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Myocardial recovery during mechanical circulatory support: cellular, molecular, genomic and organ levels

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ABSTRACT

Mechanical circulatory support is a life-saving therapy that will become either a bridge-to-transplantation or definitive therapy if heart transplantation is not possible. Failing hearts supported by a ventricular assist device were often found to recover at molecular and cellular level but translation of these changes into functionally-stable cardiac recovery allowing long-term heart transplantation/ventricular assist device -free outcomes after weaning from ventricular assist device is relatively rare and related to the etiology, severity and duration of myocardial damage. The reason for the discrepancy between high recovery rates on the cellular and molecular levels and the low rate of cardiac recovery allowing ventricular assist device explantation is unknown.

Keywords: *heart failure, ventricular assist devices, ventricular function, myocardial recovery, survival, risk factors.*

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INTRODUCTION

Long-term mechanical circulatory support (MCS) with ventricular assist devices (VADs) for end-stage heart failure (HF) is a life-saving procedure that will become either a bridge to heart transplantation (HTx) or a definitive therapy for patients not eligible for HTx. However, end-stage failing hearts have often revealed remarkable ability to recover at the cellular and structural level and, in some patients, even reverse remodeling with relevant functional recovery at organ level is possible.

Thus, initial "bridge-to-transplantation" (BTT) can turn into "bridge-to-recovery" which finally allows VAD removal followed by years of HTx-free patient outcome. Although myocardial (1-4) recovery at the cellular, molecular and genomic level has been frequently observed after VAD implantation, translation of these changes into functional recovery at organ level was observed less frequently and stable cardiac improvement which might allow long-term HTx-free outcome after VAD removal has occurred in only relatively few patients (5-

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10). It was observed that acute myocarditis and non-coronary shock can completely reverse during left ventricular assist device (LVAD) support (11). Outcome data for patients with chronic end-stage HF who were electively weaned from VADs are still relatively few but are encouraging (1-3, 12-17). The possibility of cardiac recovery during long-term MCS gives rise to three major challenges:

1) assessment of recovery after VAD implantation and decision in favor of or against VAD explantation;
2) search for additional recovery-facilitating and/or regenerative therapy, aiming to increase the number of potential weaning candidates;
3) pre-implantation prediction of possible cardiac recovery during mechanical ventricular unloading, aiming to provide the basis for possible future use of VADs as a therapeutic strategy for cardiac recovery.

The present article summarizes the knowledge about myocardial recovery during long-term VAD support and reviews the available data on its clinical relevance, its stability after VAD explantation and its assessment before any decision-making in favor of or against VAD explantation. The review also aims to provide a theoretical and practical basis for clinicians who are or intend in the future to be engaged in this field.

MYOCARDIAL REVERSE REMODELING AND FUNCTIONAL RECOVERY DURING MCS

Pathological myocardial remodeling, which characterizes failing hearts, includes myocyte defects (hypertrophy, β-adrenoceptor downregulation with desensitization, alterations in contractile properties with changes in excitation-contraction coupling, mitochondrial abnormalities with altered myocardial energetics, progressive loss and/or disarray of the cytoskeleton etc.), myocyte death (apoptosis, necrosis, autophagy) and extracellular matrix (ECM) alterations (degradation, replacement fibrosis, angiogenesis) (18). These changes induce alterations in ventricular size, geometry and function. The high wall stress due to ventricular dilation leads to coronary flow alterations (aggravated also by stroke volume reduction), increased oxidative stress with activation of genes sensitive to free-radical generation (tumor necrosis factor, interleukin-1β), sustained expression of stretch-activated genes (endothelin, angiotensin II, tumor necrosis factor) and/or activation of hypertrophic signaling pathways, which all additionally worsen the ventricular function (18).

VADs can induce reverse remodeling by a reversal of abnormalities in myocytes and ECM followed by reversal of ventricular size, geometry and functional alterations. Reverse remodeling is necessary for functional recovery but only rarely results in clinically relevant cardiac recovery (18). Today, neither the components of the process of reverse remodeling which are necessary for myocardial recovery, nor the minimum levels of reverse remodeling necessary for cardiac recovery allowing VAD removal are reliably known (18). Myocardial recovery during VAD support occurs at different levels with different rates (*Figure 1*).

Whereas at cellular, molecular and genomic level there is a high probability of relevant recovery, at organ level (heart anatomy and function) reverse remodeling and improvement of contractile function detectable by echocardiography are less frequent and, finally, clinically adequate and stable cardiac recovery which allows VAD explantation occurs in only few patients (5, 9, 10, 17-20). Patients who were successfully weaned from their VAD often showed only incom-

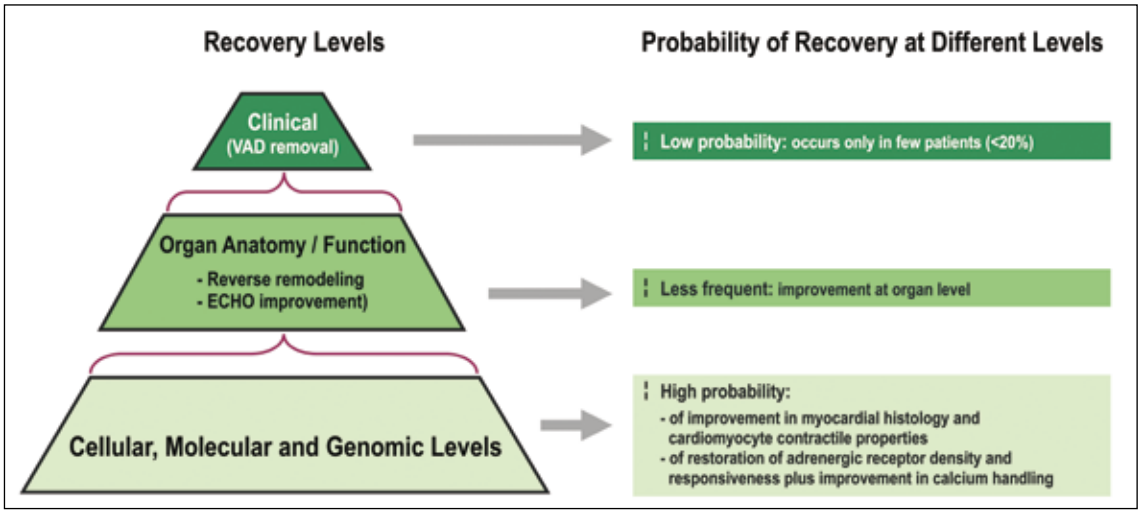

Figure 1 - *Myocardial recovery during MCS. MCS = mechanical circulatory support.*

plete recovery at the time of VAD removal and HF recurred in about one half of them during the first 10 post-weaning years (17). In many patients who become eligible for VAD explantation, HF reversal is based on "myocardial remission" (18) rather than on real "myocardial recovery" with freedom from future heart events.

Nevertheless, as long as post-explant cardiac function remains normal, it is clinically not possible to differentiate between recovery and remission.

Recovery at cellular, molecular and genomic levels

During prolonged MCS, the failing myocardium shows different degrees of reversal in genomic, molecular and histological alterations.

However, the small number of studies on reverse remodeling at cellular and sub-cellular level in weaned patients, differences in etiology and severity of HF in weaned patients and also differences in the pharmacological regimes used by different centers in VAD-supported patients all make it still difficult to understand even the basic mechanisms responsible for cardiac recovery, which allows successful weaning of some patients from their VAD.

Myocyte size, structure and function

Myocardial hypertrophy is a characteristic change in failing hearts with relevant contribution to cardiac remodeling and contractile dysfunction (10, 18, 21).

VAD support usually induces regression of hypertrophy but its relationship with unloading-promoted cardiac recovery has not been clarified (10, 21-24). Some investigators found no association between reduction of hypertrophy and clinically relevant cardiac recovery during VAD support (24). We found regression of hypertrophy in 9 of 10 patients with idiopathic dilated cardiomyopathy (IDCM) as the underlying cause for HF before LVAD implantation who improved their cardiac function during unloading to levels that allowed LVAD explantation. However, this regression appeared neither predictive for recovery, which might allow LVAD explantation, nor predictive for cardiac stability after LVAD explantation (3).

Alterations in myocyte structure and contractile function detected before LVAD implantation showed different degrees of reversibility during LVAD support (10, 20, 25-27). LVAD support often improves both developed tension (at rest and in response to beta-agonists) and relaxation rates (only at rest) at the myocyte level, but in most cases this is not associated with cardiac recovery that would allow LVAD removal (5, 10). In patients with insufficient cardiac recovery to allow VAD explantation, the sarcomeric disarray, including distortion of actin, tropomyosin, troponin C (TnC) and troponin T (TnT), detected at the pre-implantation stage, recovered only partially, and LVAD support also appeared associated with only a limited spectrum of biochemical changes (10, 27).

Thus, during LVAD support, total troponin I (TnI) phosphorylation levels appeared to be increased, whereas phosphorylation levels of TnT and tropomyosin remained unchanged (10). The increase in TNI phosphorylation might reflect normalization of β-adrenergic receptor function during LVAD support (10). Myocardial recovery in patients who were successfully weaned from LVADs appeared associated with a specific pattern of changes in sarcomeric, non-sarcomeric and membrane-associated proteins and improvement of myocyte contractile function (25, 26). In weaned patients with non-ischemic cardiomyopathy as the underlying cause of HF, comparisons of myocardial samples collected at VAD implantation and explantation showed significant increases of certain sarcomeric (i.e. myosin heavy chain, TnT and TnC, β-actin, sarcomeric actinin, α-tropomyosin and α-filamin A) and non-sarcomeric proteins (nuclear laminar protein lamin A/C, spectrin, cytoskeletal actinin, integrin β5 and α5) (25, 26). Comparing the unloading-promoted changes in sarcomeric and non-sarcomeric proteins between recovered (explanted) and non-recovered (transplanted) patients, important divergent changes were observed for syntrophin (distrophin-like protein) and vinculin, which decreased in the recovery group and increased in the non-recovery group (26). Vinculin, a major component of the linkage system that connects, via the integrins, the intra-cellular milieu with the ECM, is elevated in end-stage cardiomyopathy (DCM) and its decrease during LVAD support might be necessary to achieve clinically relevant recovery (26).

Improvement in calcium handling, mitochondrial function and response to β-AR stimulation was also observed during VAD support and it appeared often associated with improvement in myocyte contraction and relaxation (5, 6, 10, 20, 23, 28, 29).

During VAD support, relevant changes in myocardial gene expression with a major role in improvement of Ca^{2+}-handling were also found (5, 6). It was observed that sarcoendoplasmic reticulum (SR) function can recover after LVAD implantation and improved SR uptake activity appeared associated with an increased SERCA (SR Ca^{2+}-ATPase2A) protein and mRNA expression (8, 30, 31).

By restoration of calcium-handling proteins (increase in RNA expression of the Na^{+}/Ca^{2+} exchanger), VAD support results in faster sarcolemmal Ca^{2+}-entry and higher Ca^{2+} concentration in the sarcoendoplasmic reticulum, and an association between clinically relevant cardiac recovery and improvement of sarcoplasmic calcium homeostasis was also found. It was observed that the beneficial effect of VAD support on calcium handling reaches its maximum during the first 4 post-implant months, afterwards returning, with prolongation of unloading, to pathological levels (8).

This finding corresponds to the clinical observation that the probability of long-term cardiac stability after LVAD removal is

higher for patients with less than 6 months' lasting LVAD-support than for those with a longer time period of unloading before LVAD explantation (3).

Chronic HF is characterized by severely impaired myocardial β-adrenoceptor (β-AR) signaling due to β-AR downregulation and desensitization, which seems to be mainly due to phosphorylation of agonist-occupied β-ARs by the up-regulated G protein-coupled receptor-kinase-2 (GRK2) (6, 32, 33). VAD support improves β-AR signaling by inducing normalization of β-AR density and improvement in the response to β-AR stimulation (5, 6, 25, 27, 34). Improvement in β-AR signaling appeared associated with a decrease in myocardial GRK2 expression and activity (6, 35). However, LVADs can restore myocardial β-AR signaling to near normal even in patients without clinically relevant recovery and thus restoration of β-AR signaling alone does not induce recovery of adequate ventricular function to allow weaning from LVAD (6, 36). Also, the enhanced desensitization of myocardial β-ARs in chronic HF, most likely a direct consequence of the elevated expression and activity of GRK2, can be reversed by VAD support, and the improvement of myocardial β-AR signaling appeared related to a decrease in GRK2 expression and activity (6). Ventricular unloading can also improve cellular responses to oxidative stress (decrease in expression of the stress inducible protein metallothionein) (20, 23).

Apoptosis and myocardial regeneration

VAD support can reduce apoptosis and it was found that VAD implantation induces a reduction in altered expression of the anti-apoptotic protein Bcl-2 and the repair-proliferation marker "proliferating cell nuclear antigen" (5, 6, 10, 37). VAD support also induces an increase in transcription of certain anti-apoptotic genes and a reduction of DNA fragmentation (10, 36).

The evidence of an increase in circulating bone-marrow progenitor cells after LVAD implantation, as well as the detection of indirect signs for cell division or progenitor-cell proliferation in myocardial tissue specimens obtained at LVAD explantation, also suggest possible facilitation of myocardial regeneration inducible by ventricular unloading (38, 39).

Extra-cellular matrix and microvascular density

Myocardial fibrosis and reduced microvascular density are characteristic changes in failing hearts that make a relevant contribution to cardiac remodeling and contractile dysfunction (10, 18, 21). Regression of LV dilation during LVAD support following the reduction of mechanical stretch also facilitates ECM changes, and the restoration of collagen networks in turn can facilitate improvement in ventricular geometry and function (5, 10, 20, 40, 41). ECM changes, which are involved in ventricle dilation during HF development, appeared related to upregulation of matrix metalloproteinases (MMPs) that cleave matrix components and to downregulation of their inhibitors (TIMPD) (10, 20, 41, 42). LVADs can reverse this process and thus restore the collagen networks (5, 20, 41). However, analyses of collagen content yield disparate results because of the different techniques used to measure it and it is controversial whether VAD support results in an increase or decrease of interstitial fibrosis (3, 7, 21, 42, 43).

LVAD support was found to increase LV myocardial total collagen, collagen cross-linking and the ratio of collagen type I to type III (42). These changes were associated with normalization of LV chamber stiffness but also with an increase in intrinsic myocardial stiffness above the already elevated levels seen at VAD implantation. It was postulated that increased collagen content

and myocardial stiffness may prevent redilation of the LV once the recovered heart is exposed to normal filling pressures after LVAD removal (41). However, none of the LVAD-supported patients included in the above study became weaning candidates (all underwent HTx) (41). In a more recent study, LVAD implantation was followed by reduction in cardiac fibrosis and the degree of fibrosis was smaller in patients who recovered to levels allowing successful LVAD explantation (7).

Another study, focusing on microscopic examination of LV tissue collected from patients with chronic HF at LVAD implantation and explantation, revealed that unloading results in increased microvascular density accompanied by endothelial cell activation and increased interstitial fibrosis (21). The authors postulated that both increased microvascular density and fibrosis might be directly related to endothelial cell activation (21). The increase in microvascular density during prolonged LVAD support also appeared associated with upregulation of angiogenesis related genes (18, 21).

However, the functional significance of these changes is unclear because coronary flow reserve remained impaired after LVAD support (18).

A study on rats with dilated cardiomyopathy showed that prolonged ventricular unloading has the tendency to increase both myocardial stiffness (by increase in fibrosis) and apoptosis (43).

These observations might partially explain the higher HF recurrence rate observed in weaned patients with VAD support times of > 6 months before explantation in comparison with those who underwent explantation after less than 6 months of ventricular unloading (3).

Thus, most published data suggest that the response of the failing heart ECM to LVAD support might be a critical component of clinical recovery, but the exact mechanisms involved in that process are not yet fully understood (5).

Reversal of proinflammatory state

Ongoing myocardial injury distant from the initial insult is in part due to activation of the inflammatory system with production and release of inflammatory cytokines and production of autoantibodies (AABs). Thus, TNF-α (tumor necrosis factor α), an inflammatory cytokine produced by the failing myocardium but not seen in the normal heart, can substantially contribute to development and progression of HF. Intra-cardiac TNF-α expression is higher in HF patients who required LVAD support than in those who did not, and prolonged support decreases the myocardial TNF-α content (42-44). It was suggested that normalization of TNF-α content may become a marker that predicts cardiac recovery but further research is needed to confirm that hypothesis (44).

In the LV myocardium of patients with end-stage HF, proinflammatory cytokine interleukin-8 levels were also found to be significantly reduced after prolonged LVAD support (43). DCM has often appeared to be associated with elevated serum levels of AABs against cardiac proteins and those against the β_1-AR (β_1-AABs) seem to be particularly relevant from a pathophysiological point of view (45, 46). Whereas β_1-AABs are usually not detectable in healthy controls, these AABs were detected in over 80 % of patients with end-stage IDCM (46). In 33 of 34 weaned IDCM patients who tested positive for β_1-AABs before LVAD implantation we found that these AABs disappeared after 3-31 weeks of LV unloading (14).

Recovery at organ level allowing VAD explantation

Cardiac recovery allowing VAD explantation was definitely less frequently detected

than myocardial recovery at the molecular and cellular level and appeared related to the etiology of myocardial damage, the duration of heart disease and the amount of fibrosis before VAD implantation (3, 7, 9, 14, 18, 36, 47). After VAD implantation, acute myocarditis and postcardiotomy HF showed higher recovery rates than non-ischemic chronic cardiomyopathy (CCM), while recovery from ischemic CCM allowing VAD explantation is a rarity (3, 13, 16, 48, 49, 50). The overall unloading-promoted recovery rate allowing patient weaning from VAD, regardless of the etiology of the underlying cardiac disease before VAD implantation, is below 10 %.

Of 1038 patients who received a long-term VAD (BTT or permanent therapy) in our center between 1/1995 and 9/2011, 96 (9.2 %) underwent VAD explantation after clinically relevant cardiac recovery (17). The rate of recovery reported in the INTERMACS registry is only 1.2 % (51). This high discrepancy reflects the difficulty of decision-making in favor or against VAD removal and suggests that the weaning experience gained by individual centers is essential for the detection of potential weaning candidates.

Acute myocarditis and post-cardiotomy HF can completely reverse during LVAD support and therefore elective weaning from VADs was initially performed almost exclusively in such patients (10, 11, 50). However, in acute myocarditis, non-coronary post-cardiotomy HF and many cases of peripartum cardiomyopathy where reversible causes of HF can play a major role, the contribution of VADs to recovery processes might be mainly indirect (with life-saving circulatory support providing the necessary time for spontaneous and/or pharmacologically-facilitated myocardial recovery).

On the other hand, in patients with chronic life-threatening HF unresponsive to medical treatment (including inotropic support) who required emergency VAD implantation, long-term ventricular wall tension reduction by mechanical unloading appeared to have a relevant facilitating impact on myocardial recovery.

Recovery from chronic HF is often incomplete, even in patients who were successfully weaned from their VAD, and therefore only few cardiothoracic centers have performed higher numbers of elective VAD explantations in such patients (1, 3, 13, 16, 17). For non-ischemic CCM, recovery rates varying between 8 % and 60 % were reported. The high range might be in part due to differences in medical therapy during VAD support, but is probably mainly due to the different selection criteria for VAD implantation and explantation used by different centers (1, 3, 9, 11, 13, 19). The experience of individual heart centers with evaluation of cardiac recovery during short off-pump trials also plays a very important role. In a prospective multi-center study, only two (6.9 %) of 29 patients with chronic non-ischemic cardiomyopathy were weaned from their LVAD (9). However, the authors emphasized that several limitations of their study prevented them from drawing reliable conclusions on cardiac recovery rates during LVAD-support: no uniform consensus among the participant centers on the medical regimen during mechanical support, no protocol-specified criteria for explantation, measurements made with partial VAD support because not all centers were experienced with off-pump studies (9). In that study, centers were included that had not performed any elective VAD explantations before. Using a specific pharmacological regimen which included the β_2-adrenergic agonist clenbuterol, Birks et al. (Harefield study) weaned 11 (73 %) of 15 patients with non-ischemic cardiomyopathy from LVAD (13). In a more recent study using the same pharmacologic regimen, this group weaned 12 (60 %) of the 20

enrolled patients (52). However, these high recovery rates were not reproducible in the multicenter "U.S. Harefield Recovery-Protocol Trial" (50). According to the largest studies on this topic, recovery rates of between 10 % and 20 % are probably realistic for non-ischemic CCM whereas recovery rates reported for ischemic CCM were rarely above 1 % (9, 14, 16, 47). Unloading-promoted cardiac recovery rates might also depend on the type of VADs implanted. Higher recovery rates were found with pulsatile devices in comparison to continuous-flow axial pumps and it was presumed that pulsatile systems provided better unloading conditions for recovery (14, 52). However, nothing has been proved as long as there are no studies comparing pulsatile and non-pulsatile systems.

In our patients the great differences in recovery rates between those supported by pulsatile flow VADs and those supported by continuous-flow VADs might also be related to the use of more restrictive weaning criteria introduced after the use of non-pulsatile devices began (16).

The probability for HF recurrence during the first year after LVAD explantation, in patients with IDCM as the underlying cause for LVAD implantation, is usually less than 15 % (1, 3, 11, 13, 16, 47, 49, 53). In patients with non-ischemic CCM, the study with the largest number of weaned patients and the longest follow-up after weaning revealed probabilities of 67.1 ± 7.6 % and 47.3 ± 9.2 % for 5 year and 10 year freedom from HF recurrence after VAD explantation, respectively, although before explantation, only 8.7 % of the weaned patients had a LV ejection fraction (LVEF) > 50 % and the mean pre-explant LVEF value for all weaned patients was only 49 % (17). In that study there were no differences in freedom from post-weaning HF recurrence between patients weaned from pulsatile and non-pulsatile VADs (17). These data show that VAD explantation can be successful even after incomplete cardiac recovery. In another important study, the rate of freedom from death or HTx reached 69 % at both 5 and 7 years after VAD explantation and at the latest follow-up the mean LVEF was above 57 % (49).

VAD use in infants and children was introduced more recently and thus data on unloading-promoted myocardial recovery in pediatric patients are relatively scarce. In our department, of 94 children who received a Berlin Heart EXCOR system as a bridge to HTx between 1990 and 2009, 16 (16.5 %) showed cardiac recovery that allowed VAD explantation (54). The mean support-time until VAD explantation was 31.4 days, and 13 of the 16 weaned children were ≤6 years of age. Of the 16 weaned children, 7 (43.8 %) had acute myocarditis and only 3 (18.8 %) had DCM. There was one early death and one patient died 2.5 years after weaning. At the time of evaluation all the other 14 weaned patients were alive (13 without HF recurrence; one underwent HTx).

According to a multi-institutional study using the Pediatric Heart Transplant Study database (data from 23 centers in North America), of 99 children who underwent VAD implantation between 1993 and 2003, only 5 patients (5.1 %) showed cardiac recovery which allowed successful weaning from the mechanical support (55).

Describing the outcomes of 73 children (median age 2.1 years) supported with the Berlin Heart EXCOR device in North America in 2000 through 2007 (58 % with DCM, 26 % with congenital heart disease, 10 % with myocarditis), Morales et al. reported a recovery rate allowing VAD explantation of 7 % (56).

Finally, a recently published multi-center prospective cohort study involving all US children (n = 204) implanted with the Berlin Heart EXCOR Pediatric VAD between

2007 and 2010 at 47 centers, the rate of cardiac recovery which allowed patient weaning from the assist device was only 6 % (57). The higher recovery rate (16.5 %) in our children may presumably be mainly explained by our extensive weaning experience which was gained during a wide-ranging long-term weaning program for both adults and children. However, as in adults, cardiac recovery during mechanical ventricular support allowing VAD removal is also quite rare in children. For those patients who can be weaned from their VAD the chances for long-term freedom from HF recurrence are good (3, 13, 14, 54).

CONCLUSION

The reason for the discrepancy between high recovery rates on the cellular and molecular levels and the low rate of cardiac recovery allowing VAD explantation is unknown.

There are also differences in-between centers in the rate of VAD explantation that can only in part be attributed to team expertise and the different percentage of favourable etiologies such as acute myocarditis, non-coronary post-cardiotomy HF and peripartum cardiomyopathy.

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