Left ventricle unloading in extracorporeal life support

Abbreviations
CA, cardiac arrest
CS, Cardiogenic shock
IABP, Intra-aortic Balloon Pump
LV, Left Ventricle
V-A ECLS, veno-arterial extracorporeal life support

Cardiogenic shock (CS) and cardiac arrest (CA) are among the most lethal manifestation of acute cardiovascular disease, with high in-hospital mortality rates.
CA in North American and Europe approximates 50 to 100 cases per 100,000 [1] and the 30-day survival rate of out-of-hospital cardiac arrest patients who received cardiopulmonary resuscitation is only 10.7% worldwide [2]. Likewise, intensive care unit admission with CS has doubled from 4% to 8% over the past 15 years [3] and it is associated with a high mortality rate ranging from 30% to 40% [4-7].
Extracorporeal life support is increasingly used either in adults or children with acutely impaired cardiac function refractory to conventional medical management, mainly in profound cardiogenic shock and refractory cardiac arrest. In the United States, veno-arterial extracorporeal life support (V-A ECLS) use has raised from 1.613 per million in the year 2001 to 3.597 per million in 2011[8], and from 5.4 per million in the year 2000 to 44.3 per million in 2009 [9]. Despite this therapeutic advancement, mortality from CS and CA remain high [10-12]. Therefore, the efforts in improving the ECLS shortcomings have been increasing over the past decades. One of the most important concerns in V-A ECLS is the increased left ventricular (LV) pressure attributable to retrograde aortic perfusion. This could slow myocardial recovery or damage the myocardium and negatively affect survival [13]. This thesis provides a comprehensive treatise of LV unloading during V-A ECLS support, moving from a picture of the available strategies and the need of standardize the indications and treatments, through solid physiological data based on pre-clinical studies and ending to a clinical experience in a unique setting.

Scientific impact

Our work provided two main scientific improvements. First, our findings were based on a meticulous scientific methodology which firstly recognized the urgent need of experimental data supporting the use of these techniques in the daily clinical practice. This led to provide a detailed insight of the LV hemodynamics and workload investigated in a swine CS model, as shown in ***chapter 4*** and ***chapter 6***. Additionally, a comprehensive scientific treatise on the Impella use was reported in ***chapter 5***.
Second, this thesis was certainly one of the first attempt to align all the available indications and approaches. In ***chapter 2***, we firstly recognized the need of a common definition of LV overload. In addition, a multiparametric approach was proposed and, nowadays, it has been one of the few clear indications available in the literature.

Clinical impact

Chapter 2 proposed, for the first time, a detailed literature review on this topic. We analyzed in depth the available literature and systematically treated each technique with its advantages and disadvantages. Furthermore, our conclusions strongly remarked a lack of knowledge. On one hand,

approximately 60% of the selected papers evaluated in this study accounted for case reports or case series. On the other hand, grounded data regarding the hemodynamic and physiological changes related to each method were absent. The scientific interest on LV unloading has been sharply raised over the following five years.
One of the controversies, mentioned in our review, was the role of intra-aortic balloon pump (IABP) as an effective unloading technique. In ***chapter 3***, despite the limited number of patients, IABP implant will restore aortic valve opening in patients supported with V-A ECLS. Although the aortic valve dysfunction is considered only one of the LV overloading signs, the positive IABP impact confirmed its effectiveness in at least reversing this adverse event. This was a promising insight which drove the role IABP as a tool mainly when early signs of LV overload occurred. In ***chapter 4*** and ***chapter 6*** were the first studies which directly compared the effects of 3 different modalities of LV unloading during peripheral V-A ECLS. In this large animal model with profound cardiogenic shock (CS) supported with V-A ECLS, the Impella, pulmonary artery cannula and Atrial septostomy provided effective LV unloading maintaining adequate end-organ perfusion. Nevertheless, the grade of unloading significantly differed as demonstrated in our CS animal model. Besides the unique experimental data and the consequence better understanding of this phenomenon, these studies firstly provided solid proofs which may guide clinicians in their decision-making process. First, Impella was the most effective unloading technique in our experimental studies. Then, its effectiveness was further confirmed in large multicenter experiences and its use became widespread [14,15]. Second, although the role of pulmonary artery cannula as a dynamic and biventricular support was established [16], little was known regarding the effective impact on LV. Our experiment clarified and enhanced its effect as undirect LV unloading. Third, the use of atrial septostomy was supported by solid preclinical data which confirmed its effectiveness. With specific reference to the latter technique, ***chapter 7*** confirmed its benefits in a unique population of congenital heart disease patients supported V-A ECLS. To best authors' knowledge, this was the first and largest experience which demonstrated the impact of LV unloading on in-hospital survival in such population. Finally, ***chapter 8*** advanced a comprehensive algorithm as a diagnostic and therapeutic tool for properly unloading the LV during V-A ECLS. To summarize, this thesis investigated in depth the mechanisms and the hemodynamic impact of the most promising LV techniques. At the same time, we provided important insight which may support the clinicians in the decision-making process and patient selection. Finally, we opened a new research perspective regarding patients who might benefit LV unloading the most.

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