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Left Ventricular Assist Device and Resident Cardiac Stem Cells in Heart Failure: Human Heart's Potential Matter

Mariangela Peruzzi, MD[1], Giuseppe Biondi-Zoccai, MD[1], Ernesto Greco, MD[3], Antonino G.M. Marullo , MD, PhD[1], Antonio Barretta, MD[3], Piergiusto Vitulli[3], Giulio Pompilio, MD[4], Giacomo Frati, MD[1,2*]

[1]*Department of Medico-Surgical Sciences and Biotechnologies, "Sapienza" University of Rome, Latina, Italy*

[2]*Department of AngioCardioNeurology, IRCCS NeuroMed, Pozzilli, Italy*

[3]*Department of Cardiovascular, Respiratory, Nephrological, Anesthesiological, and Geriatric Sciences, Policlinico Umberto I-"Sapienza" University of Rome, Rome, Italy*

[4]*Department of Cardiac Surgery, Laboratory of Vascular Biology and Regenerative Medicine, Centro Cardiologico Monzino, IRCCS, Milan, Italy*

***Corresponding author**: Prof. Giacomo Frati, Department of Medico-Surgical Sciences and Biotechnologies, "Sapienza" University of Rome, Corso della Repubblica 79, 04100 Latina, Italy, E-mail: giacomo.frati@uniroma1.it, fraticello@inwind.it

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Heart disease is the leading cause of mortality in Western countries, accounting for 17.3 million deaths per year. The impact of cardiovascular diseases is influenced by the ability to treat and assist patients surviving acute myocardial infarction (AMI), which has resulted in a nearly epidemic of chronic heart failure (HF), with roughly 5.8 million people with this diagnosis and about 500,000 new cases every year in the U.S.A. Irrespective of the etiology and despite the fact that recent advances in medical and surgical treatments of HF have led to better treatments, 50% of patients die within a month after AMI, and 50% of those with severe HF die within a year. From a pathophysiologic point of view the hemodynamic overload generated by AMI imposes mechanical and neurohormonal challenges on cardiac walls, initially triggering compensatory left ventricular hypertrophy, but eventually activating complex biological responses evolving into maladaptive remodeling, untreatable with conventional therapy.

Ventricular remodeling describes structural changes in the left ventricle (LV) in response to chronic alterations of loading conditions, with three major patterns: concentric remodeling, when a pressure load leads to growth in cardiomyocyte thickness; eccentric hypertrophy, when a volume load produces myocyte lengthening; and myocardial infarction, a combination of patterns in which stretched and dilated infarcted tissue increases left-ventricular volume with a combined volume and pressure load on non-infarcted areas. As a result this multifaceted mechanism culminates in tissue remodeling, leading to a progressive loss of regional and global cardiac function.

The transition from apparently compensated hypertrophy to the failing heart indicates a changing balance between metalloproteinases and their inhibitors, manifold effects of reactive oxygen species (ROS), interplays involving cell death, turnover and renewal and, last, a promotion of profibrotic neurohormonal responses. An accurate intertwining of muscle growth, inflammation, and angiogenesis, coupled with changes in cardiac metabolic profile, is pivotal to ensure the adaptive hypertrophic remodeling. Alterations of this equilibrium cause the deterioration of cardiac structure and function.

These processes are hitherto slippery therapeutic targets. The American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) guidelines recommend three suitable options for these patients: 1) heart transplantation; 2) ventricular assist device (VAD); or 3) hospice care [1]. In this clinical scenario, end-stage HF patients have only two real therapeutic options: the first, heart transplantation with a claim expected to increase in reason of the prolonged expectancy of life but counterbalanced by a progressive shortage in the absolute number of donors.

Given the limited pool of suitable cardiac donors and the huge improvements in technology, it is not surprising that the second option, the employment of VAD, has increased dramatically in the last decade bringing for the first time to more VAD implantations than heart transplants [2]. Ventricular assist devices represent an alternative option either as a bridge to transplantation or as destination therapy. Ventricular assist devices implantations are thus performed with the intention that patients will either die with the VAD (destination therapy) or have the VAD awaiting heart transplantation (bridge). More recently a third option in VAD therapy is represented by the recovery of cardiac function, the so called bridge to recovery, that would be the ideal therapeutic outcome consequent to a VAD implantation.

In typical clinical settings, VAD unloaded hearts were found to have reduced myocyte size, lowered total collagen deposition, and decreased myocardial tumor necrosis factor-α (TNF-α) content suggesting positive remodeling phenomena [3]. Unfortunately, according to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), less than 5% of patients in the U.S.A achieve a VAD explantation because of an adequate recovery of function. Ventricular assist device explantation has been generally limited to patients with acute processes in young subjects with shorter duration of HF such as acute myocarditis, post-cardiotomy syndrome, and peripartum cardiomyopathy. Recently, Drakos et al. [4] investigated the longitudinal effects of unloading by continuous flow left VAD (LVAD) on cardiac structure and function, concluding that younger patients and those with earlier LVAD implantation since onset of HF achieved the largest structural improvements and the most favorable functional recovery. It is reasonable to assume that this occurs because of a condition in which several pathophysiologic mechanisms including a variety of signaling pathways interplay in a complex yet hitherto incompletely clarified fashion with the benefits of LVAD.

Important mediators in the recovery of cardiac function after LVAD implantation may include cytokines, proapoptotic genes such as caspases, micro-RNA mediating post-transcriptional gene silencing, TNF-α, with its essential regulation of maladaptive cardiac remodeling, an growth factors [5]. Another issue to be considered is the possible role of epigenomic changes that can explain a characteristic hallmark of HF, i.e. altered gene expression. Indeed, unlike the genome, which is largely stable, the epigenome is dynamic and allows organisms to respond and adapt to environmental cues. The cardiac environment subjected to stress may therefore promote epigenomic changes with consequent plasticity in gene expression and phenotype. In typical clinical settings, VAD unloaded hearts were found to have reduced myocyte size, lowered total collagen deposition, and decreased myocardial tumor necrosis factor-α (TNF-α) content suggesting positive remodeling phenomena [3]. Unfortunately, according to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), less than 5% of patients in the U.S.A achieve a VAD explantation because of an adequate recovery of function. Ventricular assist device explantation has been generally limited to patients with acute processes in young subjects with shorter duration of HF such as acute myocarditis, post-cardiotomy syndrome, and peripartum cardiomyopathy. Recently, Drakos et al. [4] investigated the longitudinal effects of unloading by continuous flow left VAD (LVAD) on cardiac structure and function, concluding that younger patients and those with earlier LVAD implantation since onset of HF achieved the largest structural improvements and the most favorable functional recovery. It is reasonable to assume that this occurs because of a condition in which several pathophysiologic mechanisms including a variety of signaling pathways interplay in a complex yet hitherto incompletely clarified fashion with the benefits of LVAD.

Furthermore, the demonstration that cardiomyocytes are not terminally differentiated cells with the capacity to reenter the cell cycle even in LVAD models strongly suggest that they also might be involved in determining which patients respond favorably or not to LVAD therapy in routine clinical practice [6-9]. The unique opportunity of studying the structural and biological changes occurring in a human natural dynamic model of resting HF, as that provided by VAD-assisted patients, would probably promote a key breakthrough in the comprehension of the human heart's regenerative potential associated with both reverse remodeling processes and the possible therapeutic effects of VAD on the pool of resident cardiac stem cell.

Even if autologous or heterologous cell therapy with extra cardiac cell sources, such as bone marrow and skeletal muscle, has been proposed for the treatment of HF, these approaches have only encountered limited success and generated conflicting results with no clear evidence of heart regeneration potential, mainly due to unsolved issues related to low survival and engraftment rate of injected cells, their limited cardiogenic differentiation abilities as well as the occurrence of harmful disorders such as arrhythmias, inflammation, and fibrosis. To ensure efficient cell regeneration, reliable cell sources are required to show undeniable cardiomyogenic differentiation abilities. Resident cardiac stem cells (CSCs) have the capacity to differentiate into cardiac myocytes, vascular smooth muscle cells and endothelial cells [10]. Consequently, CSCs represent a logical source to exploit *per se* or in association with tissue engineering approaches [11] because, unlike other adult stem cells, they are intrinsically committed to generate cardiac tissue. Cardiac stem cells achieve their benefits both by direct cardiovascular differentiation and by release of paracrine factors, which exert pro-survival and pro-angiogenic effects on the tissue, as well as by recruiting and activating endogenous repair mechanisms [12]. However, is still unknown and of great interest how the reverse remodeling process induced by VAD implantation might influence the biology, potency and features of resident CSCs in HF patients. From these preliminary considerations it seems that the therapeutic success of VAD as a bridge to recovery might be amplified as a real regenerative tool if combined with CSCs therapy, once the correct patients population and the optimal time-window sampling of resident autologous CSCs will be identified. Thus it would be ideal to identify a representative cohort of patients, in order to provide new important insights into physicians' patterns of practice related to VAD as bridge to recovery therapy allowing customized strategies to be targeted to each specific patient.

Notably these new emerging data have obvious and non-negligible theoretical and applicative implications: start from a biological/molecular core which is made of novel observations, concept and tools, aiming at wedding stem cell biology with VAD technology. Based on this new view and taken together, these advances in stem-cells biology and LVAD combined therapy may herald a new area of cardiovascular regenerative and personalized medicine in upcoming years, exploiting this body of evidence as a long-missed benchmark for the development of regenerative medicine approaches moving from insight to in-sight, and back.

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