer for hypertensive compared with normotensive individuals, a higher blood pressure prior to treatment is a predictor of better survival in patients with HF. It is likely that this correlation is a consequence of the fact that more severe cardiac dysfunction causes a decline in systemic blood pressure, making low blood pressure a marker for more advanced HF. This observation makes it difficult to study the benefits of antihypertensive therapy in this population.

Patophysiology

There are 7 pathways in the progression from hypertension to heart failure described. Hypertension progresses to concentric (thick-walled) LVH (cLVH; pathway 1). The direct pathway from hypertension to dilated cardiac failure (increased LV volume with reduced LVEF) can occur without (pathway 2) or with (pathway 3) an interval myocardial infarction (MI). Concentric hypertrophy progresses to dilated cardiac failure (transition to failure) most commonly via an interval myocardial infarction (pathway 4). Recent data suggest that it is not common for concentric hypertrophy to progress to dilated cardiac failure without interval myocardial infarction (pathway 5). Patients with concentric LVH can develop symptomatic heart failure with a preserved LVEF (pathway 6), and patients with dilated cardiac failure can develop symptomatic heart failure with reduced LVEF (pathway 7).

Treatment

When we are treating patient with heart failure and possible hypertension as etiologic factor, we need to exclude all the other possible etiology. Especially we need to exclude ischemic cardiac disease. Good anamnesis and physical examination is crucial for all further processes.

The most important thing treating hypertension is reaching target blood pressure which is 140/90mmHg in most of the subject, but treatment should be personalized. Preventing heart failure is the largest benefit associated with BP-lowering drugs .

This has been observed using diuretics, beta-blockers, ACE inhibitors and angiotensin receptor blockers (ARBs), with calcium antagonists apparently being less effective in comparative trials, at least in those trials in which they replaced diuretics. In ALLHAT an ACE inhibitor was found to be less effective than a diuretic, but the study design implied initial diuretic withdrawal and the small excess of early heart failure episodes may have resulted from this withdrawal. In the Prevention Regimen for Effectively Avoiding Secondary Strokes (PROFESS) and Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) trials, an ARB did not reduce hospitalizations for heart failure below those occurring on placebo (in which treatment consisted of non-RAS-blocking agents) and in ONTARGET an ARB appeared (non-significantly) less effective than an ACE inhibitor.

Based on evidence data and clinical experiences when there is present heart failure some classes of drugs are preferable for hypertension treatment. First we would like to block renin-angitensin system. Our first choice should be ACE inhibitor or ARB, followed by beta blockers. In most of the cases in patients with HF diuretics should be added. Choice of diuretics depends on clinical stage of the patient. If they are in stable condition long acting diuretics are preferable, in decompensating stage loop diuretics should be added, which shall be replaced later with long acting ones or spironolacton. We shall be focused on reaching target blood pressure and calcium antagonists could be of good following choice. If patient is in stable condition than also

diuretics can be abolished and only added if needed. There were some negative outcomes shown in ALLHAT study concerning use of alfa blockers, but due to the fact that BP level in the most important fact, I think that alfa blockers are useful in treating resistant hypertensives with the fact that we need to measure blood pressure also in standing position to avoid orthostatic hypotension or worsening HF because of to low blood pressure.

Due to the fact that heart failure patient usually have a lot of medication treatment in stable condition fixed dose combinations are really useful. In Slovenia we have a lot of fixed dose combinations with different dosed of long acting diuretics which could help us to maintain stable position in HF subjects. There is even fixed dose combination of a small dose diuretic combination with beta blocker which could be used for long term treatment. Beside triple combination of ACE or ARB, diuretic and calcium channel blocker is one of the good options for stable condition.

Blood pressure control is vital as a means of avoiding progression of disease or other serious cardiovascular events such as stroke. However, anti-hypertensive medication side effects are common and can be very debilitating, causing severe impact on quality of life. Patients should not have to suffer such side effects when there are alternative ways of treating them. As clinicians we need to discuss about these problems with our patients and try to avoid them. Whilst a history of hypertension is common in patients with heart failure, a raised BP can disappear when heart failure with LV systolic dysfunction develops. We face the problem how to add all the drug classes prescribed in the guidelines for HF therapy. Then administration of ACE or ARB in small doses and evening applications are applicable.

Focusing on BP control in our patients, we shall not forget on the control of other risk factors such as hyperlipidemia and diabetes which are present in most of patients with HF and hypertension. For busy clinician

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Testosterone and heart: myth or reality?

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Normal level of testosterone has an important role in cardiovascular health. Majority of basic and clinical experiments demonstrated vasodilatory effects of testosterone upon various vascular beds via endothelium-dependent and -independent mechanisms. Furthermore, existing data suggests that testosterone may beneficially enhance biological processes involved in atheroprotection, in particular, lipid deposition and inflammation within the arterial wall and in the circulation. Concurrently, potential involvement of testosterone in angiogenesis has also been demonstrated. While testosterone insufficiency impaired the mobilization and homing of CD34+ stem cells in ischemic myocardium in the early stage of myocardial infarction, testosterone- replacement therapy (TRT) significantly restored these changes and resulted in a concomitant increase in neovascularization in animal models. Further clarification of testosterone action in cardiovascular system is needed in clinical setting.

Testosterone levels in chronic heart failure

Chronic heart failure (CHF) is associated with low testosterone compared to the levels in healthy controls. Maladaptive down-regulation of gonadal axis is interrelated and linked to the neurohormonal and cytokine hyperactivation. Testosterone production in testis is suppressed directly and through the disruptive shedding of gonadotropins and gonadotropin-releasing hormone from pituitary and hypotalamus. Low testosterone portends a poor prognosis and is associated with increased mortality in CHF. Testosterone deficiency represents an independent risk factor for hospital readmission in male patients with CHF. The severity of CHF correlates with the degree of testosterone deficiency. Reduced testosterone has also been shown to correlate negatively with exercise capacity in patients with CHF. Lower testosterone has been associated with longer duration of QTc interval. In addition, a negative correlation has been demonstrated between testosterone levels and intima media thickness and severity of coronary artery disease (CAD). Finally, low testosterone has an adverse effect on several metabolic cardiovascular risk factors, which include insulin resistance, diabetes, dyslipidaemia and central adiposity. On the contrary, several epidemiological studies reported that men with endogenous testosterone in the upper normal range have reduced cardiovascular events and mortality compared to those with lower levels.

Testosterone replacement therapy in heart failure

Whether or not testosterone deficiency is a contributory factor to impaired cardiovascular health or merely a biomarker of disease remains to be elucidated. Short- term surrogate endpoints and long -term outcomes of well-designed interventional trails should be carefully charted in this population. Recent meta-analyses have shown that when TRT has been used in patients with pre-existing cardiovascular conditions, the effect on the disease has been either beneficial or neutral. Replacement of testosterone in patients with CHF significantly improved exercise capacity, without affecting LVEF via muscle generation by promoting type I muscle fiber proliferation. TRT may be able to control ventricular repolarization by shortening the length of QTc interval. Hypogonadal patients exhibit low numbers of circulating bone marrow-derived endothelial progenitor cells (ePCs) that considerably increase upon TRT. EPCs play a pivotal role in the integrity and of major arteries and the peripheral vascular system. Testosterone replacement in men diagnosed with hypogonadism where mid-normal range levels are achieved have shown a beneficial effect on several metabolic risk factors, cardiac ischaemia and improved mortality. Conversely, few results derived mainly from poorly analyzed databases and observational studies have suggested an increased

cardiovascular risk in elderly men receiving often supra-therapeutic doses of testosterone. Clinical monitoring and titration of testosterone replacement dose is therefore of paramount importance.

Recommendations

At present, current guidelines from Endocrine Society make no recommendations on whether patients with heart disease should be screened for hypogonadism. Supplementing patients with heart disease to improve survival is not recommend. Further longitudinal, placebo-controlled randomized trails of TRT in men with low testosterone are required to completely clarify the relevance of testosterone in improvement of mortality and morbidity of patients with heart disease. Existing observations seems to suggest that, of all patients with cardiovascular diseases, hypogonadal patients with CHF in particular, are most likely to benefit from testosterone treatment. In the current state of uncertainty, replacement must be individually tailored. Careful pre-treatment screening and monitoring of TRT in selected patients should reflect the lack of concluding evidence.

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Heart failure in pregnant women with heart disease

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Major hemodynamic changes occur during pregnancy. Maternal adaptation of the hemodynamic system initiates in the first trimester, as early as in fifth week of gestation, and continues throughout the puerperium. Maternal cardiac output increases by approximately 40-50% and peripheral vascular resistance is reduced. Additionally, preload is increased, afterload is reduced and the heart rate rises up to 30%. Systemic blood pressure falls early in gestation while diastolic blood pressure and is usually 10 mmHg below the baseline in the second trimester. Left ventricular remodelling occurs during pregnancy. The systolic function first increases but may then decrease in the last trimester. Reports on the diastolic function are inconsistent. During labour and delivery, cardiac output is further increased as a result of uterine contractions and maternal effort. All changes are reversed during puerperium within 3-12 months. However, some structural changes may never be completely reversed. In order to reduce blood loss during delivery, an increase in concentration of coagulation factors and diminished fibrinolysis appear which lead to hypercoagulability and an increased risk of thrombo-embolic events. In a healthy pregnancy, the NT-proBNP levels show some changes between trimesters but not over pathologic levels.

Pregnancy and heart disease

Pregnancy is an additional hemodynamic stress for the circulatory system. It can reveal latent underlying heart disease and cause its deterioration, which is associated with significant maternal and foetal morbidity and mortality. In developed countries, the risk of cardiovascular disease in pregnancy has increased due to the increasing age of first pregnancy

and a higher prevalence of cardiovascular risk factors - diabetes, hypertension and obesity. The treatment of congenital heart disease has also improved, resulting in an increased number of women with heart disease reaching childbearing age. In these countries, maternal heart disease is now the major cause of maternal death during pregnancy.

Several risk stratification models for predicting cardiac complications in pregnancy have been described. European Guidelines are based on a World Health Organization (WHO) risk score which takes into consideration cardiac pathology and co-morbidity. WHO class 1 indicates low risk, WHO class 2 indicates intermediate risk, WHO class indicates high risk and WHO 4 class indicates contraindication for pregnancy. The type of complication depends on the specific cardiac pathology and the severity of cardiac disease. Arrhythmias and heart failure are the most common complications.

Pregnancy and heart failure

The increased cardiac workload during pregnancy may precipitate heart failure. Labour and delivery are a particularly high-risk period. The predictors for heart failure during pregnancy are pre-pregnancy NYHA class ≥3, WHO class≥3, cardiomyopathy and pulmonary hypertension. The onset of heart failure during pregnancy may differ according to the underlying heart disease and appears most common in the second trimester, but may also occur during delivery or postpartum, especially in cardiomyopathies. Heart failure is more common in women with left-sided lesions than in women with right-sided lesions and shunts. Peripartum cardiomyopathy is a pregnancy-specific type of cardiomyopathy, where heart failure occurs toward the end of pregnancy or in puerperium. Elevated NT-proBNP levels during pregnancy are a predictor for cardiovascular complications. Pre-eclampsia can precipitate heart failure in patients with pre-existing heart failure. Longitudinal echocardiographic studies have shown that the systolic and diastolic function of the left ventricle is reduced during pregnancy in patients with structural heart diseases and persists even after pregnancy. The diagnosis of heart failure is associated with a significantly higher maternal mortality and foetal death occurs more often in patients with heart failure. In survivors, the birth weight is lower.

Heart failure should be treated according to guidelines on acute and chronic heart failure. During pregnancy, ACE inhibitors, ARBs and renin inhibitors are contraindicated because of fetotoxicity. Hydralazine and nitrates can be used instead of ACE inhibitors/ARBs for afterload reduction. Dopamine and levosimendan can be used for inotropic support. Treatment with beta-blockers is indicated for all patients with heart failure. Diuretics should only be used if pulmonary congestion is present. Aldosterone antagonists should be avoided. Vaginal delivery is always preferable if the patient is haemodynamically stable. Due to high metabolic demands, breastfeeding is not recommended in case of heart failure.

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Non-compaction cardiomyopathy

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Noncompaction cardiomyopathy (NCC) is a rare congenital heart disease, resulting in formation of two layers of myocardium – compacted and noncompacted. The latter is characterized by prominent myocardial trabeculations and deep intertrabecular recesses. As the embryonic compaction process results in formation of coronary microvessels, it is though that dysfunctional myocardium has decreased coronary flow reserve. Subsequent subendocardial ischemia can be the culprit for development of symptoms - signs of congestive heart failure, arrhythmias or thromboembolisms; sudden cardiac death is also described. Management of disease and therapy are extrapolated from indications for treatment of heart failure, however no studies have shown efficacy of medical therapy. Heart failure can progress rapidly, resulting in need of device therapy, resynchronization therapy or heart transplantation (HTX).

Case report 1

A 40-year old patient was presented to our clinic in 2012 due to worsening dyspnea on exertion. Echocardiography has shown dilatative cardiomyopathy with moderately enlarged left ventricle and left ventricle ejection fraction (LVEF) of 25%, without important valvular disease. Coronary artery disease has been ruled out. With magnetic resonance the diagnosis of NCC has been confirmed, myocarditis has been ruled out as well. Due to ventricular tachyarrhythmia the ICD implantation has been performed. Medical therapy has been introduced, but gradually the patient worsened. In 2015 myocardial perfusion single-photon emission computed tomography (SPECT) was performed. Images taken during pharmacologically induced stress with regadenoson have shown considerable reversible subendocardial ischemia in regions with non-compacted myocardium. In the same regions impaired strains have been recorded through speckle tracking echocardiography (STE). The heart failure symptoms gradually worsened despite optimal medical therapy. Soon inotropic support had to be started. He was put onto urgent HTX list and successfully transplanted in April 2015.

Case report 2

A 29-year old patient, healthy before onset of symptoms, complained of dyspnea, which gradually worsened and was limiting him to only mild physical exertion. Echocardiography has shown severely dilated left ventricle with severely impaired LVEF of 15-20%. In addition, akinesia of whole apex and anterior wall has been observed. Excessive trabeculations, diagnostic for NCC, have been found as well. Coronarography has shown normal coronary arteries. Due to hemodynamic instability the patient needed increasing doses of dobutamine and furosemide infusions in order to achieve cardiac compensation. We opted for HTX and have found no contraindications. As the heart failure signs worsened high inotropic support and no appropriate HTX offers were received, the implantation of LVAD (HeartMate II) as a bridging towards heart transplant was performed. After recovery he was fully compensated, in NYHA II class and discharged home. He was put on a regular list for HTX. 4 months after LVAD implantation we have received an appropriate offer for HTX, which he underwent uneventful and is, upon regular checkups, doing well.

Conclusion

NCC is a rare congenital heart disease that due to the arrest in the embryonic myocardium compaction process results in layers of non-compacted myocardium. It leads to inappropriate coronary microvessels development. Through case reports we have shown that in the regions with non-compacted myocardium there are signs of reversible subendocardial ischemia, demonstrated with myocardial perfusion SPECT. STE has shown abnormal strains in same regions. The described ischemia could be the main culprit for development of

symptoms: congestive heart failure, arrhythmias or thromboembolisms. Medical HF treatment has been extrapolated from indications for management of HF and has not been shown effective. Upon worsening of HF the use of device therapy, resynchronization therapy or heart transplantation should be considered. At the moment there is an ongoing study on our clinic to assess the association between the extent of noncompacted myocardium and heart muscle ischemia in the patients with isolated NCC.

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Which patients benefit from CRT?

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Cardiac resynchronization therapy (CRT) has been well established in multiple large trials to improve symptoms, hospitalizations, reverse remodeling, and mortality in well-selected patients with heart failure when used in addition to optimal medical therapy. Updated consensus guidelines outline patients in whom such therapy is most likely to result in substantial benefit. Consensus guidelines have identified the patients most likely to benefit from CRT as those with symptomatic HF, LVEF 35% or less, and wide QRS duration. However, pooled data have demonstrated that only approximately 70% of patients who qualify for CRT based on current indications actually respond favorably. In addition, current guidelines are based on outcomes from the carefully selected patients enrolled in clinical trials, and almost certainly fail to include all patients who might benefit from CRT.

Nonresponders

The issue of nonresponse to CRT is complicated by variability and marked discrepancy in how response to CRT is defined in various studies, the notion that patients who do not clearly benefit, but do not worsen, after CRT are considered as responders by some, and the wide array of factors that are known to modify the benefit from CRT in individual patients. Nonetheless, the quest to better identify which patients with heart failure are most likely and least likely to benefit from CRT is a laudable goal given the cost, complexity, and challenging long-term management of these patients. Improved LV systolic function and reduced LV systolic/diastolic dimensions are often used as a measure of benefit for CRT. These remodeling outcomes have the clear advantage of being quantifiable, having reasonable reproducibility, and, most importantly, correlating with long-term clinical outcomes in CRT recipients. However, hard clinical outcomes are desirable given the lack of a linear relationship between the degree of favorable LV remodeling and long-term clinical outcome.

Identification of Responders

The identification of patients most likely to benefit from CRT requires a consideration of factors beyond

these standard criteria: QRS morphology with particular consideration in patients with LBBB pattern, extent of QRS prolongation, etiology of cardiomyopathy, rhythm, and whether the patient requires or will eventually need anti-bradycardia pacing. Certainly, other factors beyond patient selection also contribute to variable response, such as optimal device programming and position of the LV lead (targeting the basal-to-mid posterior or lateral wall). Furthermore, it remains possible that more refined cardiac imaging technologies, or sophisticated electrophysiologic measurements of dyssynchrony, may eventually help reduce the proportion of nonresponders to CRT. In addition, the baseline severity of functional impairment may influence the type of benefit to be expected from CRT; for example, NYHA class I patients may derive long-term benefit in cardiac structure and function, but no improvement in survival has been shown, and no benefit in symptoms or hospitalizations can be reasonably expected. In contrast, certain NYHA class IV patients may be too sick to realize long-term mortality benefits from CRT, but improvements in functional capacity, and removal of vasoactive medications may represent vital QoL improvements in this population.

Conclusion

Although a complete understanding of the spectrum of patients who benefit from CRT is still lacking, it is clear that there is a role for CRT in improving lives and longevity for a significant proportion of heart failure patients. We need further evidence regarding the various factors that can predict positive or even detrimental responses to CRT, to help better determine who benefits most from this evolving therapy.

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Which heart failure patients should be revascularized?

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The progress achieved in the recognition and treatment of acute coronary syndrome has led to decreased early mortality in coronary artery disease (CAD) patients, resulting in an increased number of individuals who survive one or more episodes of acute myocardial injury, but are left with either scar from previous infarction(s) or viable but poorly contracting (i.e. stunned or hibernating) myocardium. In turn, this leads to dilatation of the heart with adverse ventricular (LV) remodeling, resulting in reduced systolic function over ensuing years. CAD complicated by severe LV dysfunction is associated with high morbidity and mortality with increased risk of sudden death, malignant arrhythmias and worsening heart failure (HF). Hence, the coexistence of CAD and HF indicates particularly poor prognosis with remarkable mortality and denotes a population of patients with specific diagnostic and therapeutic challenges in everyday clinical practice.

Coronary revascularization in heart failure

Coronary revascularization, establishing new blood supply to the diseased myocardium, may lead to symptomatic and prognostic improvement in these

individuals; however, due to extreme heterogonous distribution of normal versus viable-but-hypocontractile versus scarred myocardium in different cross sections of individual patient's LV myocardium, prospective identification of patients who may benefit from high-risk revascularization remains a clinical challenge. The role of coronary revascularization to improve LV function in ischemic HF has been investigated in several studies over the past decades. A meta-analysis by Allman et al published in 2002 reported on results of 24 non-randomized studies carried out between 1992 and 1999 including 3088 patients with LV ejection fraction (LVEF)<40%. It demonstrated a significant association between revascularization and improved survival in individuals with viable myocardium, no benefit with revascularization in absence of viability and high mortality in patients with viable myocardium treated medically. Yet, all in the meta-analysis included studies had several limitations, including small sample size, non-randomized design and lack of standardization of medical therapy. Additionally, there have been significant advances in medical, interventional and surgical management of CAD in the last decade, thus making it difficult to strictly translate those findings in the current clinical practice. Therefore, 3 prospective randomized studies, the STICH, HEART and PARR-2 trial, have recently contested the value of myocardial revascularization in patients with ischemic cardiomyopathy. Unfortunately, all of these studies had several major limitations (i.e. patient's crossover rate in STICH, underpowered results in HEART due to slow recruitment and funding withdrawal and high percentage of nonadherence to recommended therapy in PARR-2 trial), thus diminishing their impact on today's therapeutic approaches. However, a recent publication by Doenst et al examining the impact of crossovers in the STICH trial and performing the analysis according to the therapy received by each patient (i.e. as treated analysis) or excluding those who crossed over from one randomized treatment arm to other (i.e. per protocol analysis), reported that surgical revascularization (CABG) is superior to medical therapy alone in ischemic cardiomyopathy. Similarly, analyzing the subgroup of patients with viable myocardium that actually underwent revascularization procedure in PARR-2 trial, a statistically significant decrease in mortality was observed when compared to group of patients receiving only medical therapy.

The role of viability testing

A large body of observational evidence from studies conducted in recent decades has indicated the substantial role of myocardial viability testing for preoperative stratification and identification of patients with ischemic HF who might benefit most from myocardial revascularization. The waste majority of these studies namely showed that in the presence of viable myocardium (as demonstrated by viability imaging or angina presence, which can be considered as a clinical marker of extensive viability), revascularization leads to improvement in mortality and LV systolic function if compared to medical therapy alone. Other studies, in fact, pointed out that in individuals with ischemic LV dysfunction without viable myocardium or angina, revascularization provided no benefit in mortality and improvement in LV function. The randomized STICH and PARR-2 trials were done recently evaluating the benefit of viability study guided management of ischemic HF. Both studies failed to demonstrate a significant interaction between myocardial viability and medical versus surgical treatment with respect to all-cause mortality, suggesting that in this patient population assessment of myocardial viability does not identify those who will have greatest survival benefit from surgical revascularization versus medical therapy. However, both studies had several major limitations. In the STICH trial, the decision to pursue viability testing was optional and left to the discretion of the recruiting physician and thus making the study not truly randomized which resulted in the fact that less than 50% of all STICH patients underwent viability testing. Moreover, the study used two fundamentally different types of viability test (SPECT and dobutamine echo) with variable definitions of variability, whereas cardiac MRI which is a gold standard technique for assessment of myocardial viability by late gadolinium enhancement was not used. Furthermore, the major drawback of the PARR-2 trial was the fact that 25% of patients in the "viable myocardium" group did not undergo the

recommended revascularization therapy. In the light of the disappointing results from STICH, two separate sub-analyses to further identify a group of patients who will benefit most from revascularization were conducted by Panza et al and Stewart et al in 2014. The study by Panza, focusing on the presence of three anatomical variables: 3-vessel disease, severely reduced LVEF and extremely enlarged LV (i.e. high end-systolic volume index) showed that patients with two or more poor prognostic variables derive the greatest benefit from CABG combined with optimal medical therapy as compared to those on optimal medical therapy alone in terms of all-cause and cardiovascular mortality. The study by Stewart suggested that patients with better exercise capacity (who can walk for 300 meters and who has less limiting symptoms of dyspnea or fatigue) have improved survival with CABG compared to medical therapy.

Percutaneous vs. surgical revascularization

Managing patients with depressed LF function and complex coronary anatomy raises another question: does multi-vessel percutaneous coronary intervention (PCI) give similar outcome to surgical revascularization (CABG) in individuals with ischemic cardiomyopathy? Several propensity analyses and nonrandomized studies observing patients with depressed EF who underwent CABG or PCI with bare-metal or DES stents have demonstrated improved risk -adjusted survival with surgical revascularization. Unfortunately, high-quality comparative effectiveness data of PCI versus CABG in this high risk patient population are scant, since the waste majority of randomized clinical trials have excluded individuals with severely reduced LVEF or left main disease. However, recent reports from BARI, AWESOME, FREEDOM and SYNTAX trials have reconfirmed the superiority of CABG over PCI in individuals with multi -vessel CAD with complex anatomy (i.e. high SYNTAX score), complex and/or distal left main disease and in diabetic patients. Interestingly, according to BCIS-1 (balloon pump assisted coronary intervention study) and PROTECT II (a prospective clinical trial of hemodynamic support with Impella 2.5™ versus intra -aortic balloon pump in patients undergoing high-risk PCI) trials, ischemic HF patients treated with PCI had a significant reduction in all-cause mortality when elective hemodynamic support with IABP or Impela™ was established prior to the percutaneous intervention, whereby Impella™ provided superior hemodynamic support compared to IABP with strong trend toward decrease in major adverse effects in the first 90 days after PCI.

Conclusions

To summarize, coronary revascularization to improve LV function and improve mortality in patients with ischemic cardiomyopathy remains controversial, mainly due to significant inconsistency between the results from observational studies with known limitations and the results from inadequately designed and/or conducted randomized trials. While a large body of observational evidence suggests that individuals with dysfunctional but viable myocardium may experience improvement in mortality and LV function after revascularization, the results from randomized trials conducted in the last decade dispute the value of viability testing or coronary revascularization in improving outcomes in patients with ischemic HF. Lack of interaction between myocardial viability and benefit from revascularization in these studies suggest that the assessment of myocardial viability might not be the sole deciding factor in selecting the best therapy strategy for patients with ischemic cardiomyopathy, indicating that besides physiological variables (i.e. viability) also anatomical and functional variables (i.e. degree of CAD, LV dimension and function and exercise capacity) must be strongly considered in clinical decision-making. It namely appears that early revascularization must be strongly considered in patients who are at greater risk of suffering another acute ischemic event and who, at the same time, have a diminished cardiac ability to survive it but are otherwise healthy enough to compensate for the trauma and stress provided by surgery. Surgical revascularization is superior to PCI in individuals with multi-vessel CAD with complex anatomy, complex and/or distal left main disease and in diabetic patients. In all other cases PCI may have similar outcomes to surgical revascularization if complete revascularization is achieved. Noteworthy, hemodynamic support with IABP or LVAD established

prior to the PCI procedure offers better early- and mid-term results. However, for the final elucidation of the dilemma, more randomized studies will be needed in this sector, grouping patients to three treatment arms including optimal medical therapy versus multi-vessel PCI versus CABG with blinded assessment of myocardial viability by cardiac MRI in all patients.

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When to refer a heart failure patient for electrophysiology study and catheter ablation?

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Patients with heart failure die for two reasons: advanced circulatory insufficiency or sudden death. Ventricular tachycardia (VT) is one of the most significant causes of sudden cardiac death in patients with underlying structural heart disease and heart failure. On the other end, atrial fibrillation is increasingly affecting patients with heart failure, to an extent, that both entities have been referred to as epidemics of 21st century. These two arrhythmias represent most common indications for electrophysiological (EP) evaluation in patients with ventricular dysfunction. In the following text, indications for EP study, and potential role of treatment by catheter radiofrequency (RF) ablation will be covered, accordingly.

Ventricular tachycardia

This arrhythmia represents probably the most common indicaton for EP evaluation in patients with heart failure. In the present, solely EP study is rarely performed; in most instances patients are referred for catheter ablation of VT.

EP study for diagnostic purposes plays a limited role. It is considered in following circumstances:

- for diagnostic evaluation of patients with history of MI with symptoms suspicious of ventricular tachyarrhythmias (palpitations and presyncope or syncope).
- for the diagnostic evaluation of wide-QRS-complex tachycardias of unclear mechanism in patients with coronary artery disease.
- for risk stratification in patients with remote MI, nonsustained VT, and LVEF equal to or less than 40% to facilitated decision making regarding an ICD implantation.
- in patients with syncope of unknown cause with impaired LV function or structural heart disease to rule out, or confirm ventricular tachyarrhythmia as a cause.

Currently, EP testing is most frequently performed to guide and assess efficacy of VT ablation.

Management and role of RF ablation

Goals of treatment are directed toward managing the underlying heart disease, possible precipitating factors, such as acute myocardial ischemia, and preventing recurrent VT episodes. Management options typically include implantable cardioverter-defibrillator (ICD), sometimes with resynchronization pacemaker function (CRT-D), implantation, antiarrhythmic drugs, and catheter ablation. In most patients with structural heart disease and VT, ICD s and antiarrhythmic drugs remain mainstays for primary and secondary prevention of sudden cardiac death. Although ICDs are lifesaving, they have no influence on the underlying substrate, nor do they prevent occurrence of VT. Resulting recurrent ICD shocks importantly decrease the quality of life and cause psychological stress for these patients. Moreover, repeated ICD shocks have been shown to increase mortality and hospitalizations due to heart failure. Antiarrhythmics and beta-blockers might decrease the rate of ICD interventions, albeit with limited efficacy and considerable rate of side effects. Recurrent VT episodes can be a marker for deterioration of heart failure and mortality risk despite an ICD. Some patients warrant assessment for cardiac transplantation or LV assist device placement so that the eligibility of these options is known in the event of further deterioration. These interventions significantly decrease arrhythmia burden, however, VTs originating from scars around LVAD port insertion have been described.

Historically, catheter ablation of VT was considered only after pharmacological options had been exhausted, and after the patient had suffered recurrent VT episodes with resultant multiple ICD shocks. However, over the past decade VT ablation has evolved as promising treatment modality with potential to reduce the burden of VT, and consequently the ICD shocks. Advances in technology and understanding of VT mechanisms allow ablation of VTs with acceptable safety and efficacy. Consequently, indications for VT ablation continue to expand and are recommended earlier in the course of the disease.

In UMC Ljubljana, we performed 323 electrophysiological tests and VT ablations in 278 patients during time interval between 2000 and 2013. The most common indications for VT ablation, according to underlying pathology, were ischemic heart disease (54 %), dilative cardiomyopathy (18 %), arrhythmogenic right ventricular cardiomyopathy (9 %), and other causes (outflow tract Vts, fascicular Vts, etc) in the remaining 19 % of cases. Most common indication for VT ablation in ICD and CRT recipients at our institution was in patients with ishemic heart disease. We performed 44 ablations of ischemic VT in 34 patients. Majority (79%) had significantly lowered LV ejection fraction (< 45%). Typically, patients presented either as electrical storm with frequent VTs and several ICD discharges within 1 to 2 days (65% of patients), or recurrent sustained monomorphic VT. Our approach typically encompasses substrate mapping with electroanatomical system, to delineate ischemic scar and border zones. This is combined with pace mapping to identify VT exit site and late potential identification in the low voltage areas, which denote slow conduction areas. These areas are than targeted with goal of electrical homogenization of the scar. Non inducibillity of clinical, and ideally of any VT is the procedural end point. In cases of hemodynamically tolerable monomorphic VT, an activation mapping and entrainment techniques are utilized in addition to aforementioned. After median follow up of 12,5 month success rates for ischemic VT ablation are as follows: 56 % freedom from VT off amiodarone, additional 29 % had significantly lowered VT burden without ICD shock on beta blocker and/or amiodarone, 9 % had recurrence during follow up, and 2 patients (6 %) were acutely unsuccessful. Our results are in line with those published in the literature, which cites success rates of ischemic VT ablation between 50 % and 75 %.

In patients with non ischemic cardiomyopathy (dilative, ARVD, hypertrophic), scar-related reentry is the most common cause of sustained monomorphic VT, similarly to ischemic heart disease. Only difference being that scarring is more widespread, commonly adjacent to valves annulus, and much more likely to be located epicardial. Consecutively, endocardialy placed ablation lesions, may not reach epicardial located substrate. Therefore, more and more often, percutaneous pericardial space access is

utilized to combine endocardial with epicardial mapping and ablation of the substrate. Combined approach is necessary in about one third of cases in dilated cardiomyopathy. Despite VT ablation being more difficult than in coronary artery disease, recurrent arrhythmias are controlled in about 60% of patients.

In *conclusion,* catheter ablation of VT provides effective and reasonably safe treatment option for patients with underlying heart disease, who suffer from recurrent ICD discharges. With increasing numbers of patients receiving devices, the growing need for complex VT ablation is expected in the future.

Atrial fibrillation

Incidence of heart failure and atrial fibrillation has been in continuous increase, and is projected to do so in the future. The steadily increasing number of patients with heart failure is due partially to better treatment and "salvage" of patients with acute myocardial infarctions earlier in life. The association between AF and heart failure is well established. The reported prevalence of AF in modern heart failure series ranges from 13% to 27%. Moreover, the prevalence of AF in patients with heart failure increases in parallel with the severity of the disease, ranging from 5% in patients with mild to 10% to 26% among patients with moderate up to 50% in patients with severe heart failure. The pathophysiological relationship between AF and heart failure is complex. One condition predisposes to another, and vice versa. It has been well established, that AF may facilitate the development or progression of heart failure in several ways. The prognostic significance of AF in patients with heart failure remains somewhat controversial. However, data analyses of more recent trials have shown correlation between AF and increased mortality in patients with heart failure. From these trials, it appears that AF serves as a negative prognostic marker in patients with systolic heart failure, and the independent effect of AF on mortality is inversely related to the severity of heart failure. Therefore, it is conceivable, that achieving stable sinus rhythm might yield benefits for AF patients with concomitant heart failure. Antiarrhythmic drugs have showed limited success rates at achieving and maintaining stable sinus rhythm. Taking into account their significant adverse effects, and that many of them are contraindicated in left ventricular dysfunction, utilization of antiarrhythmics is significantly limited in the setting of heart failure. Given the limitations of current pharmacological therapy, nonpharmacological treatments of AF have evolved as promising therapeutic options. Currently, ablation techniques are considered when rate or rhythm cannot be controlled by medical treatment alone. More recently, catheter ablation was accepted also as a first line treatment option in patients with paroxysmal AF.

In view of catheter based ablation techniques as therapies for AF in heart failure, we might consider two approaches:

- AV node ablation and ventricular pacing (as a rate control option)
- Curative catheter ablation of AF (as a rhythm control option)

In patients with symptomatic AF and rapid ventricular response refractory to pharmacological therapy radiofrequency atrioventricular (AV) nodal ablation with subsequent pacemaker placement can provide functional benefit to a patient. However, long term right ventricular pacing in patients with heart failure might lead to less than favorable results due to LV dyssynchrony and consequent LV remodeling with dilatation and decreases in ejection fraction. More recently, resynchronization pacing (CRT) showed more favorable results, especially in comparison with pharmacological rate control strategies. In one such study, patients who underwent AV nodal ablation with CRT achieved significantly better symptomatic relief with improvement in their LV function.

The other approach is to try to achieve sinus rhythm and reinstitute atrioventricular synchrony, which would conceivable be especially beneficial in the setting of heart failure. Catheter ablation of AF has emerged as promising option at achieving this goal. The role of catheter ablation is not simply to restore and maintain sinus rhythm, but also to improve quality of life, and ameliorate symptoms of arrhythmia. Catheter ablation of AF also has been

shown to be effective in patients with heart failure, although volume of data is limited. Nevertheless, studies have shown that catheter ablation success rate for patients with heart failure is similar to those with normal ejection fraction. Since than, studies have shown improved quality of life and functional capacity after catheter ablation compared with pharmacological rate control therapies. In addition, recent studies demonstrated improvement in systolic function after catheter ablation of AF and concomitant heart failure. More recently, the Pulmonary-Vein Isolation for AF in Patients With Heart Failure (PABA-CHF) compared extremes of rhythm and rate control strategies. Trial demonstrated that a strategy of pulmonary vein isolation was superior to AV node ablation combined with biventricular pacing in patients with heart failure. Patients randomized to pulmonary vein isolation had a significantly higher mean ejection fraction (35% versus 28%), a longer distance on the walk test, and a higher quality-of-life score.

It is clear that optimal pharmacological therapy for heart failure has a beneficial impact on the progression of AF. The impact of new AF in the setting of heart failure can be dramatic in individual patients, and it is possible that aggressive therapy to restore sinus rhythm during this window of opportunity may have lasting benefit. In patients with new-onset and persistent AF, a test of cardioversion may be helpful to investigate whether sinus rhythm improves their symptoms of heart failure. When it is demonstrated to be important, maintenance of sinus rhythm by whatever means necessary seems reasonable. Catheter ablation of AF is a promising therapeutic intervention in achieving this goal.

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Which heart failure patients should undergo percutaneous mitral valve repair?

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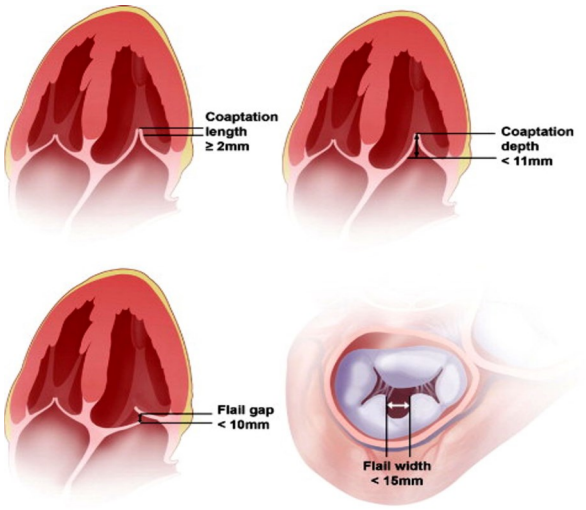
Percutaneous transcatheter mitral valve repair using the MitraClip system (MClip, Abbott Vascular, Abbott Park, Illinois, USA) is a relatively novel method for treatment of mitral regurgitation. The technique is based on the creation of a double mitral orifice, similar to surgical Alfieri's stitch, by connecting ideally the middle scallops of the anterior and the posterior leaflet of a regurgitant mitral valve. The MClip is currently the only percutaneous procedure available in routine clinical practice. According to the latest European and American guidelines it is considered as an alternative treatment for selected high-risk inoperable patients with primary mitral regurgitation. The European guidelines have included MClip as a potential option also for symptomatic patients with secondary mitral regurgitation due to ischemic or non-ischemic dilated cardiomyopathy despite optimal medical therapy and cardiac resynchronization when indicated (Table 1). Namely, surgical correction of secondary MR is controversial, because the primary pathology is left ventricular dysfunction and not the diseased mitral valve, the results of surgery are not favorable and operative mortality is much higher compared to primary mitral disease. The initial data of the EVEREST trials (Endovascular Valve Edge-to-Edge Repair Study),

including predominately patients with degenerative mitral regurgitation, demonstrated feasibility and safety of the MClip procedure. Compared to surgery percutaneous repair was less effective at reducing mitral regurgitation. Subsequent studies and registries have confirmed MClip feasibility and low procedural risk and shown promising results in terms of reducing mitral regurgitation grade, improvement of functional status and quality of life (8-11). In real-life practice there has been a shift in the indications for MClip toward secondary mitral regurgitation, which presents currently about 80% of MClip implantations in Europe.

Patient selection for the MClip therapy depends on clinical factors as well as specific anatomical criteria that need to be fulfilled. Echocardiography has an essential role in patient selection and evaluation of the final results after clip implantation. Moreover, it is the central imaging modality for guiding the procedure. The first step in the patients selection is to assess the severity of mitral regurgitation, then to determine the morphology of the mitral valve and abnormalities in left ventricular function. According to the EVEREST studies mitral regurgitation needs to be moderate to severe or severe (grade 3+ or 4+, respectively, when classifying regurgitation into four grades). The mitral valve morphology and the etiology of mitral regurgitation should be assessed in detail by transoesophageal echocardiography (TEE), as suitable morphology is essential to a successful Mitraclip procedure. For patients with secondary mitral regurgitation, the coaptation length must be at least 2 mm, and the coaptation depth < 11 mm. For patients with primary mitral regurgitation due to prolapse or flail leaflet, the gap of the prolapsed or flailed segment must be <10 mm and its width <15 mm (Figure 1). MClip is not applicable to patients not fulfilling above echocardiographic criteria, those with rheumatic mitral disease or with calcifications of the grasping area. The mitral valve area should not be less than 4 cm^2 in order to avoid creating mitral stenosis after the procedure.

Figure 1. In secondary MR the coaptation length must be at least 2 mm and coaptation depth <11 mm, so that there is some tissue for grasping with the clip. In primary MR with prolapse and/or flail, flail depth must be <10 mm and flail width <15 mm.



Conclusion

We presented first Slovenian experience with the MClip procedure. The MClip represents an exciting advancement in the field of percutaneous structural heart interventions. As for aortic valve disease with great expansion of transcatheter aortic valve implantations, the MClip system has been developed to enable mitral valve repair in patients with severe mitral regurgitation. To date more than 35.000 MClip procedures were performed worldwide. It should be offered to carefully selected patients who fulfill echocardiographic anatomical criteria and are discussed within a heart team comprising of cardiac surgeon, interventional cardiologist, referring cardiologist, imaging specialist and cardiac anesthesiologist. There is growing tendency for MClip therapy in heart failure patients with secondary mitral regurgitation, as an adjunctive treatment when optimal medical therapy fails to provide clinical improvement. There are currently ongoing prospective, randomized, comparative studies (MITRA-FR, COAPT), which will assess the MClip device efficacy in this population of patients, already on optimal medical therapy.

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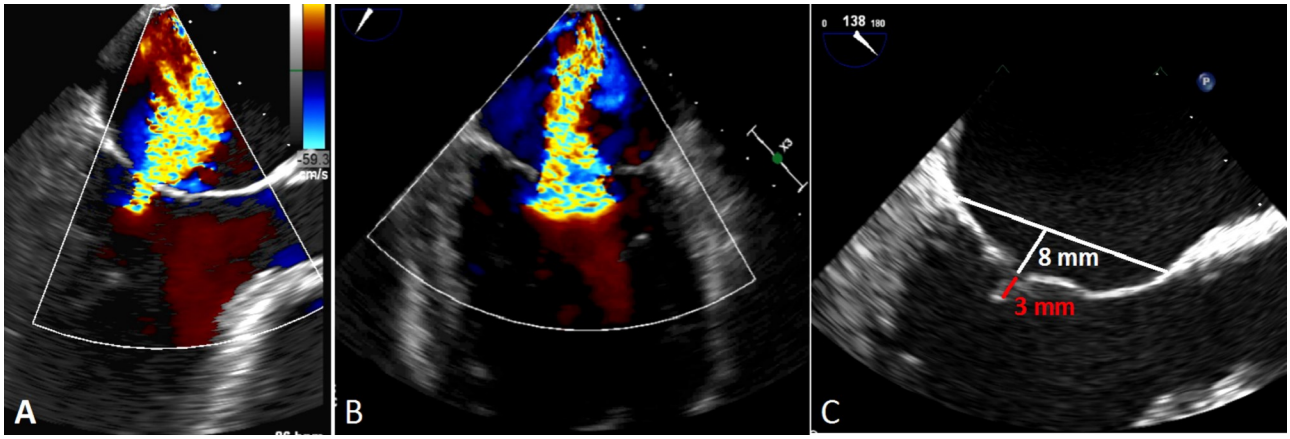
Table 1. Indications for percutaneous mitral valve repair using the Mitraclip system according to the latest European (ESC) and American guidelines (AHA/ACC).

	ESC	AHA/ACC
Percutaneous mitral valve repair may be considered in patients with symptomatic severe **primary** MR who fulfill the echo criteria of eligibility, are judged inoperable or at high surgical risk by a heart team and have life expectancy greater than 1 year	**IIb C**	**IIb B**
Percutaneous mitral valve repair may be considered in patients with symptomatic severe **secondary** MR despite optimal medical therapy (including CRT if indicated) who fulfill the echo criteria of eligibility, are judged inoperable or at high surgical risk by a heart team and have life expectancy greater than 1 year	**IIb C**	

Figure 2. 2-dimensional TEE at mid-esophageal long axis (A) and inter-commissural view (B) showing the regurgitant mitral jet which is smaller in the long axis, but much wider in inter-commissural view, pointing ellipsoid shape of the regurgitant area, typical for secondary mitral regurgitation. C illustrates tenting of the mitral valve leaflets. Remaining degree of coaptation is enough for grasping (3 mm) and the coaptation length is not too long (8 mm).



Preservation and storage techniques in heart transplantation in Slovenia

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The article describes our current technique of heart preservation and storage in heart transplantation and discusses some recent development in this field.

Technique used in Slovenia

During harvest of the heart we infuse cold (4ºC) Custodiol into the aortic root through large tubing by means of gravity. We usually place the Custodiol bag approximately one meter above the level of the heart, which gives the perfusion pressure of approximately 75 mmHg. We use three liters of Custodiol and target the 10 min run of cardioplegia. If the Custodiol is running too fast after the heart has been arrested we lower the bag to get a lower perfusion pressure of the root and slow down the perfusion flow. When perfusion ends, we excise the heart and store it in a bag that contains cold Custodiol, This bag is sealed and placed in the second bag which holds cold saline. The second bag is then sealed and placed in the third bag which contains only air, to avoid any direct contact between the heart and ice. The third bag is then sealed and placed on ice in a transport container and transported. Immediately upon arrival, when the heart is taken out of the sealed bags, the Custodiol is discarded, antegrade cannula is placed in the ascending aorta of the donor heart and our standard antegrade cold blood cardioplegia with Solumedrol is given (blood to crystalline ratio 4:1). The cold blood cardioplegia is then repeated during implantation of the heart, usually 2 to 3 times. Before we release the cross-clamp a hot-shot cardioplegia is given.

Discussion

Recent development in this field has challenged our "traditional" ways of organ storage and preservation, particularly the use of severe hypothermia and storage solution composition. Hypothermia is used to minimize metabolism in the arrested heart, however hypothermia itself induces time-dependent irreversible injury. The newly developed Somah solution focuses on maintaining active metabolism during storage by providing nutrients and high-energy phosphates and aims to protect both the myocardial and endocardial / endothelial cells. This enables storage of animal hearts not only at 4ºC but also at higher temperatures and for longer periods of time. Experiments have shown that the ideal storage temperature for Somah solution is 21ºC, which allows for prompt reanimation and complete functional recovery of the heart after reperfusion. Other currently commercially available storage solutions such as Custodiol and Celsior rely on hypothermia to minimize metabolism and lead to stone heart when used for storage for several hours at 21ºC. On the contrary, Somah solution can also be used at 4ºC and provides equal or better results than competitive solutions.

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Levosimendan in heart transplant surgery

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Inotropes are frequently used in cardiac surgery to facilitate separation of patient from cardiopulmonary bypass and treatment of low cardiac output state. Poor cardiac contractility after surgery is a consequence cardioplegia-related myocardial stunning, ischemic-reperfusion injury or preexisting disease of myocardium. In heart transplant surgery, donor, procedural and recipient factors may contribute to the development of primary graft failure, which is managed with inotropes or mechanical support. There are no guidelines for the management of inotropes in cardiac surgery. There is wide variation in their use, which is often institutional dependent and based on personal preferences. Inotropes have been shown to increase short- and long-term mortality after cardiac surgery. The incidence of common post-surgery complications – myocardial infarction, need for renal replacement therapy and stroke – is also increased. It seems that only intraoperative use to facilitate weaning from bypass is less harmful than prolonged postoperative use.

Intraoperative inotrope use

Classical inotropes (PDE inhibitors and catecholamines) increase calcium load in the cell, which increase myocardial oxygen consumption, leading to ischemia, arrhythmias, apoptosis and cell death. This could be mechanism of increased adverse outcomes. Newer inotrope levosimendan is calcium sensitizer, which does not increase the calcium load in the cell; therefore it has neutral effect on myocardial energy consumption. It also acts on K_{ATP} channels in vascular smooth muscles and mitochondria causing arteriolar and venous vasodilation and myocardial protection. It has long acting metabolite OR-1896 ($t_{1/2}$ 80-96h) with the same but even more potent clinical effects as parental drug. Since the drug doesn't act via cAMP, it can be used in patients on beta-blockers. It has been in use in cardiac surgery more than 15 years. It is more effective than other inotropes in maintaining cardiac output and stable hemodynamic state (increasing cardiac index, reducing systemic and pulmonary resistance). Several meta-analyses have shown levosimendan to be the only inotrope which reduces mortality and other adverse effects after cardiac surgery, especially in patients with reduced preoperative left ventricular function. International consensus conference in 2012 has recognized levosimendan as one of 12 non-surgical interventions that might reduce mortality in cardiac surgery. Levosimendan also prevents renal and hepatic dysfunction post cardiac surgery. The need for other inotropes and mechanical support after surgery is reduced. Taking into account the mechanism of drug action, it is obvious that levosimendan is not classical inotrope. Beside inodilatory effects it also has numerous cardio- and other organ-protective properties: pre- and post-conditioning, anti-ischemic, anti-stunning, anti-apoptotic, anti-remodeling and anti-inflammatory effects. It takes several hours for these effects to occur. If we want to take advantage of the drug as cardioprotective agent it is recommended to start infusion several hours preoperatively in high-risk patients to prevent postoperative low cardiac output syndrome.

Levosimendan in heart transplantation

In heart transplant recipients levosimendan is attractive as protective agent against primary graft failure and pulmonary vasodilator in patients with pulmonary hypertension for prevention or treatment of right heart failure. Levosimendan reduced short-term mortality, when added to other inotropes in patients with primary graft failure already present. In our hospital we use levosimendan routinely as part of multimodal protocol to prevent primary graft failure. Our group has shown reduced 30-days and 1 year mortality due to cardiac failure in heart transplant

recipients, better renal function and greater pulmonary vasodilatory effect, despite higher risk recipient group. There are very few patients not suitable for perioperative use of levosimendan (patients with recent exposure to drug, patients with uncontrollable hypotension). During drug infusion attention must be drawn to certain precautionary measures (maintaining electrolyte balance to avoid arrhythmias, avoidance of hypovolemia). Side effects are rare, except hypotension, which is usually easily managed with volume expansion or vasoconstrictors.

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Takotsubo or neurogenic stress cardiomyopathy in donor hearts

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Cardiac transplantation is severely restricted by donor availability. Among deceased organ donors, only 28% of hearts are recovered for transplantation. After brain injury, about 1/3 of patients manifest with left ventricular (LV) dysfunction. Also in patients with subarachnoid hemorrhage (SAH) and brain death, there is a 20 to 45% incidence of systolic dysfunction. Poor cardiac function is the most common reason for declining a donor offer.

Takotsubo cardiomyopathy and neurogenic stress cardiomyopathy

Catecholamine induced cardiac dysfunction in brain death donors has many similarities with reversible stress-induced cardiomyopathy known also as Takotsubo cardiomyopathy. Takotsubo cardiomyopathy is called also broken heart syndrome, or apical ballooning syndrome. Human donor heart dysfunction, on the other hand, is also known as neurogenic stress cardiomyopathy (NSC). Microscopy of the myocardium in organ donors has similar changes found in Takotsubo cardiomyopathy. Typical clinical findings in both conditions are transient LV wall motion abnormalities, EKG changes and elevation in myocardial enzymes. There are EKG changes like sinus tachycardia, ST segments elevation, prolong QTc and T-wave changes. In Takotsubo cardiomyopathy and in NSC left ventricle is typically affected with apical and middle segment hypokinesis and basal hyperkinesis, however, right ventricle can

be also affected. It can be argued that NSC and Takotsubo cardiomyopathy are the same entity, as the pathophysiology and clinical course from onset to resolution are almost identical. In most cases there is absence of obstructive coronary artery disease. The mechanism of injury is still unclear, but the trigger are high levels of catecholamines after acute medical illness or after intense emotional or physical stress. Postulated mechanisms include catecholamine excess, coronary artery spasm, microvascular dysfunction, resulting in myocardial stunning. Catecholamine storm is seen also in most brain dead donors.

Takotsubo affects postmenopausal women more often. The term »Takotsubo« was first described in Japan and is named after octopus trap, which has a shape like apical ballooning configuration of the left ventricle in systole (Figure 1)

The diagnosis NSC in brain death organ donors should be suspected when there are ECG abnormalities, typical apical ballooning and reduced systolic function on echocardiography. Mild elevated cardiac biomarkers, e.g. cardiac troponin and creatine kinase are also present. Coronary angiography normally demonstrates no critical obstructive coronary disease.

Experience in University medical center Ljubljana

We present three cases of brain dead donors who were accepted for hearth transplantation although the hearth function was impaired (Table 1). We have accepted these donors because we believe that NSC/ Takotsubo cardiomyopathy is reversible.

All three transplanted patients needed a high inotrope and vasopressor support with noradrenaline, milrinone or dobutamine and levosimendan. Adrenalin infusion was used for 2 days in the second patient (receiving hearth from donor #2). They were all on nitric oxide (NO) 20 ppm which was slowly reduced until extubation. The third patient needed intraaortic balloon pump. The cold ischemia time was 247, 150 and 234 minutes for the first, second and third donor, respectively. We could gradually reduce inotropic and vasopressor support. The EF in all three patients increased to around 40% within four to five days after transplantation. First patient was transferred to the ward only one month later because of acute renal failure requiring haemodialysis and he suffered a stroke with right hemiparesis. All three patients had almost a normal cardiac function at hospital discharge.

Figure 1. Left ventriculogram: A end-diastolic phase, B end-systolic phase, C octopus trap

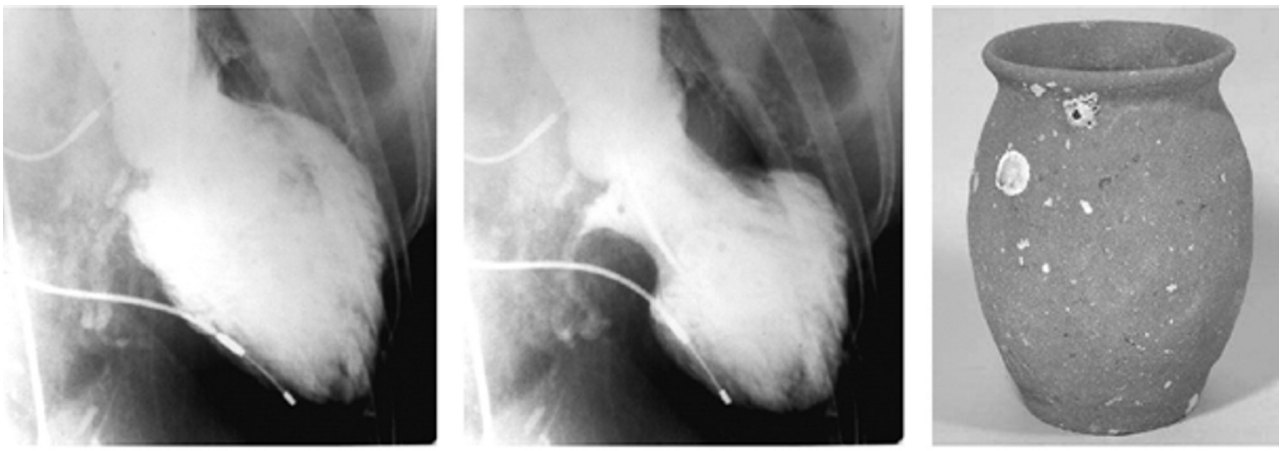

Table 1. Characteristics of three brain dead donor hearts with Takotsubo cardiomyopathy successfully transplanted. cTn, cardiac troponin; EF, ejection fraction.

DONOR	1	2	3
sex	M	F	F
age	27	49	48
Cause of death	politrauma	SAH	SAH
Cardiac arrest	/	/	CPR 20min
Medical history	healthy	healthy	healthy
troponine	cTnT =1,3 ng/ml	cTnI=0,38 µg/l	cTnT =1,12 ng/ml
TTE	1.EF=20%,2.EF=30%	EF=35-40%, takotsubo	EF=50%
ABO Rh	0 +	B+	0 +
Vasopressors, inotropes	Noradrenalin 0,25µg/ kg/min, enoksimon 2µg/kg/min	Noradrenalin 0,12µg/ kg/min	Noradrenalin 0,34-0,45µg/kg/min
Coronary angiography	/	/	EF=33%, takotsubo
Date of admission	11.8.2013	17.6.2015	29.4.2015
Brain death date	13.8.2013	18.6.2015	1.5.2015
Date of procurement	14.8.2013	19.6.2015	2.5.2015

Conclusions

Acknowledging the reversible nature of NCS/ Takotsubo cardiomyopathy may lead to fewer donor offer declines and consequently increase the availability of hearts for transplantation.

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Renal-sparing strategies in heart transplantation

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Heart transplantation (HTX) remains a gold standart for the treatment of advanced refractory heart failure. Since the long-term survival after HTX significantly increased in the past decades complications such as coronary allograft vasculopathy, malignancies and renal dysfunction have become the main determinants of the quality of life and the long-term survival after HTX. In this brief report the main etiological aspects of post-transplant renal dysfunction (TXRD) and main strategies for its prevention/minimization are discussed.

Why does post-transplant renal dysfuction matter?

Various studies reported widely variable incidence of TXRD reflecting different definitions of kidney dysfunction and methods used for its assesment. Nevertheless, Ojo et al. (1) establised an incidence of TXRD (defined as GFR < 30 mL/min/1,73m^2 BSA) of 1,9%, 6,8% and 10,9% at 1, 3 and 5 years after heart transplantation respectively. These data were later corroborated with ISHLT registry data showing the incidence of TXRD (defined as serum creatinine > 2,5mg/dL) being 6%, 11% and 16% at 1, 3 and 5 years respectively.

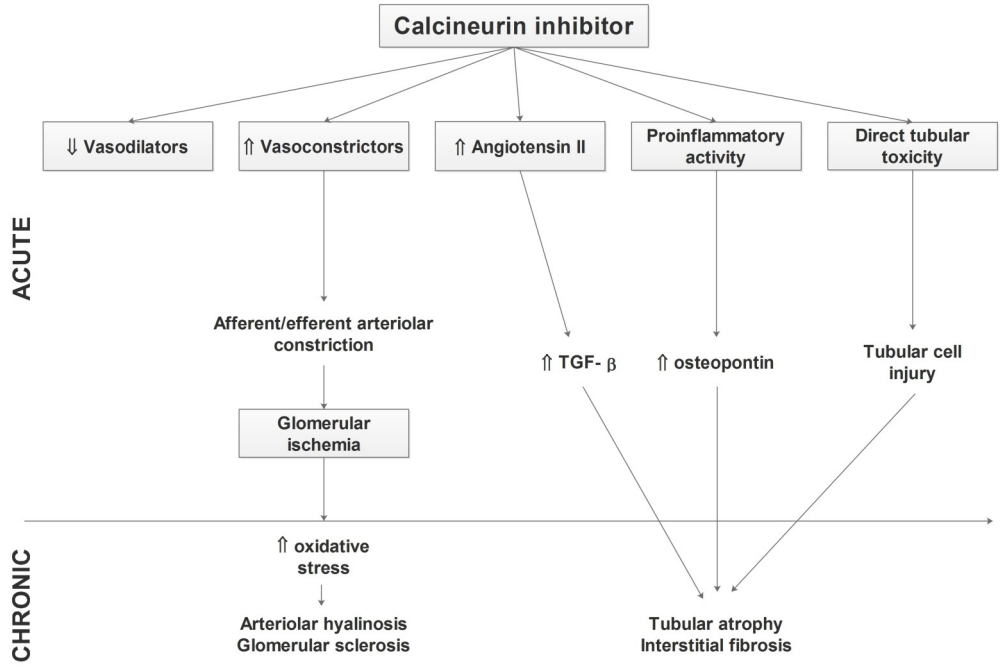
The occurence of TXRD after heart transplantation has significant prognostic implications as ISHLT data suggest TXRD has remained one of the leading specific causes of death beyond 5 years after HTX, being responsible for up to 10% of all deaths. Additionally, serum creatinine levels have repeatedly been associated with worse long-term prognosis after HTX. The increase in mortality in this patient population is mainly mediated by an increase in cardiovascular mortality. Furthermore, TXRD has been associated with an increased incidence of non-fatal major cardiovascular adverse events. To improve long-term outcome after heart transplantation TXRD, when present, clearly has to be timely and efficiently addressed.

Pathophysiology of post-transplant renal dysfunction

The evolution of renal funciton after HTX usually shows a biphasic pattern with an initial steep decline within the first two post-transplant years and is subsequently followed by a less pronouced decline thereafter. Although TXRD is a complex and multifactorial condition, current etiologic paradigm of TXRD is based on the concept of calcineurin (CNI)-related nephrotoxicity. The main factors of CNI-related nephrotoxicity are shown in Figure 1. In short, CNIs acutely cause an imbalance between endothelial vasodilators and vasoconstrictors leading to significant vasoconstriction of afferent arterioles (thus causing a decrease in GFR). The chronic CNI toxicity is mainly caused by adverse tissue effects of angiotensin II and tumor growth factor-β and is characterized not only by a decrease in GFR but also in diffuse interstitial changes such as tubular atrophy and fibrosis. Although CNI nephrotoxicity is believed to be a class effect some differences between cyclosporine and tacrolimus are thought to exist. However, conclusive advantages of tacrolimus over cyclosporin with regards to long-term renal function or long-term survival have not been conclusively demonstrated.

In addition to CNI other, more »classical«, factors such as advanced age, pre-existing renal disease, diabetes mellitus and diabetes, hyperlipidemia, extensive atherosclerosis and perioperative hemodinamic instability may also aggravate renal function in heart transplant recipients. These factors have to be meticulously addressed in the pre-transplant patient management in order to minimize the incidence and degree of TXRD. Additionally, the incidence of TXRD is also higher in patients with previous LVADs, hepatitis C and Plyoma BK infection.

Figure 1. Pathophysiology of CNI after heart transplantation.



Renal-sparing strategies after heart transplantation

Measures to prevent or minimize TXRD after HTX can be broadly divided in two groups. The first group relates to the general measures that focus on maintenance of sufficient renal perfusion, avoidance of nephrotoxic drugs and meticulous control of classic risk factors of renal dysfunction (see above). The second group of measures refers to various modifications of immunosupressive therapy.

General measures

About one third of heart transplant recipients have impaired renal function prior to transplantation. In these patients meticulous perioperative care with avoiding episodes of prolonged hypotension, hypovolemia or anemia and sparing of nephrotoxic drugs is of paramount importance. Additionally well-managed glucose metabolism and well-controlled hypertension significantly reduce the risk of TXRD occurance and progression. Some experimental data suggest that calcium channel blockers may reverse the unwanted glomerular hemodynamic effects, caused by CNIs. Furthermore renin-angiotensin blocking agents have also been shown to improve TXRD, most likely due to their anti-proteinuric effect.

Renal-sparing immunosupressive regimens

Since CNIs have been implicated as the main culprit in the pathophysiology of TXRD, several strategies to reduce CNI exposure after HTX have been proposed. These strategies have been tested in two distinct clinical settings, namely immediately after (de-novo strategy) or during the chronic phase (maintenance strategy) after HTX.

<u>De-novo strategies:</u>

The main concern with CNI reduction in a de-novo setting is the risk of allograft rejection. With their immunosupressive effect, antibody induction therapy has been proposed to enable us to delay CNI induction at the time of transplantation (especially in patients with pre-transplant renal disease). Additionally, substitution of azathioprine with more potent antiproliferative agent mycophenolate mofetil (MMF) has allowed us to lower CNI exposure after heart transplantation. More recently, proliferative signal inhibitors (mTORs) have been introduced for clinical use after HTX. Because of the lack of intrinsic nephrotoxicity, this class of drugs has been extensively investigated in various renal-sparing strategies. (5) As far as de-novo mTOR-based regimens are concerned, complete CNI replacement

has been deemed too risky option and should currently not be routinely considered. The data for the efficacy and safety of CNI/mTOR combination regimens can be summarized as follows:

- Due to mTOR-CNI interaction, the combination of these drugs will likely cause the deterioration of renal function unless CNI doses and through concentrations are significantly reduced.
- Regarding rejection prevention, mTORs are more effective as azathioprine and about equally effective as MMF.
- mTORs are superior to MMF or azathioprine with regards to prevention of allograft vasculopathy.
- mTORs have their specific type of side effects: delayed wound healing, pericardial/pleural effusions, increased risk of bacterial and fungal infections. However, an incidence of CMV infection is lower with mTORs as with other immunosupressive drugs.

Maintenance strategies:

With significantly reduced risk for rejection in the maintenance phase after HTX, both total conversion to mTORs (CNI replacement) and the use of combination of mTORs and CNIs (CNI reduction) strategies were extensively evaluated (4,6). The current experience in these approaches can be summerized in the following points:

- CNI replacement or CNI reduction strategies both result in significant improvement in renal function as compared to standard immunosupression.
- Wheather CNI reduction is superior to CNI replacement or vice-versa remains to be established as currently there are no studies comapring these strategies head-to-head.
- In CNI reduction strategy CNI through concentrations should be reduced by at least 50% of the baseline in order to obtain any clinically relevant improvement in renal function.
- The main predictor of renal recovery after CNI discontinuation is the total time of CNI exposure and not solely the degree of renal dysfunction. It has been shown that 4-5 years after HTX conversion form CNI to mTOR may even lead to worsening renal function. Thus the optimal timing for mTOR initiation remains largely undefined – currently single-center data suggest that the conversion should be considered between 3-6 months after HTX.
- In patients with preexisting proteinuria mTOR should be used cutiously.
- The major concern of CNI replacement or reduction strategies is the risk of acute allograft rejection. It has been established that CNI reduction strategy has lower rejection risk as the CNI replacement strategy. Thus an increased rejection surveillance should be considered in these patients.
- In up to 15% of patients mTORs have to be discontinued within the first year due to side effects. This high percentage of discontinuation significantly limits mTORs as an efficient renal-sparing strategy after HTX.
- The beneficial effects of mTORs on allograft vasculopathy progression remain controversial. Modest improvements may be expected in early conversion from CNI to mTOR. However, late converison (after 1 year after HTX) did not show any benefits of mTORs on CAV development or progression.

Future perspectives

Novel approaches to immunosupression

Tacrolimus is a potent immunosuppressant agent widely used for the prevention and treatment of rejection in solid organ transplantation. While tacrolimus is typically administered in two divided doses per day, a new oral formulation with modified-release characteristics has recently been developed and licensed for use. Due to different dissolution properties, this preparation is typically released further along the gastrointestinal tract. Specifically formulated to enable once daily dosing, it has been suggested that the primary benefit of the prolonged-release preparation maybe improved compliance with medication administration.

In addition to improved patient compliance, modified-release tacrolimus has also been associated with lower trough concentration (C0) variability when compared to standard twice-daily tacrolimus regimen in stable kidney transplant recipients. Since the reduced C0 tacrolimus variability has been shown to be associated with improvements in renal fuction, modified-release formulation tacrolimus could also lead to clinical benefits. Indeed, in a recent meta-

analysis of modified vs. standard release tacrolimus in kidney transplant recipients, 50% of the included trials reported better renal function in the single dosing arm at 6 months after transplantation.

In heart transplant recipients there is evidence for successful conversion from standard to modified-release tacrolimus on a 1:1 (mg/mg) total daily dose basis. Both formulations were well tolerated, with adverse events reported by approximately one-tenth of patients receiving standard tacrolimus and a quarter of those who received modified release regimen. Although these data suggest the safety and feasibility of such treatment approach, the relation between tacrolimus C0 variability and renal function in heart transplant patients treated with modified-release tacrolimus remains to be defined.

Improved perioperative renal protection

Levosimendan has been shown to improve renal function in end-stage heart failure patients awaiting heart transplantation. This beneficial effect is thought to be a combination of increase in cardiac output and a direct effect of levosimendan on renal afferent arteries, causing increased glomerular filtration. Rencently, it has been shown that patients, who recieved levosimendan perioperatively during heart transplantation also exhibit significantly better renal function than patients managed on »classical« inotropes. Thus, modification of perioperative management using levosimendan may also contribute to renal sparing in these patients.

Conclusion

TXRD represents a major complication after heart transplantation. Although TXRD is multifactorial, CNI therapy carries a key pathophysiological role. Several novel immunosupressive strategies have been developed to reduce CNI exposure in early and late period after HTX. Currently, the use of mTORs carries a promise of better renal protection, however its wide use is hampered by the lack of conclusive evidence on one hand and the high incidence of side effects on the other hand. Further trials are needed to further the field of renal-sparing immunupression regimens after heart transplantation. Additionally, other measures of renal protection should also be further explored. Only throug integration of tailored immunosupression and optimization of general measures the optimal prevention/reduction of TXRD can be achieved.

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Total artificial heart: a long-term solution?

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Heart failure (HF) is a serious health care issue and a primary contributor to cardiovascular mortality affecting more than 20 million people worldwide, and the prevalence of HF is rising rapidly even in developing countries. Heart transplantation can provide a remarkable improvement in quality of life and survival in selected patients with end-stage HF, but a shortage of donor hearts will always limit this option. An estimated 6,300 heart transplantations are performed worldwide each year, with a median survival of 11 years and >90% reporting normal functional capacity. These numbers have remained consistent over the past several years and affirm that heart transplantation is a viable and effective therapy for select patients with stage D heart failure. However, the therapy is limited by the availability of donor organs, so patient selection is critical.

Concerted efforts in mechanical circulatory support have yielded a broad array of device options tailored for short term or extended periods of hemodynamic support. These various options play central roles in the treatment of advanced heart failure. One of the most impactful developments in this rapidly evolving field has been the advent of durable, implantable left ventricular assist devices (LVADs). More widespread adoption of this technology has resulted in a steady increase in LVAD implants from approximately 100 per year in 2006 to over 2,500 in 2014, a 2500% increase in only 8 years. Strategies for LVAD implantation are largely predicated on candidacy for cardiac transplantation, and thus primarily intended as either a bridge to transplant or destination therapy for those deemed transplant ineligible. The fraction of patients implanted for destination therapy indications continues to increase, comprising over 40% of all cases.

For a subset of patients with heart failure, left ventricular support alone will not suffice, and some modality of biventricular assistance must be instituted.

HF stage D medical treatment

In the landmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, stage D patients who were treated medically experienced 75% mortality at 1 year and virtually no survival at 2 years. Optimally treated patients in the Investigation of Non–Transplant-Eligible Patients Who Are Inotrope Dependent (INTREPID) trial had survival rates of 22% at 6 months and 11% at 1 year. In a random population-based sample from Olmstead County, Minnesota, USA, stage D heart failure was associated with only 20% 5-year survival. Patients bridging to end of life on continuous inotropes have the poorest survival: 6% at 1 year.

Myocardial recovery from stage D

In some patients with stage D heart failure, MCS devices may provide an opportunity for "bridge to recovery." The clinical occurrence of MCS-facilitated myocardial recovery varies widely in published reports, but it probably occurs in 5%–10% in most centers. In the most recent Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) report, the rate of recovery at 1 year in bridge-to-transplantation continuous-flow LVADs was only 1%. Despite the enthusiasm for myocardial recovery, it remains an elusive therapeutic end point for most patients.

Total artificial heart

At a 1957 meeting of the American Society of Artificial Internal Organs, the idea of an intracorporeal implantable artificial organ was received with mixed feelings, and they remark that the challenges in developing these potentially lifesaving technologies were comparable to a "trip to the moon."

Zuhdi and colleagues described what were some basic

requirements to develop a permanently implanted heart that would "assist circulation and maintain life for indefinite periods of time." In addition, they identified the major criteria for a "total bypass implantable heart" device: (1) it is inert, (2) it deters clot formation, (3) it does not destroy blood elements, (4) it can provide reproducible performance over long periods (approximately 20 years), (5) it is of sufficient size to be placed in a pleural cavity, and (6) it has a source of energy that is small, portable, preferably implantable, reliable, and long lasting. These device design criteria remain important characteristics for today's LVADs and total artificial hearts (TAHs) as well. Research into TAH devices began in the United States in 1963. The studies soon encountered myriad difficulties related to biocompatibility, autoregulation, device dimensions, practicality of implant and postimplant lifestyle, energy delivery, and long-term durability. Significant advances have been made in our understanding of the progression and pathophysiology of HF since the initial conceptualization of TAHs using the mechanical device from the laboratory of Willem Kolff (Figure 1).

Figure 1. Willem Johan ''Pim' Kolff (above), Total artificial heart from 1957 (below)

During the past four decades several groups in the USA and Europe have developed and clinically implemented different cardiac prostheses or TAH—the Cooley/Liotta TAH, Jarvik7 TAH, Bücherl Heart TAH, AbioCor TAH, and CardioWest TAH (TAH-t), which is currently in use.

Total replacement of the patient's heart with a mechanical device-TAH continues to be an option – or even essential – in specific groups of patients, for example, those with single-ventricle physiology, those who are not candidates for isolated left ventricular support by a VAD due to impaired right ventricular function, those with malignant cardiac tumors, those with irreparabile acquired VSD and those with cardiac allograft failure. Approximately 70% of patients with a TAH are successfully 'bridged' to cardiac allotransplantation, though the mortality on the device is approximately 25%. Systemic infection (incidence of approximately 50%), driveline infection (25%), and thromboembolic/hemorrhagic events (30%) remain major complications.

MCS devices, such as percutaneous and durable VADs and TAHs, have experienced a dramatic and exponential growth in utilization, driven mostly by the availability of durable continuous-flow pumps, expected to last for several years, and improved survival statistics. Clinical trial data suggest that anticipated survival with LVADs could be expected to be ~85% at 1 year with an average survival of ~3 years. There have now been >24,000 continuous-flow VADs implanted. DT has expanded MCS to a large population of older patients and those with significant comorbidities that preclude cardiac transplantation.

However, up to 44% of patients needing LVADs also have significant right ventricular failure, for which the only feasible solutions are heart transplantation, biventricular assist devices, or a TAH.

TAH today

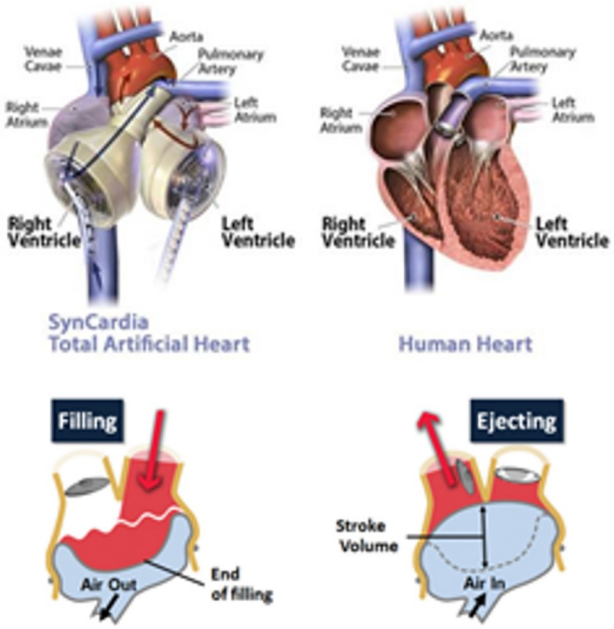
In contrast to LVADs, existing clinical TAHs are all volume-displacement pulsatile-flow pumps: a temporary pneumatic system (CardioWest; SynCardia, Tucson, Arizona, USA), and a permanent

electrohydraulically driven system (Carmat TAH; Carmat, Vélizy Villacoublay, France).

Approved by the FDA for bridge to transplantation in 2007, the SynCardia total artificial heart is a pneumatically driven, pulsatile pump, designed to orthotopically replace the native ventricles and all four valves. Surgically, this entails bilateral ventriculectomy and fashioning atrial cuffs that are anastamosed to rigid, spherical polyurethane chambers that serve as ventricles. Each chamber houses two outflow mechanical valves. Two subcutaneously tunneled drivelines are connected to pneumatic drivers within the external console (Figure 2). Once implanted, total output from the total artificial heart is 7–8 L/min. Certain body size criteria must be met to accommodate the device, including a minimal body surface area (BSA) of 1.7 m^2 and a thoracic diameter of at least 10 cm. In the seminal report by Copeland et al. in 2004, the total artificial heart successfully bridged 79% patients to heart transplant compared to 46% in the control group. In this prospective multicenter study of 130 patients between 1993 and 2002, survival following transplantation in the total artificial heart group was 86% and 65% at 1 and 5 years, respectively, on par with international registry benchmarks. On March 31, 2015 SynCardia Systems, Inc. has received FDA approval to conduct an Investigational Device Exemption (IDE) clinical study on the effective use of its smaller 50cc SynCardia temporary Total Artificial Heart, which is intended to fit most women, adults of smaller stature and many adolescents with BSA < 1.85 m^2 and shorter sternum-T10 diameter.

Alain Carpentier and colleagues have developed a novel bioprosthetic total artificial heart, the CARMAT-TAH (C-TAH), on which they report in *The Lancet*. The idea behind the C-TAH is to create a device with almost entirely haemocompatible blood chamber surfaces (polytetrafluoroethylene plus treated bovine pericardial tissue) and physiological pulsatile flow (enabled by Carpentier-Edwards biological heart valves), as well as viscoelastic contractility providing physiological pressure curves and a right-left side filling algorithm. With its volume-compensating elastic shell this novel, electro-hydraulically actuated

Figure 2. SynCardia TAH (above), Cardiac Output Adjusts with Venous Return "Starling Principle" (below)



pulsatile and biological artificial heart resembles the natural heart (Figure). A disadvantage is that since the actuator is integrated, the device is fairly large (displacement volume 750 mL) and thus suitable only for selected patients. Carpentier and colleagues describe successful implementation of the C-TAH for the treatment of biventricular heart failure in two patients aged 76 and 68 years as part of a feasibility and safety trial. After implantation, both TAH recipients presented fast recovery in terms of almost normalised cardiac output, satisfactory end-organ function, and good mental status during an accumulated 344 days of support. Both patients unfortunately died after 74 days and 270 days of support, respectively, due to fatal failure of electronics, but no mechanical failure nor thrombotic dysfunction was detected. In the first patient, the use of haemocompatible materials had an important role, allowing all anticoagulants to be withdrawn during the 50 days after the onset of bleeding complications. The second patient, after discharge, was receiving low-level anticoagulation with acetylsalicylic acid and low-molecular-weight heparin only.

The most extensive clinical experience has been acquired using the SynCardia CardioWest TAH with

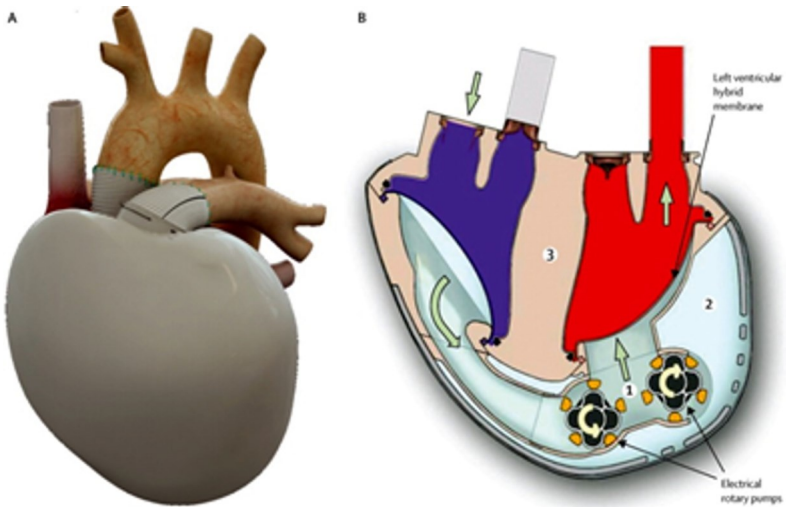


Figure 3. The CARMAT bioprosthetic total artificial heart.All components, except batteries, are embodied in a single device mimicking a normal heart. The polyurethane sac serves as a compliant chamber. (A) External view. (B) Internal view. Electrical rotary pumps (1) activate silicone oil (2) deploying back and forth hybrid membranes. Electronic components are located in the interventricular septum (3).

more than 1,500 implants, accounting for more than 400 patient years of support worldwide.

Due to technically demanding implantation of TAH, and the known inherent limitations to pulsatile pump designs, alternatives to biventricular support have been explored and implemented. A notable example is the off-label use of two HeartWare® HVADs in a biventricular support configuration. While limited to published case reports and small series, proof of principle in these isolated patient experiences will likely spurn further efforts to optimize biventricular support modalities.

At present, usage of the total artificial heart is favorable in transplant eligible patients with established biventricular failure refractory to optimal medical management. This would include patients presenting at INTERMACS levels 2 through 4, with a low likelihood of right ventricular recovery following unloading of the left ventricle alone with an LVAD.

Future directions

The aim of TAHs is to mimic native heart anatomy and function, fitting into the pericardial cavity and providing pulsatile unidirectional blood flow from the atria to the great arteries in patients with end-stage biventricular heart failure. These systems require excision of the patient's native ventricles and are mechanical, non-biological devices.

During the past several years, continuous-flow (CF) rotary pumps have replaced volume-displacement pulsatile-flow pumps because of their simplicity, increased mechanical reliability, improved durability, smaller size, and better outcomes. All (100%) LVADs implanted in 2012 and 2013 were CF LVADs, which clearly indicates the future direction of this therapy. The reduced mechanical complexity of rotary pumps dramatically improves their durability and makes them less expensive to produce. In addition, these pumps are smaller, quieter, and more energy-efficient than pulsatile pumps (PP). Finally, rotary pumps are inflow-pressure sensitive. They closely imitate the native heart by autonomously increasing pump flow in response to an increasing preload. Therefore, constant-flow technology may be ideally suited for integration into the next generation of TAHs.

Since all the devices bring the blood into contact with artificial materials, anticoagulation therapy is obligatory postoperatively to prevent thrombus formation. Fatal complications due to anticoagulation and device-related infection, together with limited durability of the mechanical components (multilayer membranes, mechanical valves, pushing mechanisms, drivelines) lead to diminished clinical application of TAH implantation compared with heart transplantation.

Efforts to develop a continuous-flow total artificial heart are also in progress and have shown success in preclinical studies. Looking farther into the future, durable mechanical circulatory support technology would be a completely implantable, wireless system. Untethering patients from a driveline would be a major achievement and vastly improve VAD

outcomes. To that end, the concept of Free-Range Resonant Electrical Energy Delivery (FREE-D) has surfaced as a viable approach to wirelessly power a LVAD. Using an implanted physiologic controller coupled with a FREE-D receiver coil investigators from the Bonde Artificial Heart Laboratory at Yale, USA, were able to wirelessly power an LVAD for 2 weeks. To sustain this continuous energy transfer, one might envision a future where transmitting power coils are preinstalled throughout a patient's home. It remains to be seen how long before these and other key milestones will be reached in the field of mechanical circulatory support. What is certain is that many significant strides have already been made, and boundless potential exists for the care of patients with advanced heart failure.

Conclusion

Although many significant technological advances with mechanical circulatory support have been made over the past 50 years, our field still faces many hurdles to overcome—namely, reducing adverse events related to the patient-device interface. As a technology to treat advanced heart failure, we have not "walked on the moon" yet, but we continue to "shoot for the stars" as a potential treatment and cure for millions of patients with advanced heart failure that will ultimately require something beyond medical therapy.

Over the next decade, as costs decrease, patient selection is further refined, and technologies that remove the requirement for external driveline progress, it is likely that destination therapy will become an accepted part of advanced heart failure management. There will be an increase in the variety of chronic MCS available from partial support at one end of the severe heart failure spectrum, to complete heart replacement at the other. Although LVADs will remain the mainstay of temporary support for the majority of patients while waiting for transplant, with ongoing improvements in MCS, it is likely that the next decade will bring the first clinical trial of mechanical organ replacement versus human organ transplantation.

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Stem cell therapy for chronic heart failure

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Despite advances that have been achieved in medical and device therapy over the past decades, heart failure (HF) represents an increasingly common, debilitating disorder that carries an adverse prognosis. Although current HF treatment options have shown to improve survival and reduce HF symptoms, no therapy to date has been shown to promote the regeneration of myocardial damageor replacement of lost myocardial tissue, which represent the main underlying pathophysiologic mechanisms of heart failure development and progression. Ever since the first successful use of bone marrow stem cells in experimental model of acute myocardial infarction was published in 2001 there has been a growing interest in the HF community to apply stem cell therapy for the treatment of chronic HF. Although the results of numerous preclinical and clinical studies conducted in the last decade support the potential of stem cells to improve myocardial function and affect adverse ventricular remodelling, there is a number of clinical questions that remain poorly defined. Thus, the aim of this review is to discuss recent advances in clinical aspects of stem cell therapy in HF patients, with emphasis on patient selection and stem cell types.

Stem cells represent a cell population with self-renewal properties and the potential to generate daughter cells that are capable of differentiation along specific cell lineages. To date, several stem cell types have been consideredfor the treatment of patients with ischemic and non-ischemic chronic HF.

Skeletal myoblasts (SM)

SMs are derived from skeletal muscle satellite cells. Due to the easy access, quick in-vitro expansion and relative resistance to hypoxic environment SMs were initially considered to represent an ideal cell population for myocardial regeneration. In animal models of HF, SMs have been shown to differentiate into myotubes and form viable skeletal muscle-like grafts. This was associated with improved myocardial performance, attenuated adverse ventricular remodelling and decreased myocardial fibrosis. These encouraging preclinical data were the basis for three clinical trials (MAGIC, POZNAN and CAUSMIC) that, however, failed to show a consistent benefit of this stem cell population. Also, a risk of life-threatening ventricular arrhythias using SMs has raised significant concerns. With other stem cell types becomming more accessible, the interest in SMs has decreased in the recent years and currently no large randomized control trial is exploring the role of SM in patients with chronic heart failure.

Bone marrow-derived stem cells

Bone marrow is the source of mixed population of hematopoetic and nonhematopoetic stem cells. Both groups have been shown to possessthe ability for transdifferentiation into different cell lineages.Due to the easy access and procurement, this group of stem cells has gained the most attention in preclinical and clinical settings in the recent years. The results of studies using bone marrow mononuclear cells (BMMCs) for the treatment of chronic ischemic heart failure have been conflicting. The first study to evaluate BMMCs in patients with ischemic HF demonstrated a significant improvement in left ventricular ejection fraction and reduction in end-systolic volume in treated patients at 2 and 4 months after the procedure. Additionally, an increase in myocardial perfusion and patents'exercise capacity was demonstrated. These results were corroborated by other studies that used intramyocardial injections of BMMCs in peri-scar area. Interestingly, BMMCs injections directly into the scar tissue failed to produce comparable results. In TOPCARE-CHD study intracoronary infusion of BMMC vs. endothelial progenitor cells (EPC) in patients with ischemic heart failure was analysed. Left ventricular ejection fraction improved significantly in BMMC group but not in EPC

group, the exact underlying mechanisms remaining undefined. Registry data from TOPCARE-CHD further suggested that BMMC stem cell therapy significantly decreases neurohumoral activantion as early as 3 moths after therapy. Additionally, it was shown that infusion of BMMCs with high functional capacity was associated with improved long-term survival in this patient cohort. However, in contrast to these findings, the FOCUS-CCTRN trial, one of the largest trials to evaluate the effects of BMMCs in patients with ischemic HF, failed to show any benefit of stem cell therapy on myocardial performance, volumes or perfusion. Nevertheless, a post-hoc analysis showed that $CD34^+$ stem cell count in BMMC sample correlated significantly with the improvement of myocardial performance, suggesting that specific bone marrow cell subpopulations may be responsible for the beneficial effects of BMMC therapy.

Unselected BMMCs were used also in patients with non-ischemic HF. In TOPCARE-DCM study intracoronary BMMC infusion into the left anterior descending coronary artery resulted in improved regional wall motion of the injected area and global left ventricular myocardial performance (19).In ABCD trial, the investigators enrolled patients with non-ischemic HF, who received either intracoronary injection of BMCMs or sham control. During the 3-year follow-up the LVEF improved in the treatment arm by 5.9%. Similarly, in a study of patients with refractory non-ischemic HF, infusion of BMMCs into the left main coronary artery was associated with improved myocardial performance, maximal oxygen consumption, and quality of life. These data may suggest that that BMMC therapy may be of more benefit in patients with non-ischemic HF than in patients with HF due to coronary artery disease; however, the variations in BMMC populations, patient selection criteria and delivery methods make direct comparisons between the studies very difficult.

Hematopoietic stem cells (HSC)

HSC represent a part of hematopoetic cell compartment of the bone marrow and differentiate into mature cells along lymphoid and myeloid lineages. When HSCs are released in the peripheral circulation they becomeEPCs. Both cell types are positive for $CD34^+$ surface marker and together they form a population of $CD34^+$ stem cells, which have been shown to have a potential to differentiate into endothelial cells and promote neovascularization. Initially, $CD34^+$ cells were used in ischemic HF patients undergoing cardiac surgery. In this population, it was shown that transepicardial $CD34^+$ stem cell injections around the scar area at the time of surgical revasularization may significantly improve myocardial performance when compared to surgical revascularization alone. However, a recent study evaluating the effects of HSC in patients with ischemic HF undergoing surgical revasularization failed to confirm these findings. Therefore, it appears that when injected at the time of cardiac surgery, $CD34^+$ cells may not exert consistent beneficial effects on myocardial performance and structure. Alternaltively, when $CD34^+$ cells were injected via percutaneous transendocardial approach in patients with chronic ischemic HF, such therapy led to a significant improvement in left ventricular global function (mainly driven by improved contraction of injected segments), improvement of exercise capacity and reduced neurohumoral activation. Similar findings were found when using a novel population of $CD34^+$ stem cells, ALDH-bright cells, which were shown to be safe and to have a potential to reverse left ventricular remodelling.

In patients with non-ischemic HF, transplantation of $CD34^+$ stem cells obtained through periheral blood apheresis and immunomagnetic selection, significantly improved myocardial performance, patients' functional capacity and neurohumoral activation (Figure 1). Of note, these positive effects persisted through the 5-year follow-up period and translated in significantly improved survival of patients receiving $CD34^+$ cell therapy.

Mesenchymal stem cells (MSC)

MSCs represent a part of nonhematopoetic cell compartment and have been reported to differentiate into cardiomyocytes and endothelial cells. The potential advantage of these cells is that they are immunoprivileged and thus do not cause the activation of immune response, which enables them to be used in an allogeneic setting. The POSEIDON

studywas the first to explore dose-effect relationship of MSCsand compared clinical effects of autologous and allogeneic MSCs in patients with ischemic HF. The authors were able to show that both, autologous and allogeneic MSCs exert favorable effect of patients' quality of life, functional performance and ventricular remodelling. Furthermore, POSEIDON data showed that although scar size reduction was evident in all myocardial segments, scar size reduction and ventricular functional responses predominantely occurred in the segments that were injected with MSCs. These results were confirmed by the PROMETHEUS trial, where surgical application of MSCs was associated with a significant scar reduction, improvement in myocardial perfusion, and regional function that occurred predominantly at the site of transepicardial MSC injection. When compared to unselected BMMCs in TAC-HFT trial, MSCs were shown to outperform BMMCs with regards to scar reduction and improvements in myocardial function. Thus, it appears that both autologous and allogeneic MSC therapy may be effective in improving heart function in patients with ischemic HF, and can potentially also lead to beneficial clinical outcome in this patient population. This may represent an important step towards development of a standardized stem cell product for widespread clinical use. To date, there is no data on the effects of MSC in non-ischemic HF and almost completed POSEIDON-DCM study is aiming to evaluate this therapy in HF patients without coronary artery disease.

Cardiac stem cells (CSC)

Recently, it has been hypothesized that CSCs are responsible for continuous myocardial regeneration and that they have the capacity to differentiate into cardiomyocytes, endothelial cells and fibroblasts. Several preclinical studies consistently demostrated the positive effects of CSCs on left ventricular regeneration. The first human study of CSCs, SCIPIO trial, evaluated the effects of this stem cell type in

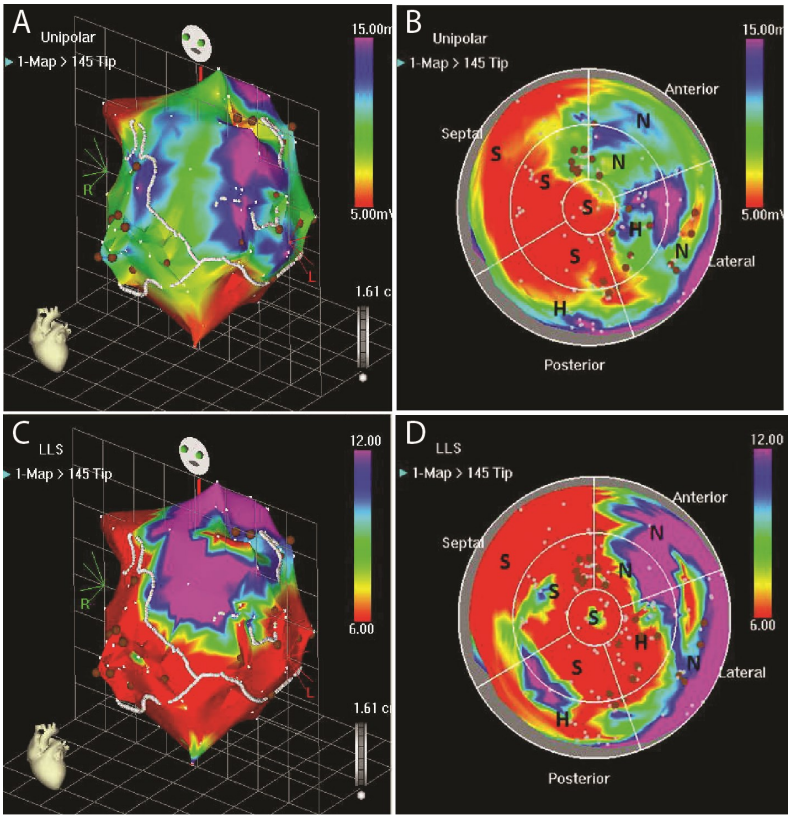

Figure 1. Exemplary 3D (Figure 1A and 1C) and corresponding 2D (Figure 1B and D) quantitative polar maps of a patient with non-ischemic DCM, showing unipolar voltage and linear shortening. Segments with predominance of high unipolar voltage and high LLS (purple, blue, or green color on both panels) are defined as normal myocardium (N); segments with predominance of low unipolar voltage and low LLS (red and yellow color on both panels) are defined as scarred myocardium (S); and segments with a predominance of high unipolar voltage (purple, blue, or green on left panel) and low LLS (red or yellow on right panel) are defined as hibernating myocardium (H). Brown dots represent sites of transedocardial CD34+ cell injections.

patients with ischemic heart failure undergoing surgical revascularization. CSCs were isolated from the myocardial biopsy at the time of cardiac surgery and subsequently expanded in-vitro. At 4 months after the surgery, these cells were injected via intracoronary route. The results of the study were in accordance with the animal data and showed significant improvement of myocardial performance in stem cell group but not in the control group. Additionally, CSCs were shown to reduce the amount of scar in the myocardium as assesed by cardiac MRI. These positive effects persisted over the period of 12 months.

Cardiosphere-derived cells (CDC)

CDCs represent a heterogeneous mix of cells, derived from myocardial biopsy specimens and comprise of cells that express hematopoetical and mesenchymal antigens. CDCs were shown to differentiate in cardiomyocytes, and animal data suggested intracoronary injections of CDCs may promote myocardial regeneration. The CADUCEUS trial was the first to evaluate the effects of CDCs in patients with ischemic HF. CDCs were implanted via intracoronary route and three different stem cell doses were evaluated. In treated patients, CDCs were shown to significantly reduce myocardial scar burden with concomitant increase in viable tissue and regional systolic wall thickening. CDCs, however, failed to increase left ventricular ejection fraction, reduce left ventricular systolic and diastolic volumes or improve patients' NYHA functional class.

Conclusions

In summary, several types of stem cells for the treatment of ischemic and nonishcemic HF have been evaluated in clinical settings. Although many small trials have shown promising results with regards to regional or global improvement of myocardial performance, myocardial scar reduction, improvement of patients' functional capacitiy and quality of life, the findings have not been uniform. However, given the wide heterogeneity of patients with chronic HF it may be difficult to define a stem cell therapy that would fit all subsets of patients; instead, future stem cell therapeutic strategies should aim for more personalized approach by establishing optimal stem cell type, dose, and delivery method for an individual patient and stage of the disease.

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