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HEMODYNAMIC ADAPTATION MECHANISMS OF HEART FAILURE TO PERCUTANEOUS VENOARTERIAL EXTRACORPOREAL CIRCULATORY SUPPORT

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While learning about the principles of circulatory supports, facilities of the Experimental laboratory at Albertov became an amazing place where our initial ideas were transformed into real practice. In team cooperation with fellow laboratorians, scientists, and doctors, we were able to design and set novel experiments to help me understand and explain pathophysiological mechanisms of circulatory supports. It was a school of great value and pleasant nature at the same time.

I can hardly imagine to acquire better practical skills and medical knowledge than during my fellowship at Na Homolce Hospital. I found here inspiration for research and source of clinical observations, which come together with perfect leadership for my training.

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I endlessly value the facts that on this long and winding road many of my close friends helped and many of my colleagues became my friends. Without their little help, the presented work would never get by. A shared passion became our motivation for every day in the life of physiology, medicine, and research.

Abbreviations

ANP, BNP – atrial and brain natriuretic peptides
CO – cardiac output
dP/dt_{max} – maximal positive pressure change
dP/dV – diastolic stiffness
Ea – effective arterial elastance
EBF – extracorporeal blood flow
ECLS - extracorporeal life support
ECMO – extracorporeal membrane oxygenation
EDA, ESA – end-diastolic and end-systolic area
EDD – end-diastolic diameter
EDP, ESP – end-diastolic and end-systolic pressure
EDV, ESV – end-diastolic and end-systolic volume
Ees – slope of ESPVR
EF – ejection fraction
ELSO – Extracorporeal Life Support Organization
FAC – fractional area change
HF – heart failure
HR – heart rate
LV – left ventricle
LVAD – LV assist device
MVO_2 – myocardial oxygen consumption
PE – myocardial potential energy
PI – pulsatility index
PV (loop) – pressure-volume (loop)
PVR – pressure-volume relationship
rSO_2 – regional tissue oxygenation
RV – right ventricle
SV – stroke volume
SvO_2 – mixed venous blood saturation
SW – stroke work
TAPSE – tricuspid annular plane systolic excursion
VPO – ventricular power output

Abstract

Introduction:
Venoarterial extracorporeal membrane oxygenation (VA ECMO) is widely used in the treatment of circulatory failure, but repeatedly, its negative effects on the left ventricle (LV) have been observed. The purpose of this study is to assess the influence of extracorporeal blood flow (EBF) on systemic hemodynamic changes and LV performance parameters during VA ECMO therapy of decompensated heart failure.
Methods:
Porcine models of low-output chronic and acute heart failure were developed by long-term fast cardiac pacing and coronary hypoxemia, respectively. Profound signs of circulatory decompensation were defined by reduced cardiac output and tissue hypoperfusion. Subsequently, under total anesthesia and artificial ventilation, VA ECMO was introduced. LV performance and organ specific parameters were recorded at different levels of EBF using an LV pressure-volume loop analysis, arterial flow probes on carotid and subclavian arteries, and transcutaneous probes positioned to measure cerebral and forelimb regional tissue oxygen saturations.
Results:
Conditions of severely decompensated heart failure led to systemic hypotension, low tissue and mixed venous oxygen saturations, and increase in LV end-diastolic pressure. By increasing the EBF from minimal flow to 5 L/min, we observed a gradual increase of LV peak pressure, reduced arterial flow pulsatility, and an improvement in organ perfusion. On the other hand, cardiac performance parameters revealed higher demands put on LV function: LV end-systolic volume and end-diastolic pressure and volume all significantly increased (all $P < 0.001$). Consequently, the LV stroke work increased ($P < 0.05$) but LV ejection fraction did not. Also, the isovolumetric contractility index did not change significantly.
Conclusions:
In decompensated chronic and acute heart failure, excessive VA ECMO flow increases demands on left ventricular workload and can be potentially harmful. To protect the myocardium, VA ECMO flow should be adjusted with respect to not only systemic perfusion, but also to LV parameters.
Key words:
Extracorporeal membrane oxygenation; Heart failure; Hemodynamics; Heart ventricles; Artificial cardiac pacing

1 Introduction

Patients diagnosed with heart failure (HF) require intensive and highly specialized management from the onset of disease. Combination of life style, medication and implantable electrical devices is considered conventional therapy. Despite of full supportive treatment, patient's hemodynamic status can change abruptly into acute decompensation of HF while causing a severe prognosis (Jackson et al. 2000).

In situations when circulatory failure may not be possible to treat with conventional methods, extracorporeal life supports (ECLS) can temporarily substitute function of heart and lungs and provide time for treatment of underlying condition (Abrams et al. 2014). These advantages in combination with ease of circuit introduction led to wide spread of ECLS for decompensated circulatory failure (Thiagarajan et al. 2017).

The artificial circuit can substitute the pump function of heart (Pranikoff et al. 1994, Combes et al. 2008), but due to changes in hemodynamics, its reinfusion flow to the arterial system increases afterload of left ventricle (LV), and thus puts higher demands on heart work (Seo et al. 1991, Burkhoff et al. 2015, Broome and Donker 2016, Ostadal et al. 2015, Hála et al. 2020). Further hemodynamic complications like LV dilation or pulmonary edema were described but risk factors remain unclear (Barbone et al. 2011, Soleimani and Pae 2012, Boulate et al. 2013).

Therefore, detailed monitoring and better understanding of heart hemodynamics during ECLS might alleviate its negative impacts and improve prognosis (Soleimani and Pae 2012, Truby et al. 2017, Na et al. 2019). This text will focus on the current use and effects of ECLS during acute decompensation of HF and available methods of hemodynamic assessment.

1.1 Heart failure

The performance of the heart depends on the following components: stroke volume (SV; influenced by contractility, preload, and afterload) and heart rate. HF describes situations when the heart is unable to maintain adequate cardiac output (CO) to meet body requirements. Common classification distinguishes between acute and chronic HF by the speed of symptoms onset.

1.1.1 Pathophysiology of HF

HF is a progressive disorder initiated after an index event with an abrupt, gradual, or insidious onset and a common corresponding classification distinguishes between acute and chronic forms. The HF syndrome can result from a decline in SV that is due to systolic dysfunction, diastolic dysfunction, or a combination of the two. Typically, causes for HF can be impaired myocardial work itself or can lie in its excessive volume or pressure overload, like in arterial hypertension or valvular disease. With slow onset of advanced myocardial exhaustion pathways, increased afterload or preload can progress into reduction of CO. This chronic course is then associated with prolonged neurohormonal activation (Floras 2009, Hartupee and Mann 2017) and allows to fully develop systemic adaptation mechanisms (Ošťádal and Vízek 2005). With rapid onset of the pathophysiological pathways, adaptation responses might be insufficient and acute cardiac decompensation may occur; in severe cases the circulatory failure can progress into cardiogenic shock with severe reduction in CO despite adequate ventricular filling. With the progression to long-lasting HF, the continuing activation of neurohormonal and cytokine systems leads to vascular and left ventricular changes (Toischer et al. 2010).

1.1.2 Integration of Cardiac and Vascular Changes

Decreased cardiac output in HF leads to changes in intravascular volume, vascular resistance, and venous pressures. The interaction of cardiac and vascular changes can be examined in graph by using venous return curves and cardiac function curves (Guyton 1955) as presented in Figure 1. Here, by equating corresponding curves, an equilibrium point of the CO, venous return, and right atrial pressure is established. In heart failure, changes of preload help to mitigate the reduced cardiac performance (Borlaug and Kass 2008), however, elevation of the venous pressure can contribute to edemas. Moreover, concurrent systemic vasoconstriction adds to LV afterload, thus LV systolic ejection and cardiac output can be further depressed (Borlaug and Kass 2008, Marti et al. 2012). In addition, connecting an extracorporeal circulatory support changes the cardiac-vascular equilibrium by affecting both preload and afterload.

1.1.3 Compensatory mechanisms in HF

If CO is reduced but allows temporary survival, series of compensatory adaptations are activated to maintain homeostasis and preserve systemic perfusion. These initially provide valuable support in order to mitigate the depressed hemodynamics by improving contraction and maintaining integrity of the circulation. But in cases of prolonged activation, their exhaustion or the

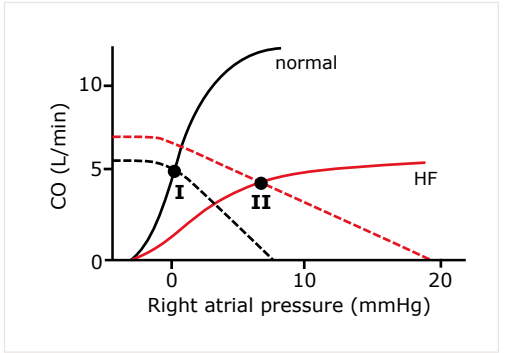

Figure 1. Schematics of cardiac output and venous return interactions. For normal heart (black) and for heart failure with reduced pumping effectivity (red) the cardiac output curves (solid lines) are intersecting with venous return curves (dashed lines) at marked equilibrium points (I and II). Each vascular curve intersects with x-axis at the value of corresponding mean circulatory filling pressure and its slope reflects resistance to venous return. The marked equilibrium points allow to assess the cardiac output (CO), which is equal to the venous return, for normal circulation (point I) and for heart failure with activated adaptation of increased intravascular volume and resistance to venous return (point II). Adapted from Guyton (1955) and Klabunde (2012).

intensification of their negative impacts result in a vicious cycle of circulatory decompensation (Ošťádal and Vízek 2005). Consequent cardiogenic shock can lead to death if not adequately supported.

Following compensatory mechanisms play important roles in HF pathophysiology.

Sympathetic nervous system

Early in the course, the sympathetic nervous system is quickly activated via chemo- and baroreceptors in an attempt to maintain CO (Floras 2009). Rise in plasma catecholamines (and concomitant withdrawal of the parasympathetic tone) leads to chronotropic stimulation and to increased force of contraction and vascular tone. Consequently, higher oxygen consumption is demanded by the myocardium, but the diastolic time shortens and limits the coronary perfusion. Elevated resting heart rate is considered one of independent prognostic factors of HF (Reil and Bohm 2008).

In long-term, chronic high catecholamine concentrations lead to down regulation of beta receptors on cardiomyocytes, so the sympathetic effects are attenuated and reduction in heart rate variability can be observed. In addition, vagal parasympathetic activity to the heart is reduced.

Renin-angiotensin-aldosterone system

Activation of this pathway occurs comparatively later in HF. Angiotensin II

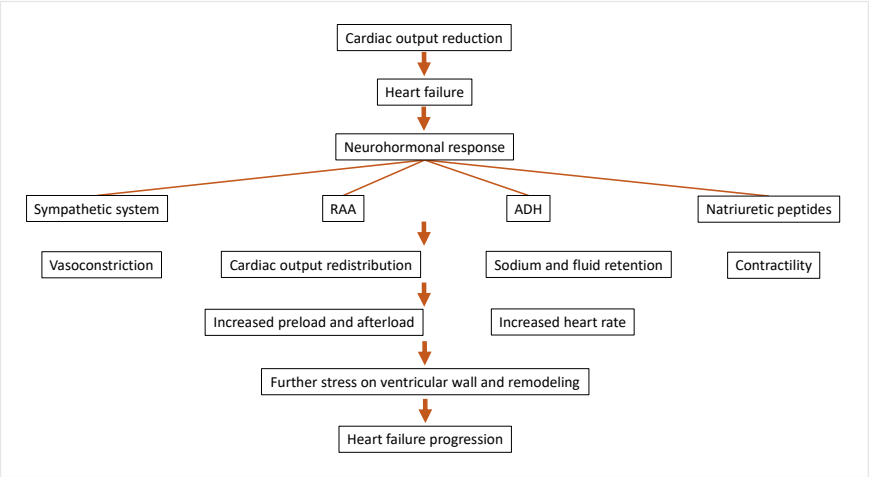

Figure 2. Neurohormonal activation and compensatory mechanisms in heart failure. Other factors include endothelin or intrinsic nitric oxide release. RAA – Renin-angiotensin-aldosterone system, ADH – Antidiuretic hormone/vasopressin.

is a potent vasoconstrictor of renal efferent arterioles and systemic circulation. It also stimulates sympathetic but suppresses vagal tone, which contributes to endothelial dysfunction (Guang et al. 2012). Further, aldosterone effect on renal sodium reuptake add to extracellular fluid expansion, thus it elevates both ventricular filling pressures and afterload (Packer 1992).

Natriuretic peptides

Several natriuretic peptides, of similar structure, have been isolated and their function on the heart, kidneys, and nervous system described. Natriuretic peptides released from the atria and ventricles in response to wall stretch have main effects on natriuresis and vasodilation. Their concentration increase in response to volume expansion and physiologically mitigates the effects of angiotensin and aldosterone (Volpe et al. 2016). This fact allows to use concentration of the natriuretic peptides in plasma as diagnostic and prognostic markers (Gardner et al. 2003).

Other hormonal and non-hormonal mechanisms

Antidiuretic hormone (vasopressin) concentrations are inappropriately high in both severe acute and chronic HF. It has a fluid retention effect and in high concentrations contributes to peripheral vasoconstriction typical for advanced HF. Several other molecules have been recognized to participate in the pathophysiology of HF. Endothelin is secreted by endothelial cells and acts as a potent vasoconstrictor. Up to some extent, this is opposed by endogenous nitric

oxide, prostaglandins E2 and I2, or bradykinin from kallikrein-kinin system.

Lastly, the CO is modulated by non-hormonal cellular and hemodynamic mechanisms. Alterations in filling time and consequent changes in preload will effect the resultant inotropy. In addition, at increased heart rates, the higher aortic elastance will increase LV afterload and the phenomenon of force-frequency relationship will contribute to increased strength of myocardial contraction. However, in chronic course of HF this force-frequency relationship becomes blunted or even negative (Davies et al. 1995).

In summary, key neurohormonal systems maintain CO with an increase in heart rate, contractility, peripheral vasoconstriction, and increase in blood volume with retention of salt and water. Temporarily, compensatory mechanisms help for the cost of higher energy demands, but when persisting, the overexpression of biologically active molecules have detrimental effects on vascular compliance, heart remodeling, and systemic organs, which contributes to disease progression. On the other hand, when these mechanisms are not sufficient and fail, acute decompensation of HF occurs and requires immediate treatment.

1.1.4 Clinical presentation

In typical scenario of chronic HF with slow progression, the body can tolerate more profound decreases in CO as compensatory mechanisms have enough time to develop. Most prominent symptoms include dyspnea, fatigue, and lethargy as a consequence of tissue underperfusion. Fluid retention and capillary hydrodynamic pressure increase lead to edemas in predisposing tissues, effusions, and in severe cases to pulmonary edema. Physical signs include elevated jugular venous pressure, tachypnea, orthopnea, reduced exercise tolerance, pulmonary crepitation, swelling.

Classification of HF severity is traditionally based on exercise capacity and is used to monitor the response to treatment. New York Heart Association (NYHA) classification distinguishes between four groups: I) asymptomatic with no limitation of normal physical activity, II) mild limitations, III) moderate, and IV) severe with symptoms at rest.

Killip classification grades the severity of decompensated HF into four classes: I) no signs of LV dysfunction, II) pulmonary congestion, III) pulmonary edema, and IV) shock syndrome. Associated hospital mortality increases from 6% for class I to 90% for class IV.