

Heterotopic Abdominal Rat Heart Transplantation as a Model to Investigate Volume Dependency of Myocardial Remodeling

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Abstract: Heterotopic abdominal rat heart transplantation has been extensively used to investigate ischemic-reperfusion injury, immunological consequences during heart transplantations and also to study remodeling of the myocardium due to volume unloading. We provide a unique review on the latter and present a summary of the experimental studies on rat heart transplantation to illustrate changes that occur to the myocardium due to volume unloading. We divided the literature based on whether normal or failing rat heart models were used. This analysis may provide a basis to understand the physiological effects of mechanical circulatory support therapy.

(*Transplantation* 2017;101: 498–505)

Hear failure (HF) is the abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues.¹ The incidence of end-stage HF is increasing across all developed countries, partly due to the aging populations and the effectiveness of salvaging patients presenting with acute myocardial infarction.² Although heart transplantation remains the definitive therapy for end-stage HF, the supply of organ donors cannot keep pace with the ever-rising demand and many untreated patients are left to struggle with a poor quality of life and limited life expectancy. For these individuals, mechanical circulatory support (MCS) may offer a benefit by buying more time for the patient as a bridge to transplantation or in some cases, may be a substitute for cardiac transplantation or destination therapy.³

Animal models are frequently used in research studies to provide insight into certain clinical settings, such as MCS therapy. Large animal models (eg, bovine, canine, caprine, porcine and ovine) all provide reasonably close approximations to the anatomy and function of the human heart.

Consequently, preclinical left ventricular assist device (LVAD) implantation studies are often carried out on (mostly healthy) large animals.⁴ However, these experiments mainly focused on the surgical steps and feasibility of device implantation, device function, and its acute hemodynamic effects. Meanwhile in the clinical setting, patients implanted with LVADs are often supported for several months or years. Yet, little is known about the physiological effects of mechanical unloading on the myocardium. The rat is a relatively inexpensive animal model which has been widely used to investigate the effects of left ventricle (LV) unloading. However, these animal models have limitations and sometimes fail to predict human responses precisely. Therefore, results from these studies must be interpreted with caution. In this article, we attempted to provide a review of rat models that gave important insight to the static and dynamic myocardial changes due to mechanical unloading, and highlighted their limitations.

In the present review, a PubMed search was performed to identify relevant literature including the following term: rat heart transplantation, with limitation of English language and publication dates 2000 to 2016. This yielded approximately 2900 publications. We included studies that explicitly focused on transplanted hearts and investigated the time and volume dependency of myocardial remodeling by unloading of healthy and/or failing rat hearts (37 articles). We excluded experiments that targeted the evaluation of immunological events and ischemic/reperfusion injury either with or without pharmacological therapy. However, we selected out certain key articles to provide a more rounded introduction and to highlight other opportunities provided by the heterotopic abdominal heart transplant (HAHT) model (17 articles). Publications that fit our aims based on these criteria constituted the main structure of our review, and further completion with clinical implications (35 articles) was assured when relevant.

Received 10 July 2016. Revision received 25 October 2016.

Accepted 26 October 2016.

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The authors declare no funding or conflicts of interest.

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ISSN: 0041-1337/17/10103-498

DOI: 10.1097/TP.0000000000001585

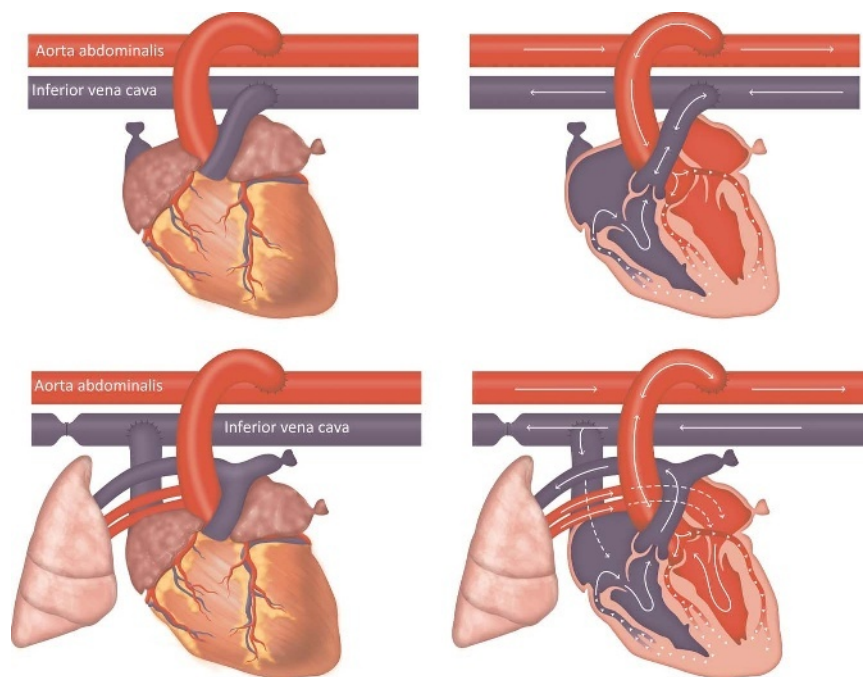


FIGURE 1. In the unloaded model of cardiac transplantation the implantation of the heart is performed as a heterotopic infra-renal graft where the end-to-side anastomosis of the Ao to the recipient Ao, and end-to-side anastomosis of the donor PA to the recipient IVC. Blood flows from the recipient Ao into the Ao root of the donor, and because the donor aortic valve is competent, coronaries are perfused without entering the LV. The greater amount of coronary flow is returned to the RA through the coronary sinus. This blood is ejected by the RV through the PA back into the venous circulation of the recipient via the IVC. Under these conditions, much smaller amount of blood originating from the coronaries are forwarded through the thebesian veins (intramural veins of LV) opening directly into the LV, thus excluding the right ventricle. Theoretically, this insignificant amount of blood is the only input to the left chamber and is occasionally ejected through the aortic valve. This model is appreciated mainly because of preserving the anatomical features of the rat heart. Below the partially loaded heart transplantation model is a combined heart-lung transplantation, where the right ventricle of the graft heart receives blood from the IVC of the host through the right atrium, which is then pumped to the donor lungs, filling the left ventricle via the left atrium. Afterwards, the blood is transmitted back to the recipient abdominal aorta. RA, right atrium; RV, right ventricle.

The purpose of this review is to provide an overall insight into the experiments with HAHT model to explore the functional and structural changes elicited by volume unloading, to better understand the pathophysiological consequences of LVAD therapy in the clinical setting.

Heterotopic Abdominal Rat Heart Transplantation Model

Abbott et al⁵ first described the HAHT in 1964. Later, Tomita⁶ introduced end-to-side anastomoses, and further improvements were made by Ono and Lindsey⁷ in 1969, which is now considered to be the classical unloaded heart model in rats. The implantation of the heart is performed as a heterotopic infra-renal graft where the end-to-side anastomosis of

the donor aorta (Ao) to the recipient Ao, and end-to-side anastomosis of the donor pulmonary artery (PA) to the recipient inferior vena cava (IVC) (Figure 1). This produces a donor LV that is virtually completely unloaded.⁸ Modifications of the original unloaded model have been made to produce the loaded,⁹ partially loaded (heart-lung transplantation) (Figure 1) and the reloaded model¹⁰ (Table 1).

HAHT is suitable for the measurement of hemodynamic parameters and ischemic/reperfusion injury of the transplanted heart as our research group¹¹⁻¹³ and others^{14,15} have previously described by performing the procedure between isogenic rats (eg, Lewis-to-Lewis) to avoid rejection. Allogenic HAHT is suitable for immunological research,^{16,17} to study various aspects of acute^{18,19} and chronic cardiac graft injury.²⁰

TABLE 1. Certain surgical properties and clinical relevance of each heterotopic abdominal rat heart transplantation model			
	Unloaded	Loaded (may include lungs)	Partially loaded (with lungs)
Difficulty	Moderate	Extremely difficult	Difficult
Duration of operation	40-60 min	60-120 min	60-120 min
Number of anastomoses	2	2	1
Clinical relevance	LVAD therapy; effects of mechanical unloading on postinfarction healing dynamics; load-dependency of myocardial remodeling; HLHS	immunological investigation (acute and chronic rejection); load dependency of myocardial remodeling	load dependency of myocardial remodeling; can be transformed to reloaded model (with a second anastomosis), imitates the situation of LVAD removal

HLHS, hypoplastic left heart syndrome.

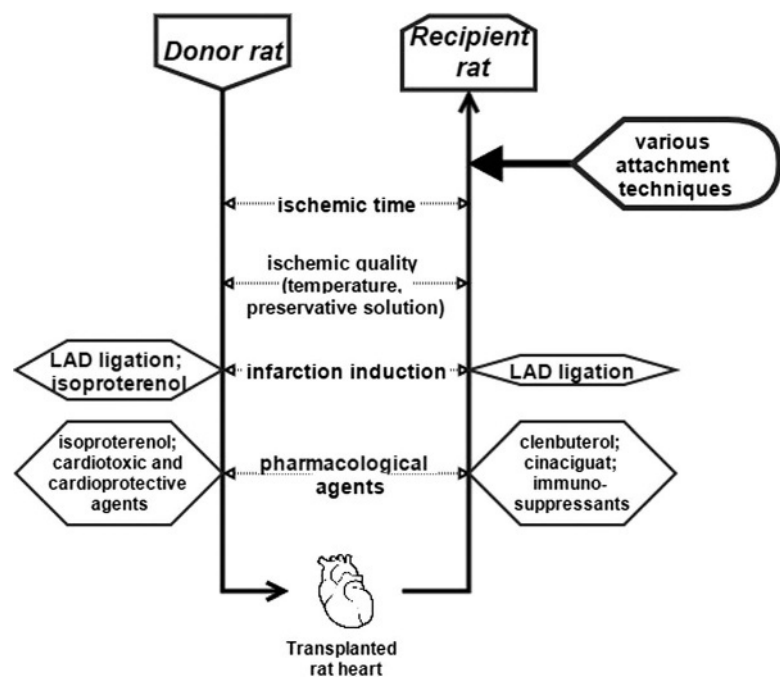


FIGURE 2. The extreme customizability of the rat heart transplantation technique relies on several stages. The transplanted rat heart can be modified, whereas in the donor, after the explantation (eg, ischemia time and quality) and with application of various attachment techniques. Furthermore, postoperative manipulation is also feasible in the recipients (not depicted on the figure, eg, reloaded model).

This model can also be used to study the combined effects of immune tolerance and ischemic/reperfusion injury.^{21,22} These models demonstrate the versatility of the HAHT model (Figure 2).

In the following sections, we focus on the alterations of myocardial parameters due to volume unloading in the HAHT model, based on whether normal or failing rat hearts were used. Table 2 summarizes the structural and functional changes of the unloaded myocardium.

Unloading of Normal Rat Hearts

Doenst and colleagues⁴¹ used subtractive hybridization technique to systematically identify differentially expressed genes in HAHT with normal rat hearts (ie, physiological atrophy) compared to unloaded, failing human hearts. The authors found that respiratory chain and metabolic genes were downregulated and stress genes were upregulated in response to mechanical unloading in both healthy rat and failing human hearts. These findings resulted in the conclusion that similarities

in gene expression profiles between unloaded failing human and normal rat hearts are independent of species differences and underlying disease, rendering HAHT a relevant model to investigate the effects of unloading.

After 2 weeks of unloading of normal rat hearts, Welsh and colleagues⁴² found intact contractile function at both cellular and tissue level. Consistent with these findings, Ito et al⁴³ reported intact fractional cell shortening and peak-systolic intracellular calcium concentration under baseline conditions and in response to extracellular calcium stimulation 2 weeks after unloading of normal rat hearts compared with control hearts. In other studies, systolic function was maintained after 4 weeks of unloading.^{44,45} However, unloading for 5 weeks resulted in severely defective fractional cell shortening and peak-systolic intracellular calcium concentration in response to high extracellular calcium concentration.⁴³ This was related to depressed sarcoplasmic calcium uptake capacity.^{43,46} These studies indicated a time-dependent depression of contractile reserve in normal rat hearts when subjected to prolonged

TABLE 2.
The mechanical unloading of the heart (either with LVAD or by HAHT) results in structural modifications on the cardiomyocyte level that in some cases later attracts functional alterations on the clinical level

Structural changes	Functional changes
Decreased sizes of cardiomyocytes ²³⁻²⁵	Amelioration of myocyte performance ^{26,27}
Alleviated rate of apoptosis ²⁸	Hemodynamic improvement of cardiac function ^{29,30}
Regeneration of mitochondrial function ^{31,32}	Recovery of cardiac dimensions from spherical to a more elliptical shape with reduction of HF indices ³³⁻³⁶
Increased modulatory neurohormonal responsiveness ²³	
Extent of fibrosis (elevated ^{30,33,35,37} ; decreased ^{25,38})	
Decreased deposition of cytokines ^{39,40}	

However, translation of structural amelioration to sustainable clinical functional recovery remains uncertain and is heavily investigated. These findings are not necessarily specific to LVAD use, but may be partially an effect of pharmacological therapy of HF.

unloading. Interestingly, there were no differences in the contractile responses to isoproterenol between unloaded (2 or 5 weeks) and normal rat hearts.⁴³

With regard to diastolic function, the half-relaxation time of isolated cardiomyocytes from healthy rat hearts remained unchanged after 2 weeks of mechanical unloading,⁴² but became significantly prolonged after 4⁴⁴ or 5 weeks^{43,47} of unloading. This was due to damages to intracellular calcium handling of cardiomyocytes with reduced myofilament sensitivity to calcium (also present in failing rat⁴⁸ and human⁴⁹ myocardium samples) and increased stiffness. Ibrahim et al⁵⁰⁻⁵² showed that normal t-tubule structure and optimal local calcium induced calcium release are dependent on a normal range of volume-loading, indicating that both volume overloading and unloading result in aberration of t-tubule structure with consequential damage to Ca²⁺ handling and excitation-contraction coupling. Studies in human heart biopsies also demonstrated loss of t-tubules and irregular surface membrane architecture in the setting of HF^{53,54} but improved calcium handling after LVAD therapy.^{26,55,56}

Although, an atrophic remodeling process of the myocardium was observed in HAHT normal rat hearts (most intensive at 2-4 days), Razeghi et al⁵⁷ confirmed simultaneous activation of both proteolysis and protein synthesis. Nevertheless, the rate of proteolysis peaked only at 7 days, indicating a “time-lag” between atrophy and proteolysis. Interestingly, the mammalian target of rapamycin (mTOR) signaling was activated in the myocardium reflecting increased protein synthesis. The research team evidenced that pharmacological inhibition of the mTOR pathway by rapamycin significantly accelerated and augmented the atrophy of HAHT rat hearts, indicating the crucial role of mTOR driven protein synthesis as a feedback mechanism to prevent excessive cardiac atrophy during unloading. These data indicate an elevated turnover rate of proteins in hearts with atrophic remodeling, similar to cardiac hypertrophic remodeling.⁵⁸ On the contrary, Klein and colleagues⁵⁹ found reduced capacity for protein synthesis due to decreased ribosomal RNA content of heterotopically unloaded rat hearts, even though the efficacy of protein synthesis remained unchanged. In the clinical setting, the so-called disuse atrophy is a major concern of long-term LVAD therapy in bridge-to-recovery patients, which may result in failure to wean from MCS. This underscores the importance of identifying the optimal duration of LV unloading and the need to prevent such excessive atrophy.

In an attempt to investigate the possible reversibility of atrophic remodeling, Tsuneyoshi et al⁶⁰ examined the effects of clenbuterol in a HAHT using normal rat hearts, a β_2 agonist, which is considered to cause “physiological” cardiac hypertrophy.⁶¹ Clenbuterol failed to prevent cardiac atrophy after 2 weeks of unloading, but potentially restricted apoptosis and ameliorated the gene expression profile (sarco/endoplasmic reticulum Ca²⁺-ATPase [SERCA2], myosin heavy chain [MHC]- β) and adrenergic responsiveness with no change in papillary muscle generated tension.⁶⁰

Brinks et al⁶² described several patterns of gene expression when normal rat hearts were unloaded for 3, 8, 15, and 30 days. First of all, gene expression of proteins participating in contractility achieved a new steady-state immediately after rat heart transplantation and unloading. Although MHC- β increased, MHC- α decreased resulting in reduced MHC- α /

MHC- β ratio⁶² indicating the activation of fetal gene program similar to hypertrophied rat hearts.⁶³ This pattern is the same as that observed in human hearts when LVAD therapy is applied.⁶⁴ This reactivation of fetal gene program is likely to be beneficial for the diseased myocardium and is associated with survival,⁶⁵ and share transcriptional regulation homologies with the aging myocardium.⁶⁶ Peroxisome proliferator-activated receptor- α , which plays a pivotal role in switching the energy metabolism from fat consumption to glucose oxidation in hypertrophied hearts,⁶⁷ also decreased sharply in the first days of unloading.^{62,68} Second, the expression of genes associated with extracellular matrix (ECM) remodeling (fibroblast growth factor 2, tissue inhibitor of matrix metalloproteinase 1 [TIMP-1]) progressively increased over time,⁶² just like atrial natriuretic peptide and brain natriuretic peptide (BNP)⁶² (also elevated in hypertrophied rat hearts⁶³), whereas matrix metalloproteinase (MMP)-2 and MMP-9 together with TGF- β remained unchanged over the 60 days of unloading. Finally, apoptotic gene expression profile remained unchanged in the first 30 days of unloading, but sharply increased by 60 days.⁶² On the contrary, atrophic remodeling was accelerated in the first weeks after unloading, reaching its peak by 15 days. These results prove that cellular atrophy is the primary mechanism that accounts for the myocardial weight reduction after ventricular unloading. Furthermore, the relative increase in the interstitial compartment in the first 30 days of unloading was a result of a disproportionate elevation of the ECM compared with the cardiomyocyte portion, and this ratio remained constant during 3 month of unloading.⁴⁵

Schwoerer and colleagues⁶⁹ investigated ion fluxes in isolated cardiomyocytes of 2-week unloaded normal rat hearts and reported that the unloaded myocardium undergoes electrophysiological remodeling in addition to anatomic and functional changes. These included prolongation of action potential (ie, prolongation of QT interval) with downregulation of repolarizing K⁺ and up regulation of the L-type Ca²⁺ channels. These changes resemble those of cardiac hypertrophy in rats.⁷⁰ Interestingly, prolongation of the QT interval was observable during the first days of LVAD implantation⁷¹ and was associated with higher incidence of ventricular arrhythmias⁷² after device implantation.

Liu et al⁷³ recently published their study in which hearts of partially loaded (heart-lung model) and unloaded heterotopic rat heart transplantation models were compared 4 weeks after the procedures. Macroscopic and microscopic atrophy, depression of cardiac function and reduction of glucose uptake were more severe in unloaded versus partially loaded hearts. However, increase in total collagen content and impairment of relaxation were comparable between groups. The authors speculated that the completely unloaded model may mimic pulsatile LVAD support, whereas the characteristics of the partially loaded model differed from continuous-flow LVAD support.⁷³ Didié and colleagues⁷⁴ conducted a similar study and reported that systolic function is better preserved and atrophy is less pronounced in the partially loaded versus the unloaded rat heart, whilst the extent of fibrosis remained comparable. Furthermore, myosin content was found to be higher in loaded rat hearts. Conversely, they reported no difference in glucose metabolism between the 2 models which is consistent with another previous study.⁷⁵ Schena et al⁷⁶ reported that apoptotic indices were

elevated but not significantly different between working and nonworking transplanted rat hearts.

Unloading of Failing Rat Hearts

In the setting of chronic HF, impairment of calcium handling together with ventricular remodeling is attributed to the heart's "response to injury."⁷⁷ Because HF is an umbrella term for a variety of cardiac diseases that result in diastolic and systolic dysfunction, we grouped the literature based on the etiology of the failing rat heart studied.

McGowan and colleagues⁷⁸ induced volume overload of the rat heart with an arteriovenous fistula. After 32 days, a compensated eccentric hypertrophied heart model (high output HF) resulted. The response of hypertrophied rat hearts to surgical unloading for 7 days was found to be similar to that of the normal rat heart. Both groups demonstrated loss of myocyte volume (ie, atrophy) with corresponding increases in collagen content. MMP/TIMP ratios were comparable in both normal and hypertrophied unloaded hearts. However, increase in collagen crosslinking after 1 week of unloading was only observed in the hypertrophied hearts, indicating differences in the dynamics of ECM homeostasis between the 2 models.

Xu et al⁷⁹ investigated the effects of unloading after compensated myocardial hypertrophy (hypertensive HF) was induced by abdominal aortic constriction (for 6 weeks). Atrophy was evident in these hearts after 2 weeks of unloading with a significant reduction of cross sectional area compared with intact hypertrophied rat hearts. Interestingly, the elevated collagen content of hypertrophied hearts was further increased by unloading. Elevations in LV crosslinked collagen content have also been reported in nonischemic HF hearts after LVAD support.³⁷ Schaefer and colleagues⁸⁰ recently described a transverse aortic constriction procedure that produced decompensated hypertrophy of the rat hearts. The effects of mechanical unloading on these hearts can also be studied with the HAHT model.

Left anterior descending (LAD) artery ligation is extensively used to induce myocardial infarction in rat hearts which later may result in HF. Unloading of these hearts show a time-dependent atrophic remodeling after 2 weeks.⁸¹ When Oriyhan and colleagues⁸² unloaded LAD artery-ligated rat hearts, the optimal duration of unloading was found to be 2 weeks which was characterized by functional recovery of the heart with an increase in SERCA2a gene expression, a reduction of BNP expression and restoration of adrenergic responsiveness of the myocardium. In the clinical setting with LVAD unloading of a failing human heart, there is an early increase in SERCA2a gene expression²⁶ with molecular recovery peaking at 20 days and complete reverse remodeling by 40 days.⁸³ Similarly, mechanical support in humans restore adrenergic responsiveness of the cardiac tissue.^{84,85} However, in the LAD artery-ligated failing rat heart, unloading for more than 4 weeks induced cardiac atrophy and deterioration of the normalized cardiac functions,⁸² indicating that there is an optimal duration for LV unloading. This is supported by clinical findings, where Xydias et al⁸⁶ reported cardiac recovery peaking at 60 days of LVAD support, but there were anatomical and functional deterioration thereafter. Wang et al⁸⁷ investigated both time and volume-dependency of the myocardial reverse remodeling by studying partially loaded (heart-lung model) and unloaded rat hearts for 2 and

4 weeks. Although contractile function deteriorated and down-regulation of SERCA2a with time was evident, partial loading but not complete unloading improved the functional response to β -adrenergic stimulation and normalized the expression of BNP and β -adrenergic receptors in failing rat hearts. They reported similar results previously when only partially loaded failing hearts were investigated for 4 weeks.⁸⁸ Nakamura and colleagues⁸⁹ investigated the relationship between the HAHT LAD artery-ligated rat hearts and the intact, native hearts of the same recipient rats and showed a significant deterioration of cardiac function and anatomy of the intact, native hearts of the recipient rats but not in the transplanted hearts due to excessive TNF- α expression. These findings suggest the key role of TNF- α in cardiac remodeling, and indicate that when LAD artery-ligated rat hearts are unloaded and investigated, utilization of the recipient rat hearts as controls may be incorrect. Finally, immediately after HAHT, Zhou et al⁹⁰ performed LAD artery ligation of the donor hearts to investigate the effects of volume unloading on the recovery of acute myocardial infarction. They demonstrated remarkable myocardial sparing with significant reduction in infarct size compared with LAD artery-ligated rat hearts in situ (ie, not transplanted). The infarcted site showed less fibrosis with disorganized and retarded collagen fibers, and decreased inflammation with enhanced angiogenesis, whereas noninfarcted areas of the myocardium were more fibrotic. In a recent study, Ruping and colleagues⁹¹ reported improvement in electrophysiological properties of the infarction zone, opposite zone and border zone in LAD artery-ligated unloaded hearts compared with nontransplanted infarcted hearts, indicating a beneficial electrophysiological state of infarcted hearts after unloading. Finally, we mentioned earlier that when normal rat hearts were unloaded, clenbuterol did not prevent cardiac atrophy. In contrast, when Soppa and colleagues⁹² unloaded LAD artery-ligated failing rat hearts for 1 week, clenbuterol significantly reduced atrophy and provided an ameliorated sarcomere contraction and relaxation with normalized Ca^{2+} handling and sensitivity together with improvement of electrophysiological characteristics. Clenbuterol has become part of a pharmacological regimen used for patients with LVAD, the so-called Harefield protocol^{93,94} due to its reported clinical benefits. Ivabradine, a heart rate reduction agent used in certain patients with HF, did not prevent disuse atrophy of LAD artery-ligated grafts that were unloaded for 4 weeks, whereas metoprolol did.⁹⁵

Muranaka et al⁹⁶ induced autoimmune dilated cardiomyopathy (DCM) in rats, and 6 weeks later they unloaded some of these hearts for 2 and 4 weeks. They found preserved myocardial contractility and adrenergic responsiveness but worsened myocardial relaxation with increased ratio of fibrotic area and myocardial apoptosis in the unloaded DCM hearts compared with nonunloaded DCM hearts. However, no differences in these changes were found between 2 and 4 weeks of unloading. LVAD therapy is also reported to increase myocardial stiffness.⁹⁷

DISCUSSION

In this review, we summarized the most relevant experimental findings regarding the volume dependent remodeling of the normal and failing rat hearts, coupling them with

clinical implications. In spite of the broad spectrum of literature using the heterotopic abdominal rat heart transplantation technique to investigate possible effects of mechanical unloading, there are obvious limitations of this model.

First of all, LVADs are applied to failing human hearts but the majority of these experimental rat heart transplantation studies were carried out with healthy hearts. However, some of the studies demonstrated that mechanical unloading elicits surprisingly similar responses in the failing human heart and the healthy rat myocardium, irrespective of species differences and underlying disease,^{41,98,99} a fact which is often cited by researchers of the topic.^{62,69}

Second, heterotopic transplantation of rat hearts requires a short duration of ischemia, even in the hands of experts. Therefore, one cannot rule out that certain functional and structural changes of the implanted grafts might be the result of that ischemic injury. Nonetheless, skillful surgeons using modern myocardial protection protocols should minimize the effects of ischaemic injury. Highly inbred (eg, Lewis) rats are used to eliminate potential effects of any immunological responses.

Third, failing rat hearts originating from HF animals that had abnormal neurohormonal regulation (as part of HF), are implanted into a healthy recipient, where such impaired regulatory state is immediately rectified. This is clearly different from the clinical setting after LVAD implantation in which the abnormal neurohormonal milieu persists. However, the healthy recipient rats provides normal coronary blood flow to the failing rat cardiac graft which is similar to the higher coronary perfusion pressures seen after LVAD implantation in humans.

Finally, LV reverse remodeling appears to vary depending on the nature of LVAD support, namely pulsatile versus continuous flow.¹⁰⁰ Such differences cannot be easily investigated with the unloaded rat heart model. However, these can be approached to some extent by comparing fully unloaded and partially loaded grafts.⁷³

Despite abovementioned limitations, the heterotopic rat heart transplantation model may have a role to elucidate some of the pathways of reverse remodeling during mechanical unloading and to identify key therapeutic targets (ie, pharmacological, gene or cell therapy) to improve myocardial function during mechanical unloading of the failing heart. These adjunctive therapies are urgently needed as more and more patients with advanced HF are being treated with LVAD implantation. With worsening shortages of donor hearts, only a limited proportion of LVAD-supported patients will be ever be bridged to transplantation whilst the majority of these will remain on long-term LVAD support unless they can be “bridged-to-recovery.” Although survival with LVAD support has improved significantly over the last decade, the incidence of adverse events as well as hospital readmission rates remain significantly higher than patients treated with transplantation.

Currently, the rate of successful and durable cardiac recovery after LVAD implantation remains low. Better rates of recovery could be expected from combining LVADs with regenerative therapies, such as gene therapy, biomaterials, and cell-based therapies. The small number of LVAD patients does not allow clinical testing of the numerous potential combinations of therapies.¹⁰¹ As novel adjunctive therapies emerge, clinically relevant animal models will be required for preclinical testing.

In the present review, we summarized the potentials and limitations of the heterotopic rat heart transplantation model for the evaluation of mechanical ventricular unloading and provided an overview of research studies using this model. We believe that this rodent model provides a simple and inexpensive means for investigating myocardial unloading and preclinical testing of novel therapies for improving myocardial function in the unloaded heart toward myocardial recovery.

CONCLUSIONS

In the clinical setting, it is challenging to separate the progression of cardiac failure from the effects of mechanical unloading, when LVAD therapy is applied to failing human hearts. Furthermore, the optimal duration of MCS therapy is still in question because myocardial remodeling due to unloading is poorly understood. These create a gap in our knowledge, assuring the importance of heterotopic abdominal rat heart transplantation to address such issues. With careful interpretation of the acquired results, heterotopic abdominal rat heart transplantation may play a major role in our further understanding of the effects of mechanical unloading.

ACKNOWLEDGMENTS

The professional language support of Professor Steven Tsui, MD (Papworth Hospital, Cambridge, UK) and Dr. Nicola Hellen PhD (Imperial College London, UK) is greatly acknowledged.

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