Acute Right Heart Failure

Acute Right Heart Failure:

An Overview of the Heart's Prodigal Chamber

Edited by

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FOREWORD

This book is a review of the latest breaking issues and information concerning acute right heart failure, available in medical literature. The author collected this information and compiled it in this easy to read and practical guide. Acute right heart failure is a complex clinical syndrome which is incompletely highlighted in the literature due to the disproportionate attention that has been given to left heart failure. This volume gathers all the precursors that lead to this life-threatening syndrome, starting from normal right heart physiology to different right heart pathophysiologies and ending with a protocol for treating this disease in the acute setting. The book embraces the current research, as well as clinical and experimental trials on acute right heart failure. It contains a special chapter dedicated to actual clinical cases of acute right heart failure, which discusses the difficulties and traps encountered during daily practice in diagnosing and treating this condition. The major impact of the book is its practicality as a guide for everyday clinical practitioners, destined to ease the approach, the diagnosis, and treatment of acute right heart failure.

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I would like to thank GOD for giving me the opportunity and strength to write this book. I also am thankful to my beloved wife for her support and encouragement during this project. I am grateful for my children Natan and Debora, who gave me all the joy in writing and to whom I dedicate this book.

My deep consideration goes out to my mentor in heart failure Dr. Dan Darabantiu and Professor Maria Puschita for their professional advice.

In loving memory of my grandfather who will remain forever in my heart.

INTRODUCTION

For many years, the left ventricle (LV) was the center of attention in most cardiac diseases whereas the physiological importance of the right ventricle (RV) was underestimated and its contractile force was not considered important from a hemodynamic point of view. Nevertheless, the last decade brought changes and the RV function is now recognized as a major predictor of mortality in left heart failure (LHF), pulmonary hypertension (PH), congenital heart disease (CHD) and cardiothoracic surgery. Due to its unique-complex shape and its coupling to a low hydraulic impedance pulmonary vascular bed, the RV is a highly energetically-efficient pump. The RV contraction is sequential and primarily influenced by its loading conditions. This is why any abrupt changes in overload or afterload will lead to impaired RV filling, increased right atrial pressures eventually resulting in RV failure.

The most relevant factors responsible for altered RV loading conditions are pulmonary hypertension, ischemia, cardiomyopathies and arrhythmias.

Acute right heart failure (ARHF) is a clinical syndrome characterized by the incapacity of the RV to eject sufficient blood through the pulmonary vasculature to achieve adequate LV filling. ARHF can occur suddenly in a previously healthy heart, for example in the cases of massive pulmonary embolism (PE) or RV myocardial infarction. Nevertheless, in most cases, it is encountered in left heart failure, exacerbated lung diseases or in the intensive care setting. Nearly one-third of all the admissions with acute heart failure (AHF) syndromes are determined by right ventricle failure -- this is why recognizing RV dysfunction in the early stages of the disease might improve the outcome through specific therapy. Thus, new non-invasive techniques such as tissue Doppler and speckle tracking echocardiography, or tissue characterization by cardiac magnetic resonance might enable to detect RV dysfunction in early stages.

The RV and the LV are enclosed in a pericardial sack, share the same interventricular septum and are part of a closed circulatory system. This is why ventriculoarterial coupling, ventricular interdependence and pericardial constraint become crucial mechanisms in understanding the RV's response to stress and injury with the possibility of developing cardiogenic shock.

Due to the complexity of right ventricular anatomy and hemodynamics, there is a lack of specific treatment focused on this pathology. The usage of common treatment such as fluid management, inotropes and vasopressors might increase mortality if they are not adjusted properly. For the successful management of the RV failure, the followings are required: reducing or reversing afterload (pulmonary vascular resistance - PVR) with the use of selective pulmonary vasodilators in low doses to not induce systemic hypotension; avoiding judicious fluid loading; maintaining RV perfusion with the use of inotropes, vasopressors or assist devices whenever required; and adjusting a focused RV protection strategy for mechanical ventilation.

This volume reviews the latest breaking issues and information available in medical literature and collects them for a better understanding of the RV physiopathology and proper management of the acute right heart failure syndrome.

ABBREVIATIONS

LV – left ventricle
RV – right ventricle
LHF – left heart failure
PH – pulmonary hypertension
CHD – congenital heart disease
ARHF – acute right heart failure
PE – pulmonary embolism
AHF – acute heart failure
PVR – pulmonary vascular resistance
RCA – right coronary artery
CX – circumflex coronary artery
PDA – posterior descendent artery
LAD – left anterior descendent artery
PAH – pulmonary arterial hypertension
PA – pulmonary artery
FAC – fractional area change
TAPSE – tricuspid annular plane systolic excursion
TDI – tissue Doppler image
PAWP – pulmonary artery wedge pressure
COPD – chronic obstructive pulmonary disease
ARDS – acute respiratory distress syndrome
ACP – acute cor pulmonale
HFPEF – heart failure with preserved ejection
IVC – inferior vena cava
RA – right atrium
ECMO – extracorporeal membrane oxygenation
RVAD – right ventricular assist device
ESC – European Society of Cardiology
BP – blood pressure
FOP – foramen ovale patent
DVT – deep vein thrombosis
TEE – transesophageal echocardiography
CRS – cardio-renal syndrome
AKI – acute kidney injury
ACLI – acute cardiogenic liver injury
LVAD – left ventricular assist device

CHAPTER 1

ANATOMY AND PHYSIOLOGY OF THE RIGHT VENTRICLE

ADINA POP-MOLDOVAN, IOAN RADU LALA

The RV is situated behind the sternum, thus being the most anterior positioned chamber in a normal heart. It consists of three components: (1) the inlet, formed of the tricuspid valve, chordae tendineae and papillary muscles; (2) the trabeculated apical myocardium; and (3) the infundibulum which corresponds the outflow tract.[1] (Image 1)

The RV is divided into three walls: the anterior, lateral and inferior ones, with their corresponding basal, mid and apical sections. As a distinctive feature, the RV presents three prominent muscular bands: the parietal, septomarginal and moderator band. The parietal band, along with the infundibular septum, form the crista supraventricularis.[2] The septomarginal band unites on an inferior level with the moderator band and attaches to the anterior papillary muscle.[2] As opposed to the ellipsoidal shape of the LV, the RV is triangular and wrapped around the LV, having a larger volume than the LV with its mass being one-sixth of that of the LV.[3] Furthermore, the RV presents a ventriculoinfundibular fold that separates the tricuspid from the pulmonary valve, whereas in the LV, the aortic and mitral valve presents a fibrous continuity.

The perfusion of the RV is provided depending on the dominance of the coronary system which can be either right dominant (80% of the time) where the right coronary artery (RCA) supplies most of the RV; or left dominant (20% of the time) where the circumflex coronary artery (CX) supplies most of the RV.[4] In other words, the dominance is given by the

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[1] Ho SY, Nihoyannopoulos P. *Heart*. 2006;92(suppl 1): i2–i13.
[2] Farb A, Burke AP, Virmani R. *Cardiol Clin*. 1992;10:1–21.
[3] Lorenz CH, Walker ES, Morgan VL, Klein SS, Graham TP Jr. *J Cardiovasc Magn Reson*. 1999;1:7–21.
[4] Dell'Italia LJ. *Curr Probl Cardiol*. 1991;16:653–720.

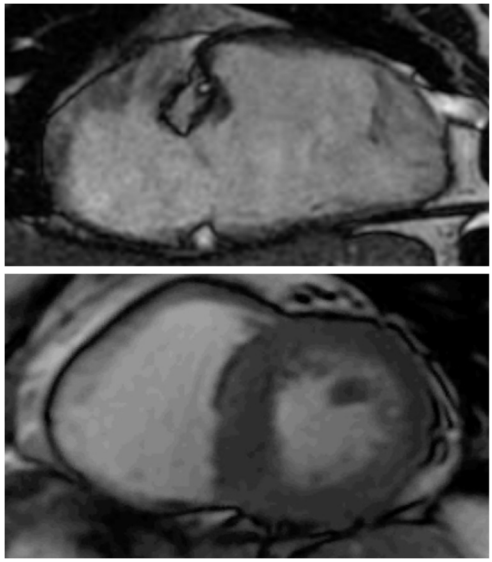

Image 1 – MRI look on the anatomy of the RV- inflow tract, trabeculated apex, outflow tract (infundibulum)

coronary artery (RCA or CX) which gives off the posterior descendent artery (PDA). The PDA irrigates the inferoseptal wall, the posterior wall and the posteromedial papillary muscle. The lateral wall of the RV is irrigated by marginal branches from the RCA and the anterior wall of the RV is irrigated by branches from the left anterior descendent artery (LAD). The infundibulum region is supplied by the conal artery which in 30% of cases has a separate ostial origin. The RV is rather resistant to ischemic injury and this can be explained by lower oxygen consumption, having a more extensive collateral system provided by the moderator band artery that is given by the LAD, and last but not least, the RV's capability to increase oxygen consumption.[5]

The myocardial fibers that form the RV are displayed in two layers: the superficial and the deep layer. The superficial layer is composed of circumferential fibers that turn obliquely towards the apex and continue with the superficial fibers of the LV.[1 4] The deep superficial layer is formed of longitudinally-arranged myofibers from the base to the apex. The existence of functional continuity between ventricles through the superficial layers is the cornerstone of the RV free wall traction during systole caused

[5] Haupt HM, Hutchins GM, Moore GW. *Circulation*. 1983;67:1268 –1272.

by LV contraction.[6] The superficial myocardial layer continuity alongside the interventricular septum and pericardium are responsible for the ventricular interdependence.[4] The RV contraction starts from the inlet and trabeculated myocardium and ends with the infundibulum contraction with a 25 to 50 ms delay, thus facilitating the ejection of blood through its crescent-shaped cavity.[4] The mechanical process of the RV contraction consists of the followings: an inward movement of the free wall; the shortening of the RV long axis through the longitudinal myocardial fibers which moves the tricuspid annulus towards the apex; and finally, the traction of the free wall through the superficial myocardial layer continuity between the ventricles.[6] Longitudinal shortening has a greater contribution to the RV stroke volume than circumferential shortening.[7] In normal physiological conditions, the RV ejects blood in a low impedance, highly distensible pulmonary vascular system. Because of low pulmonary vascular resistance and greater artery distensibility, the RV isovolumic contraction time is shorter because RV systolic pressures will rapidly exceed the low pulmonary diastolic pressure.[8]

The RV performance is influenced by preload, afterload, heart rhythm, interventricular synchrony and ventricular interdependence.[9] RV preload represents the load before its contraction while RV afterload stands for the load which has to be overcome during ejection. Because of the thin wall (RV is coupled to the pulmonary vasculature, a low impedance hydraulic system), any acute changes in afterload will lead to a decline in its performance.[10] Studies have pointed out that the RV contractility is best reflected by maximal RV elastance described through the pressure-volume loops that show end-systolic linearity.[11]

The RV filling is influenced by numerous factors such as intravascular volume status, ventricular relaxation and compliance, heart rate, atrial characteristics, LV filling and pericardial constraint.[12]

The mechanical forces enabled during breathing impose a major impact on RV hemodynamics. For example, during inspiration, each small change in intrapleural pressure will lead to an increase of venous return and

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[6] Haddad F, Hunt SA, Rosenthal DN, Murphy DJ. *Circulation.* 2008, vol. 117 (pg. 1436-48)
[7] Petitjean C, Rougon N, Cluzel P. *J Cardiovasc Magn Reson*. 2005;7:501–516.
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[11] Dell'Italia LJ, Walsh RA. *Cardiovasc Res*. 1988;22: 864–874.
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RV preload.[10] However, as mean airway pressure increases the RV, the stroke volume will decline.[1] In the late 1950s, Cournand first showed that positive pressure ventilation leads to a fall in cardiac output by increasing intrathoracic pressure and thus reducing venous return. This clearly shows the heart-lung interactions and the impact of the afterload on RV contractility.[10]

It is important to mention the role of ventricular interdependence in RV performance. Ventricular interdependence refers to the influence of one ventricle's parameters such as size, shape or compliance on the other ventricle's parameters through direct mechanical interactions.[9]

The function of the RV is regulated by different mechanisms that also act on the LV function. These are: the autonomic nervous system, the Frank-Starling mechanism and the heart rate.[6] An example is set by the case of the autonomic nervous system which promotes different effects in the inflow and outflow region of the RV: sympathetic stimulation abolishes the delay of sequence activation between these regions whereas vagal stimulation prolongs the sequence of activation and contraction.[4] Regarding the heart rate and rhythm, it is crucial to maintain sinus rhythm and a rate within the normal range in case of RV dysfunction because atrial fibrillation or any supraventricular arrhythmia will severely alter the RV function. Furthermore, conduction abnormalities such as right bundle branch block or RV dyssynchrony due to unicameral pacing could lead to reduced cardiac output and high filling pressures.[13] The RV in different types of disorders like arrhythmogenic RV dysplasia, myocardial infarction, cardiac surgery can be a promotor for ventricular arrhythmias with a left bundle branch block morphology.[14]

The shape, architecture and structure of the RV are complex and explains its loading conditions, contractility, ventricular interaction with the left chambers and pericardium. Good knowledge of these features provides a better understanding of the pathophysiological insights of right heart disorders and their proper management.

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[14] Hoch DH, Rosenfeld LE. *Cardiol Clin*. 1992; 10:151–164.

CHAPTER 2

PATHOPHYSIOLOGY OF THE RIGHT VENTRICLE: RV DYSFUNCTION AND FAILURE

IOAN RADU LALA, ADINA POP-MOLDOVAN

The right ventricular dysfunction is defined as an abnormality in the filling or contraction of the RV without any signs and symptoms of heart failure.[1]

RV failure is a complex clinical syndrome defined as a structural or functional abnormality of the myocardium that alters RV filling and contraction which manifests clinically by systemic fluid retention (peripheral edema, ascites, hepatomegaly, anasarca), low cardiac output (hypotension, fatigue, exercise intolerance and even shock) or cardiac arrhythmias.[15]

RV dysfunction results from numerous stress and injury factors such as pressure or volume overload, myocardial ischemia, intrinsic myocardial disease, and pericardial constraint. The most common cause of RV dysfunction is left-sided heart failure where post-capillary PH is the key link that leads to RV impairment. Of course, there are also diseases which primarily affect the pulmonary artery tree (pulmonary artery hypertension-PAH, chronic thromboembolic PH, lung disease and CHD).[15]

The RV adapts better to volume than to pressure overload, as the RV systolic function is preserved for a longer period. However, certain studies associate volume overload with poor prognosis.[2] The latter observation could be explained by the fact that the interventricular septum is responsible for generating up to 40% of the RV's systolic function

[1] Haddad F, Doyle R, Murphy DJ. *Circulation*. 2008, vol. 117 (pg. 1717-31)
[2] Messika-Zeitoun D, Thomson H, Bellamy M et al. *J Thorac Cardiovasc Surg*.2004;128:296–302.

through its septal oblique/transverse oriented myocardial fibers.[9] [3] Oblique myocardial fibers develop more contractile power than the transverse ones.[4] This means that in the case of RV volume overload due to tricuspid regurgitation, through dilation, the RV geometry and the orientation of the myocardial fibers will change. The septal fibers will develop a more transverse configuration that implies the loss of contractility.[5]

Pressure overload will lead to both systolic and diastolic dysfunction, dilation and eventually RV failure. Right myocardium histological changes are more pronounced in pressure-overload states where a higher density of connective tissue and fibrosis is seen in both animal and human studies.[6] [7] A normal RV in case of acute massive pulmonary embolism is not capable to adapt to a rapid increase of pulmonary pressure (mean PA > 40 mmHg) and will lead to ischemia and RV failure with shock.[8] Although PAH leads quite early to RV dysfunction, dilation and failure, these changes can often be seen in later stages in different individuals and PH etiologies.[15] Studies show that an explanation for this observation might lay in altered gene expression such as the downregulation of the alfa-myosin heavy chain gene and the upregulation of the fetal beta-myosin heavy chain.[9] For example, Eisenmenger syndrome is a condition characterized by the presence of severe PH to which the RV adapts well by concentric hypertrophy, while failure is seen late in the end-stages of the disease.[10]

In RV failure, the sympathetic nervous system, the renin-angiotensin-aldosterone, natriuretic peptides, the endothelin system and cytokines are all exacerbated leading to adverse ventricular remodeling.[15] High levels of catecholamines were shown to correlate with increased pulmonary vascular resistance and low cardiac index in patients with PAH-RV failure.[11] It seems that the endothelin system plays an important role in

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[7] Kasimir MT, Seebacher G, Jaksch P, Winkler G, Schmid K, Marta GM, Simon P, Klepetko W. *Eur J Cardiothorac Surg*. 2004;26:776–781.
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[11] Nootens M, Kaufmann E, Rector T, Toher C, Judd D, Francis GS, Rich S. *J Am Coll Cardiol*. 1995;26:1581–1585.

pulmonary hypertension and right heart failure. This was first demonstrated by the upregulation of the endothelin-1 gene expression and endothelin receptors in the right ventricle. Secondly, it was shown by the pharmacological blockage of the endothelin system that led to the improvement of pulmonary vascular resistance, RV hypertrophy and fibrosis.[12] [13] The blockage of the endothelin system did not lead to any improvement in LH failure despite its upregulation which is also present in the LV.[14] Furthermore, the presence of increased levels of TNF-alfa and endotoxin is associated with more symptomatic disease in RV failure.[15]

The acute rise in pulmonary pressure, that is, afterload, is the most frequent cause of acute right heart failure.[16] Left heart failure is the leading cause of right heart failure by promoting secondary pulmonary hypertension.[17] That is, through backward transmission, the increased LV filling pressures determine the rise of post-capillary pulmonary venous pressures, the decrease in pulmonary vascular compliance, stiffening of the pulmonary arteries, the increase of RV wall stress which eventually leads to RV dysfunction.[18]

Pulmonary hypertension in the setting of right heart failure is the result of the increase of pulmonary vascular resistance, pulmonary blood flow, pulmonary venous pressure, or the combination of these parameters, where PVR is the most important determinant of PH.[19] [20] [21] Elevated pulmonary pressure defined as a mean arterial pulmonary pressure at rest over 25 mmHg will reflect on the RV, determining it to adapt with measures to counter this burden leading to heart failure.[22] The first adaptive response of the burdened ventricle is the heterometric right chamber dimension adaptation (a diastolic effect) applying Frank-Starling's law which will soon be counteracted by the homeometric adaptive response (a systolic effect)

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[12] Mulder P, Richard V, Derumeaux G et al. *Circulation*. 1997;96:1976–1982.
[13] Channick RN, Simonneau G, Sitbon O et al. *Lancet*. 2001;358: 1119 –1123.
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[22] Hoeper MM, Bogaard HJ, Condliffe R et al. *J Am Coll Cardiol* 2013;62(Suppl): D42–D50

with an increase of RV contractility.[23] [24] The homeometric reply is governed by Anrep's law in which the contractility strength of the myocardial fibers is independent of the end-diastolic fiber length, extrinsic factors or neuroendocrine stimulation.[25]

The abrupt rise in the RV afterload due to altered pulmonary vascular load will lead to the inefficiency of the homeometric response in compensating the loading conditions and will eventually be lost leaving room only for the heterometric adaptive response to persist and try to compensate.[26] This will lead to a vicious circle where the increase of the RV size will determine the increase in RV end-diastolic volume and right ventricular filling pressures which enhances wall tension and cardiomyocyte stretch with consequent higher oxygen demand, impaired coronary perfusion and eventually RV ischemia.[27] Furthermore, diastolic ventricular interaction will apply and thus competition for space will take place within a non-distensible pericardial sack due to sudden changes in end-diastolic volumes and pressures in one ventricle that will determine the loss of compliance of the other ventricle.[28] The diastolic ventricular interaction is mediated by the shared structures of the ventricles: the interventricular septum and pericardium with its constraining effects.[42] As a result, increasing volumes and filling pressures of the RV will determine the increase of pericardial pressure and will thus lead to pericardial constraint that limits RV free wall-stretch and compensatory Frank-Starling mechanism.[29] This will result in the interventricular septum shifting towards the LV cavity with consequent compression and impaired filling of the left chamber.[15] [37] By altering LV compliance and diastolic properties, LV end-diastolic pressures will rise while LV end-diastolic volumes will be reduced leading to a decline in LV output.[30] [31] With the decrease of LV preload and output, hypotension will occur further aggravating myocardial perfusion that will eventually lead to cardiogenic shock. (Figure 1) RV filling

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[31] Shapiro BP, Nishimura RA, McGoon MD, Redfield MM. *Adv Pulmon Hypertens.* 2006;5:13-27

pressures over 4 mmHG will determine the increase of pericardial pressures in a parallel manner thus exerting constraint.[32] It is prudent to avoid fluid loading when RV filling pressure is above 10-15mmHg because it will only worsen the hemodynamic status with further shifting of the septum towards the LV and decreasing in stroke volume.[33] Pericardium constraint will affect both RV and LV fillings.[34]

RV dilation determines tricuspid annulus dilation with consequent functional tricuspid insufficiency which leads to systemic congestion and a fall in RV output. Tricuspid regurgitation combined with pulmonary hypertension results in less blood ejected from the RV towards the pulmonary vasculature and the left chambers leading to a decrease in LV preload – stroke volume thus further aggravates the state of shock.[15] [47] Pulmonary hypertension itself can lead to RV ischemia by prolonging the isovolumetric contraction and ejection and thus the increase of RV oxygen demand.[35] The increase of oxygen demand has to be compensated by the increase of RCA-perfusion which in this case has to be > 45 mmHg to avoid ischemia (in normal conditions RCA-perfusion is maintained at pressures below 25 mmHg).[36] While in most cases ARHF is accompanied by hypotension or the patient presents RCA stenosis, this compensatory mechanism is altered and further ischemia will further worsen the RV function.[37]

To summarize, the pathophysiology of acute RV failure is complex and characterized by RV dilation with increased filling pressures, decreased RV output, impaired LV compliance, accompanied by clinical signs of venous congestion, high central venous pressures and multi-organ dysfunction (especially liver-kidney damage). The performance of the RV will determine the performance of the LV, meaning that the reduction of RV output imposes lesser LV preload with a consequent decrease in stroke volume through the so-called “series effect”.

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[36] Urabe Y, Tomoike H, Ohzono K, et al. *Circ Res.* 1985; 57: 96–104.

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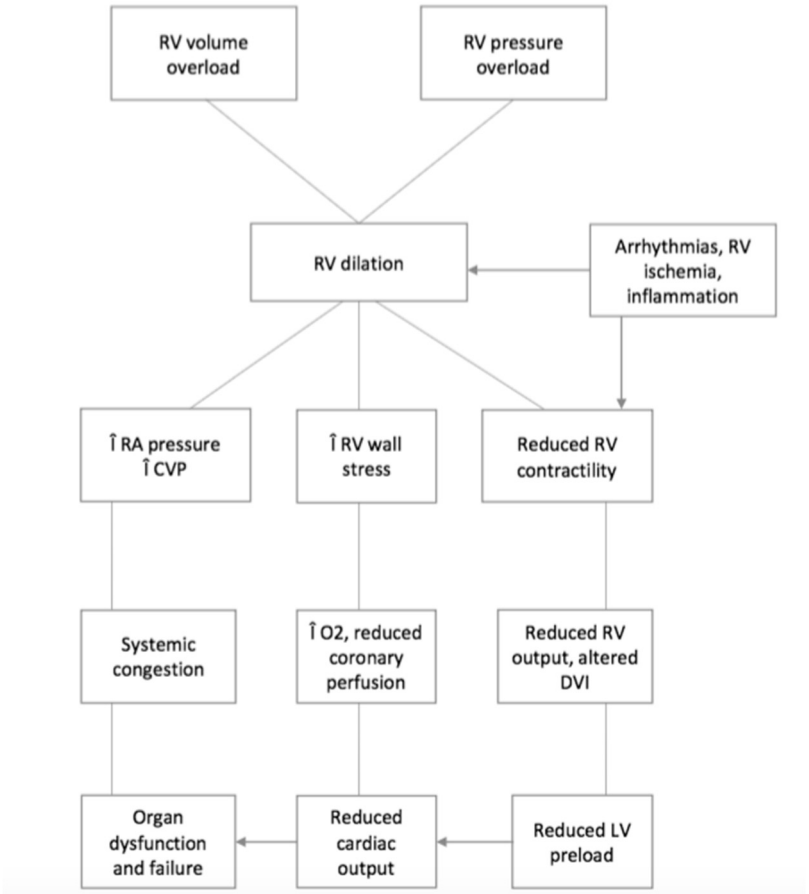

Figure 1 - ARHF Pathophysiology

Cardiorenal syndrome and acute right heart failure

The kidney function is one of the main promoters of the worst outcome in patients with acute heart failure. The hemodynamic interactions between the heart and kidneys have led to the development of a new term known as "cardiorenal syndrome" (CRS). This syndrome encompasses a wide range of disorders that affect both the heart and kidneys and in which acute or chronic dysfunction of one organ will lead to dysfunction in the other organ.[38]

The Acute Dialysis Quality Initiative has reached a classification consensus where the cardiorenal syndrome was classified into 5 types of which CRS type 1 is characterized by acute kidney injury (AKI) due to an acute cardiac event (for example acute coronary syndrome resulting in cardiogenic shock and AKI or acute heart failure resulting in AKI).[39] [40] Thus, acute right heart failure would be responsible for CRS type 1. Most of the studies and trials investigating acute kidney injury in the context of acute heart failure mainly focused on left ventricular failure with reduced ejection fraction. However, greater attention has been recently given to congestion as the key player responsible for acute renal dysfunction rather than low cardiac output in the context of heart failure. This led to intense investigations of the pathophysiological mechanisms behind acute isolated right heart failure and acute decompensated pulmonary hypertension that might result in acute kidney injury. The following arguments will mainly focus on the mechanisms responsible for renal dysfunction in the context of right heart failure.

At first glance, the abrupt increase of central venous pressure with a consequent rise of renal vein pressure is primarily responsible for worsening renal function regardless of the cardiac output levels.[41] Renal perfusion pressure is dependent not only on arterial blood pressure but also on trans-renal perfusion pressure which is defined by mean arterial pressure minus central venous pressure.[42] In as early as 1861, Ludwig showed that a rise in renal vein pressure over 10 mmHg will determine a reduction in

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urinary flow and this was attributed to mechanical compression of the tubules by the overdistended surrounding venules.[43] Damman et al. showed that increased central venous pressure and jugular venous pressure determined by clinical examination is associated with impaired renal function.[55]

Systemic congestion (visceral edema, ascites, abdominal wall edema) is responsible for the increase of the intra-abdominal pressure in acute right heart failure.[56] Additional factors such as bowel distension, obesity, the elevation of the head on the bed with over 30 degrees are responsible for further aggravation of intra-abdominal pressure.[56] Intra-abdominal hypertension is defined by a pressure higher than 12 mmHg.[44 45] Renal blood flow is mediated by the abdominal perfusion pressure which is the result of the mean arterial pressure minus intra-abdominal pressure.[46] An abdominal perfusion pressure of 60 mmHg is considered normal. Venous congestion determines the increase in renal venous pressure with consequent intrarenal vein distension which may stimulate local mechanoreceptors.[56] This will lead to local sympathetic renal nerve stimulation that results in intrarenal arterial vasoconstriction with consequent fall in the glomerular filtration rate. In acute right heart failure, besides venous congestion, the following are also present: hyperactivation of the renin-angiotensin-aldosterone system, arginine-vasopressin, endothelin and other neurohormones that promote the worsening of the renal function.[47] Endothelial cells react to venous congestion due to the circumferential stretch of the vessel and transform into active secretory cells. They produce pro-inflammatory and vasoconstricting factors such as cytokines, tumor necrosis factor and interleukin-6 which will impair renal function by stimulating renin secretion and determine tubulointerstitial inflammation.[48]

Another factor responsible for the worsening of the renal function in acute right heart failure is reduced cardiac output. The drop in cardiac output is the result of several mechanisms: increased RV afterload which leads to the decrease of RV output and secondary to LV atrial and ventricle filling pressures, RV volume overload through diastolic ventricular

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[43] Ludwig C. Lehrhuch der Physiologie des Menschen 2, 2nd edn, Leipzig. 1861; 373.
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interaction limiting LV filling, as well as RV pressure overload which leads to prolonged RV free wall contraction with consequent right to left trans-septal pressure gradient in early LV diastole, dyssynchrony and leftward septal bowing.[49] Reduced RV end-systolic contraction with impaired LV filling results in decreased LV stroke volume and cardiac output with consequent renal ischemia. In patients with known pulmonary diseases (COPD, sleep apnea), hypoxia and hypercapnia are responsible for decreased systemic vascular resistance, neurohormonal activation, reduced renal blood flow and renal oxidative stress.[63]

In a study on 140 patients with acute heart failure Uthoff et al. showed that central venous pressure alone at baseline and discharge did not correlate with the glomerular filtration rate; instead, low systolic blood pressure with high central venous pressure at presentation was significantly associated with low glomerular filtration.[50] This could be explained by the fact that decreased intraglomerular pressures and low glomerular filtration are mainly driven by preglomerular vasoconstriction due to extreme RAAS and neurohormonal activation.[52] In another study by Mullens et al. on low-output-decompensated failure, venous congestion was the strongest hemodynamic factor responsible for worsening renal function.[51] Also patients with pulmonary hypertension, the worsening of the renal function were seen in those with increased central venous pressure and low cardiac index.[65] It was shown, on animal studies, that right ventricular dysfunction provoked by graded pulmonary stenosis results in decreased renal blood flow and sodium retention.[52]

Patients with pathologies associated with right ventricular dysfunction such as obesity, sleep apnea, cor pulmonale are prone to develop acute kidney injury.[53] [54] [55] In one interesting study in patients with acute right heart failure due to pulmonary embolism, diuretic therapy with furosemide was delivered as a complementary therapy rather than volume expansion in the initial phase, showing an improvement in renal function by the decrease in creatinine levels.[56] In an analysis of the ESCAPE trial, right atrial pressure was associated with baseline renal dysfunction, an observation that

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was later confirmed in patients that underwent right-heart catheterization; it was also shown that increased central venous pressure is associated with reduced glomerular filtration rate and all-cause mortality.[57] The right ventricular stroke work index is an important prognostic factor for kidney dysfunction in right heart failure.[58] Elevated intra-abdominal pressures in the setting of acute right heart failure may impair renal function through renal compression and reduced perfusion.[59]

Thus, the pathophysiology of impaired renal function in acute right heart failure is rather complex and is not solely attributed to one mechanism but rather to a combination of both decreased cardiac output and increased central venous pressure.

Clinical features are described by reduced urine output, worsening fluid retention and diuretic resistance.[60]

Concluding, impaired renal function characterized by high levels of serum creatinine and blood urea nitrogen is responsible for adverse outcomes in the setting of an acute event if signs of considerable decongestion are not present.

Cardiohepatic syndrome and acute right heart failure

Acute cardiogenic liver injury (ACLI) is the term used to describe a sudden release of hepatic proteins due to tissue hypoxia and cell death after an acute cardiac event in which cardiac output is insufficient to meet the metabolic needs of the liver.[61] [62] This typical pattern, historically named "ischemic hepatitis" is often described in patients with cardiogenic shock. However, a low cardiac output state that impairs hepatic blood flow is not fully responsible for inducing acute liver injury.[76]

A study performed by Henrion et al. in patients admitted to the intensive coronary care unit with low output heart failure, showed that those patients with increased central venous pressures presented a higher incidence of acute cardiogenic liver injury compared to those with lower

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[58] Kanjanahattakij N, Sirinvaravong N, Aguilar F, Agrawal A, Krishnamoorthy P, Gupta S. *Cardiorenal Med*. 2018;8:123–129. doi: 10.1159/000486629

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[60] Konstam MA, Kiernan MS, Bernstein D et al. *Circulation.* 2018; 137:e578–e622. doi: 10.1161/CIR.0000000000000560

[61] Henrion J. Liver Int 2012; 32:1039–52.

[62] Henrion J, Schapira M, Luwaert R et al. Medicine (Baltimore) 2003;82:392–406.

central venous pressures.[63] In other words, acute liver injury is not linked to a sole hemodynamic insult but rather to a combination of decreased hepatic blood flow and hepatic venous congestion.[77] Elevated central venous pressure is transmitted backward towards the hepatic sinusoidal bed leading to peri-sinusoidal edema and the decrease of oxygen diffusion to the hepatic cells.[64] Chronic sinusoidal congestion is also responsible for exudate formation into the space of Disse, the fluid that will be eventually drained in the peritoneal cavity when the capacity of the hepatic lymphatics is exceeded leading to cardiac ascites.[78] The histological landmark of acute cardiogenic liver injury is the necrosis of the hepatocytes that surround the central vein where oxygenation is usually poor.[65] The degree of necrosis around the central veins with possible extension towards the mid-zonal hepatocytes depends on how prolonged the hemodynamic insult is.[79]

Typical laboratory findings of acute cardiogenic liver injury consist of the following: a rapid rise in levels of liver enzymes, aminotransferase and lactate dehydrogenase usually up to 20 times above normal in the first 24 hours without any evidence of other liver etiologies.[77] Liver enzymes levels will decrease to normal in 7 to 10 days if hemodynamic correction is achieved.[75] The early rise in lactate dehydrogenase is highly specific to acute cardiogenic liver injury and also a ratio of serum alanine aminotransferase to lactate dehydrogenase (ALT/LDH) < 1.5 can distinguish in the early phase between cardiogenic liver injury and other etiologies of acute hepatitis.[66] Other laboratory abnormalities may show the rise in serum bilirubin, gamma-glutamyl transpeptidase, alkaline phosphatase and prolongation of the prothrombin time.[75] Abnormal phosphatase-alkaline has been associated with increased right-sided filling pressures and systemic congestion whereas increased transaminases are linked to hypoperfusion.[67] Liver function abnormalities, particularly markers of cholestasis are considered independent risk factors for mortality in patients with acute right heart failure.[68] It has been demonstrated that bilirubin is an independent prognostic marker for cardiovascular death, all-cause mortality and postprocedure right ventricular failure.[81] Bilirubin has also been introduced

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[63] Henrion J, Descamps O, Luwaert R, Schapira M, Parfonry A, Heller F. *J Hepatol*. 1994;21:696–703.
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as part of a risk score that predicts right ventricular failure after left ventricular assist device (LVAD) procedure or transplantation.[69] [70]

The clinical profile of patients with ACLI includes weakness, apathy, mental confusion, tremor, hepatic coma, jaundice, bleeding diathesis.[71]

The management of ACLI in the context of acute right heart failure involves restoring cardiac output and reducing right-side filling pressures. The primary target in restoring normal liver function remains to treat the underlying cardiac condition. This can be achieved by diuretics which may relieve hepatic congestion but in severe cases with shock, the use of inotropes to enhance cardiac output may be required. In refractory cases, therapeutic approaches such as paracentesis or ultrafiltration may be useful to remove ascites or edema if the patient is unresponsive to diuretic therapy.[72]

Acute liver injury is common in the setting of acute right heart failure and is associated with worse outcomes. Thus, the recognition of this high-risk group from the early stages with the help of the liver biochemical profile is important as patients may benefit from intensified treatment.

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