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Physiological aspects of myocardial function improving during mechanical circulatory support

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In recent years, the mechanical support of blood circulation has proved to be a vital therapy for a terminal heart failure, and is considered as a "bridge" to transplantation or is used on a permanent basis in a patient who can not be included in the waiting list for a donor organ. Recent studies of the critical heart failure treatment during an assist device in situ have shown the myocardial recovery at the molecular and cellular levels. However, the transition of these changes to a functionally stable recovery of the heart function, which would allow the long-term results to be achieved without a heart transplant or switching off the mechanical support, is now rather an exception to the rule. At this time, the cause of the discrepancy between the high rate of recovery at the cellular and molecular levels and the low rate of cardiac function recovery remains poorly understood. Patients with chronic

progressive heart failure can demonstrate the normalization of many structural myocardial abnormalities after a mechanical support that is actually a reverse remodeling. However, the reverse remodeling is not always considered equivalent to clinical recovery. The aim of this research is to study a significant improvement in the structure and function of the myocardium during the mechanical support of blood circulation.
Keywords: heart failure, mechanical circulatory support, myocardial remodeling, reverse myocardial remodeling, heart transplantation

HF, heart failure

HT, heart transplantation

LV, left ventricle

MCS, mechanical circulatory support

Rationale

Technological advances in cardiac surgery in recent years have rapidly gained momentum. Mechanical circulatory support (MCS) during times of donor organ shortage is currently an important tool in the treatment of critical heart failure (HF). Being used as a bridge to transplantation or the therapy of choice, the MCS devices improve the quality of life and overall survival of patients when all other conservative treatment options are exhausted [1-3]. HF-associated remodeling that includes changes in cellular, structural and functional changes in the myocardium, until recently, has been considered unidirectional, progressive, and irreversible. However, it has been shown that irreversibility can be avoided in whole or in part after unloading the myocardium by using circulatory assist devices.

Thus, the initial “bridge to transplantation” can turn into a “bridge to recovery”, which ultimately allows you to remove an MCS device without subsequent heart transplantation (HT). Although myocardial recovery at the cellular, molecular, and genomic levels was often observed after a MCS device implantation [4–7], the transformation of these changes ino a functional recovery at the organ level was less frequently observed; and a stable improvement in heart function, which could provide a long-term result without HT after MCS removal was observed in a relatively small number of patients [8–13]. It was noted that acute myocarditis and some variants of cardiomyopathy could completely regress with use the left ventricle (LV) assist device [14].

There is still little data on the results of patients after MCS removal, but their results are encouraging [4–6, 15–20].

This article summarizes the knowledge on myocardial recovery during a long-term MC use.

"Remodeling of the heart"

Myocardium remodeling is characterized as an acquired pathological heart condition leading to a rearrangement of normally existing structures, and, as a rule, affects two components of the cardiovascular system, namely myocardium and blood vessels, which structures can be altered by adverse conditions caused by several harmful factors that increase cell stress [21]. In response to the increased load, individual cardiomyocytes respond by an adaptive hypertrophic growth, that is, they increase the size, volume, and mass of cells or undergo apoptosis, respectively [22, 23]. The result is the expansion of the heart and increased sphericity [21]. Despite the fact that the dilatation and sphericity are compensatory and damper mechanisms, all this

ultimately leads to a chronic heart failure [22, 23]. The dilation is accompanied by increased tensions of ventricle walls, which leads to a decreased coronary blood flow, an impaired pumping function, and a decreased cardiac output [24]. In addition, interstitial fibrosis is observed, which further complicates the systolic and diastolic functions of the heart [25].

"Reverse remodeling of the heart"

After MCS, a decrease in hypertrophy and myocardial dilatation may be observed. Echocardiography revealed a decrease in the LV diameter and an increase in the ejection fraction [26–28]. A significant decrease in the diameter of cardiomyocytes was shown. A decrease in the length and volume of cardiomyocytes has been repeatedly described as a morphological relationship of a decrease in myocardial hypertrophy [29, 30].

Mechanical circulatory support effects at the tissular, cellular, and subcellular levels

Cardiomyocytes

Cardiomyocytes account for ≈ 35% of the number of cells in the heart, and 70% of the total heart mass [31]. It has been shown many times that LV unloading leads to the regression of cardiomyocyte hypertrophy [32, 33]. Cardiomyocytes undergo severe remodeling during progressive heart failure, while changing the volume. Hematoxylin and eosin staining of myocardial samples from patients with end-stage HF shows an increase in a cardiomyocyte size, followed by a decrease after a long-term MCS [33, 3 4]. At the same time, the regression of cell hypertrophy occurring during LV unloading is not necessarily associated with clinical and functional recovery

[13]. However, the issue of whether a long-term mechanical unloading has an effect on the main pathways of the degradation of proteins that have been implicated in cardiac hypertrophy and remodeling, is still poorly known [35 - 37].

Contractile dysfunction, Ca^{2+} metabolism, and cytoskeletal proteins

It was shown that contractile defects of cardiomyocytes gradually regressed after LV unloading, showing improved shortening and relaxation [13, 38]. These interesting effects on the contractile dysfunction can be partially explained by the improvement in Ca^{2+} metabolism, namely: a faster intake of sarcolemmal Ca^{2+} and a shorter duration of action potential, a higher Ca^{2+} content in the sarcoplasmic reticulum, and beneficial changes in the calcium L-type channel, an improved function of ryanodine receptors [8, 12, 28, 39]. The above effects are also associated with favorable changes in cytoskeletal proteins: sarcomeric and non-sarcomeric ones, as well as in improving the interaction between the integrins being transmembrane heterodimeric cell receptors, and the extracellular matrix. The shape of the cell and its mobility depend on these bonds [40–44].

Metabolism and bioenergy

LV unloading has been shown to be associated with an improvement in the respiratory ability of mitochondria, and with an increase in the endogenous NO-mediated regulation of mitochondrial respiration [45, 46]. In addition, it was shown that cardiolipin, a lipid component of the mitochondrial membrane, important for the formation of adenosine triphosphoric acid and the substrate transport, is normalized after the LV pulsing unloading [47]. Also, a number of studies have shown that after a

prolonged MCS, the genes and proteins involved in myocardial remodeling are expressed [27, 29, 48, 49].

Apoptosis and myocardial regeneration

Apoptosis contributes to the loss of cardiomyocytes and a progressive decrease in LV function. Autophagy markers have been shown to be suppressed at mechanical support of the LV [27, 50]. These favorable changes are supplemented by a decrease in myocardial stress that is indicated by a decrease in stress proteins of metallothionein and hemoxygenase-1 [51, 52]. The evidence of an increase in circulating bone marrow progenitor cells after MCS device implantation, as well as the detection of indirect signs of a cell division or the proliferation of progenitor cells in myocardial tissue samples obtained during MCS device explantation, also indicate a possible myocardial regeneration [53, 54].

Extracellular matrix

Extracellular matrix provides the support necessary for regular work of cardiomyocytes. Several studies reported a reduction in fibrosis; when using digital microscopy methods of analysis, it was found that myocardial tissue from patients with heart failure after mechanical support compared with normal myocardium had increased interstitial and total fibrosis. However, the contents of interstitial and total collagen increased even more after MCS in those patients [55]. Whether the observed increase in fibrosis and increase in collagen are the manifestations of the further progression of heart remodeling, or this is a direct result of MCS, has not been clear yet.

Gene expression

The mechanical myocardial support causes significant changes in the expression of myocardial genes involved in remodeling, given the genomes being significantly different before and after support. Thus, the reverse remodeling is associated with a specific pattern of gene expression [56 - 60].

Natriuretic peptides, cytokines, and neurohormones

Against the mechanical support, there occurs a decrease in the level of atrial and brain natriuretic peptides, as well as tumor necrosis factor-α in both serum and myocardial tissue [12, 61, 62]. Changes in the levels of other key neurohormones involved in the progression of HF syndrome have been assessed ambiguously. Specifically, the levels of circulating adrenaline, noradrenaline, renin, angiotensin II, and vasopressin have been shown to decrease during MCS [63].

Endothelium and microvasculature

MCS was associated with changes in the expression of genes involved in the regulation of vascular organization and migration [64]. Also immunohistochemical and ultrastructural evidence of endothelial cell activation has been obtained, which is consistent with the observed increase in microvessel density [42].

Beta-adrenergic signaling and sympathetic innervation

LV unloading has been shown to result in an improved density, localization, and nature of beta-adrenergic receptors, a better contractile response to beta-adrenergic stimuli and a higher adenylcyclase activity. [8, 13, 26]. A recent study, using scintigraphy, has shown that MCS leads to the

improved sympathetic innervation in HF, which is accompanied by clinical, functional, and hemodynamic improvements [65].

The problem of disagreement between clinical and biological results

Meanwhile, the main question arises, why, with such obvious positive effects at the cellular and subcellular levels, the circulatory assist devices are not considered the main technique for correcting the heart failure. The main reasons, in our opinion, are as follows: an attempt to compare the results of different clinical and biological studies; the use of high doses of drugs to treat the heart failure; a different duration of mechanical circulatory support; the change in the generation of mechanical pumps from pulsating to non-pulsating ones; collecting biopsy from different sites of the left ventricle; a lack of a centralized base to analyse and compare such patients; a lack of uniform guidelines for weaning from MCS.

We must also take into account the fact that, despite the considerable advances in understanding the pathophysiology of heart failure in recent years, many questions on the heart failure mechanism remain unresolved. So, in their study L. Mann and R. Bristow showed that current hemodynamic, cardiorenal, and neurohormonal models of the heart failure pathophysiology are insufficient to explain all aspects of the heart failure syndrome. Most importantly, these models can not adequately explain the progression of the disease [66].

It is likely that the reverse process of heart remodeling will become clear after understanding the mechanisms of the heart failure development. In addition, the “reverse cardiac remodeling” and a sustained “clinical myocardial recovery” are not necessarily synonymous; several studies have

shown that a partial or sometimes almost complete change in the HF phenotype at structural, cellular, or molecular levels (i.e. “reverse remodeling of the heart”) is not always accompanied by a sustained clinical “myocardial recovery” to a similar extent [67–69]. It is important to note that this process may reveal new potential therapeutic targets in heart failure. Given that a significant number of previously conducted studies related both to heart failure, and to general cardiovascular diseases have focused on predicting adverse outcomes, it may now be necessary to focus on understanding the process of myocardial recovery.

Conclusion

Numerous etiological factors, such as chronic ischemia, inflammation, or genetic changes, can affect the myocardium and cause quite nonspecific compensatory and adaptive changes, including cardiomyocyte hypertrophy. And although these adaptive properties initially act as a compensatory mechanism, at the final length, they lead to an impairment of the cardiac function. An increased myocardial wall tension, and the local ischemia might be the mechanisms that activate numerous molecular and cellular responses. As a result, the myocardium cannot adapt to increased biomechanical stress. Neurohormonal activation, inflammatory mediators, changes in beta-adrenergic signaling and Ca^{2+} metabolism, as well as interstitial fibrosis, further impair the heart function.

Despite constantly improving medical strategies, heart transplantation remains the only approach with good long-term results. Due to a shortage of suitable donor organs, the mechanical circulatory support is currently used to maintain cardiac activity in patients with end-stage heart failure prior to transplantation, or in patients as a permanent therapy. As mentioned above,

the use of mechanical circulatory support is associated with changes at the cellular, molecular, and genetic levels. Although these results are encouraging, only a small number of patients can be weaned from circulatory assist devices and avoid transplantation. The approach combining the mechanical circulatory support and medical treatment provides satisfactory long-term results in patients with various forms of myocarditis, as well as with some forms of cardiomyopathy. Another problem in this area is the lack of a suitable serum/plasma biomarker that would accurately indicate the myocardial recovery during mechanical circulatory support and could, possibly, predict the clinical outcome and changes for successful weaning from MCS. In conclusion, despite a limited number of patients with satisfactory results, a better understanding of the basic biological mechanisms of "reverse myocardial remodeling" is crucial for developing future therapeutic strategies in this, still intriguing field of science.

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