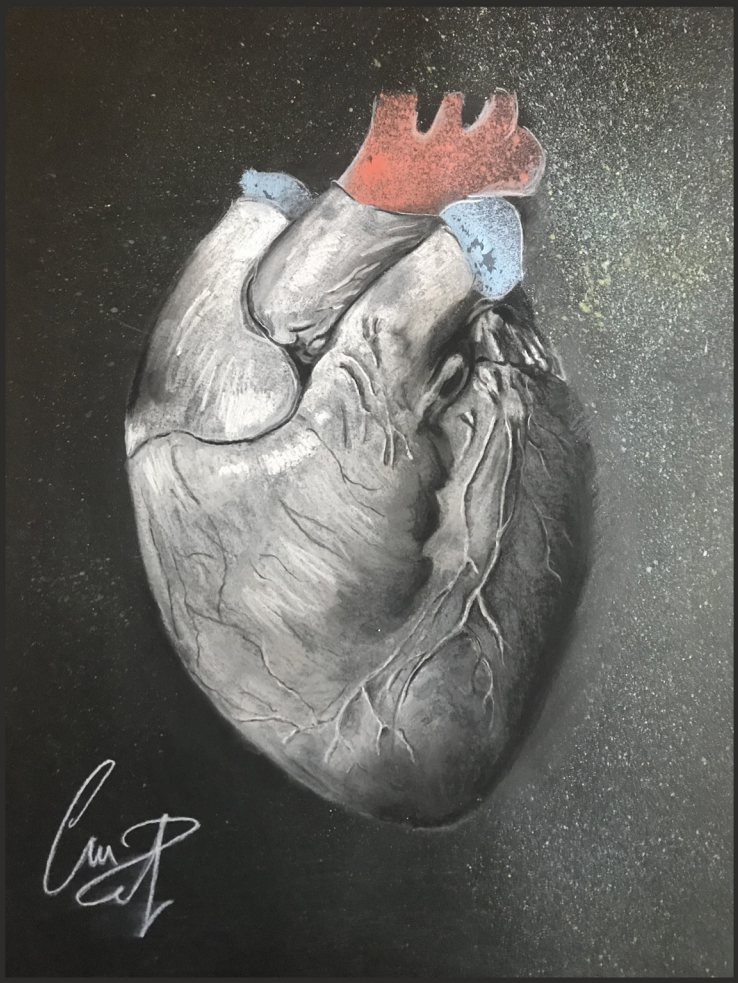
Acute Right Heart Failure

An Overview of the Heart's Prodigal Chamber



Edited by Ioan Radu Lala

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Cambridge Scholars Publishing

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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

[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.

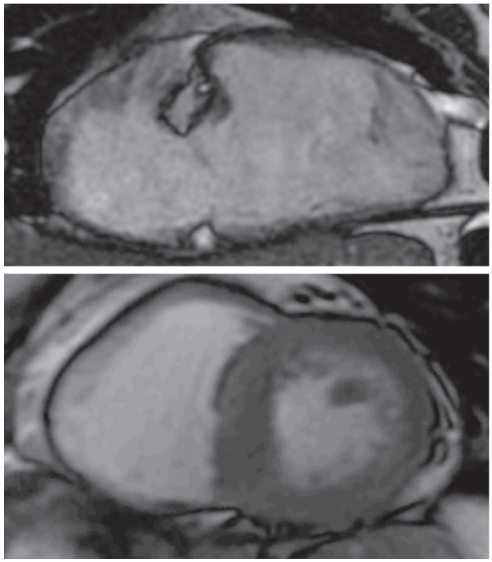

Image 1 – MRI look on the anatomy of the RV- inflow tract, trabeculated apex, outflow tract (infundibulum)

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.
[8] Dell'Italia LJ, Walsh RA. *Am Heart J*. 1988;116:1289–1297.
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[11] Dell'Italia LJ, Walsh RA. *Cardiovasc Res*. 1988;22: 864–874.
[12] Burgess MI, Mogulkoc N, Bright-Thomas RJ, Bishop P, Egan JJ, Ray SG. *J Am Soc Echocardiogr*. 2002;15: 633–639.

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.

[13] Dubin AM, Janousek J, Rhee E et al. *J Am Coll Cardiol*. 2005;46: 2277–2283.
[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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[3] Hoffman D, Sisto D, Frater RW, Nikolic SD. *J Thorac Cardiovasc Surg*. 1994;107:1496 –1502.
[4] Salin EA. *Biophys J.* 9:954-964, 1969.
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[6] Marino TA, Kent RL, Uboh CE, Fernandez E, Thompson EW, Cooper G. *Am J Physiol*. 1985;249:H371–H379.
[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.
[8] Logeart D, Isnard R, Resche-Rigon M et al. *Eur J Heart Fail.* 2013;15:465 – 476.
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[10] Hopkins WE, Waggoner AD. *Am J Cardiol*. 2002;89:34–38.
[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.
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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

[23] Naeije R, Brimioulle S, Dewachter L. *Pulm Circ.* 2014;4: 395 – 406.
[24] Naeije R, Manes A. *Eur Respir Rev.* 2014;23:476–487.
[25] Sarnoff SJ, Mitchell JH, Gilmore JP, Remensmyder JP. *Circ Res.* 1960 8 1077 1091
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[29] Belenkie I, Dani R, Smith ER, Tyberg JV. *Circulation*. 1989, vol. 80 (pg. 178-188)
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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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[35] Brooks H, Kirk ES, Vokonas PS, Urschel CW, Sonnenblick EH. *J Clin Invest.* 1971 50:2176–2183

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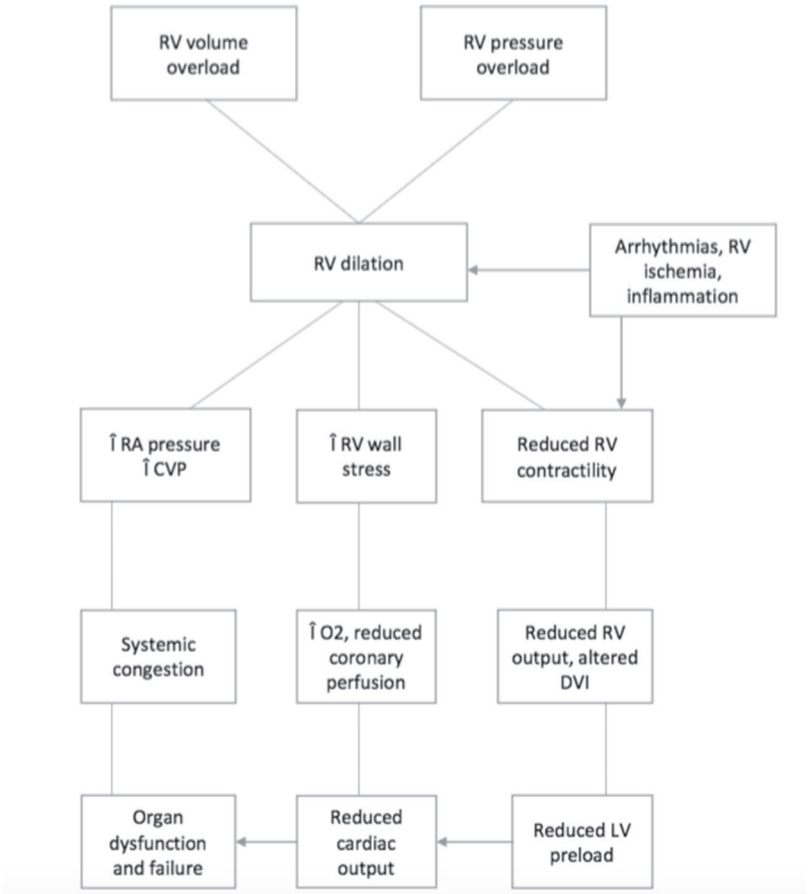

Figure 1 - ARHF Pathophysiology

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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[38] Rangaswami J, Chair V, Bhalla V, Blair JEA, Chang TI, Costa S. *Circulation.* 2019;139:e840–e78.

[39] Ronco C, McCullough P, Anker SD et al. *Eur Heart J*. 2010;31:703– 711.

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[42] Gnanaraj JF, von Haehling S, Anker SD, Raj DS, Radhakrishnan J. *Kidney Int*. 2013; 83:384–391

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.
[44] Sugrue M. *Curr Opin Crit Care.* 2005; 11: 333–338.
[45] Lambert DM, Marceau S, Forse RA. *Obes Surg.* 2005; 15: 1225–1232.
[46] Cheatham M, White MW, Sagraves SG et al. *J Trauma*. 2000; 49: 621–626.
[47] Schrier RW. *J Am Coll Cardiol.* 2006; 47: 1–8.
[48] Gimbrone MA Jr, Topper JN, Nagel T et al. *Ann N Y Acad Sci*. 2000; 902: 230–239.

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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[49] S Bansal, A Prasad, S Linas. *Am Soc Nephrol.* 29 (7) (2018), pp. 1795-1798
[50] Uthoff H, Breidthardt T, Klima T et al. *Eur J Heart Fail.* 2011, vol. 13 (pg. 432-439)
[51] Mullens W, Abrahams Z, Francis GS et al. *J Am Coll Cardiol.* 2009;53:589 – 596.
[52] Barger AC, Yates FE, Rudolph AM. *Am J Physiol.* 200: 601–608, 1961
[53] Danziger J, Chen KP, Lee J et al. *Crit Care Med.* 2011, in press
[54] de Louw EJ, Sun PO, Lee J et al. *Crit Care.* 30: 619–623, 2015
[55] Chen Y, Li Y, Jiang Q et al. *Arch Iran Med.* 18: 827–833, 2015
[56] Ternacle J, Gallet R, Mekontso-Dessap A et al. *Circ J.* 77: 2612–2618, 2013

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

[57] Nohria A, Hasselblad V, Stebbins A et al. *J Am Coll Cardiol*. 2008;51:1268–1274. doi: 10.1016/j.jacc.2007.08.072

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

[59] Mullens W, Abrahams Z, Skouri HN et al. *J Am Coll Cardiol*. 2008;51:300–306. doi: 10.1016/j.jacc.2007.09.043

[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.
[64] Sundaram V, Fang JC. *Circulation.* 2016;133:16961703.
[65] Sherlock S. *Br Heart J.* 1951;13:273–93.
[66] Cassidy WM, Reynolds TB. *J Clin Gastro- enteral.* 1994;19:118–21.
[67] Allen LA, Felker GM, Pocock S, et al. *Eur J Heart Fail.* 2009;11:170–7.
[68] Poelzl G, Ess M, Mussner-Seeber C, Pachinger O, Frick M, Ulmer H. *Eur J Clin Invest*. 2012;42:153–163. doi: 10.1111/j.1365-2362.2011.02573.x.

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.

[69] Matthews JC, Koelling TM, Pagani FD, Aaronson KD. *J Am Coll Cardiol.* 2008;51:2163–72.
[70] Singh TP, Almond CS, Semigran MJ, Piercey G, Gauvreau K. *Circ Heart Fail.* 2012;5:259–66.
[71] Naschitz JE, Slobodin G, Lewis RJ, Zuckerman E, Yeshurun D. *Am Heart J.* 2000;140:111–20.
[72] Kisloff B, Schaffer G. Fulminant hepatic failure secondary to congestive heart failure. *Dig Dis Sci.* 1976;21:895–900.

CHAPTER 3

ETIOLOGY AND EPIDEMIOLOGY OF ACUTE RIGHT HEART FAILURE

DAN DARABANTIU

Acute right heart failure occurs as a consequence of an increase in right ventricular (RV) afterload, preload and/or a decrease in right ventricular contractility. Pulmonary embolism, acidosis or hypoxia can suddenly increase RV afterload, while RV infarction, postcardiotomy injury or myocarditis can produce a decrease in RV contractility.

The prevalence of acute RV failure is around 3-9% of all acute heart failure admissions with in-hospital mortality of 5-17%.[1] In the ESC-HF Long-Term Registry, the clinical phenotype of acute RV failure at admission was present in 3.5% of the patients. The one-year mortality rate in these patients was as high as 34%, being surpassed only by that of patients with cardiogenic shock.[2] These figures underline the prognostic importance of acute RV failure as a disease with an unfavorable outcome.

The main causes of acute RV failure are the following:

- Acute pulmonary embolism
- Acute right ventricular infarction
- Acute respiratory distress syndrome
- Postcardiothoracic surgery
- Pericardial tamponade
- Sepsis
- After heart transplantation or left ventricular assist device implantation
- Right heart valvular diseases

[1] Maggioni AP, Dahlstrom U, Filippatos G et al. *Eur J Heart Fail.* 2010, 12, 1076-1084

[2] Chioncel O, Mebazaa A, Harjola VP et al. *Eur J Heart Fail.* 2017, 19, 1242-1254

- Acute left ventricular failure
- Myocarditis
- Acute decompensation of chronic pulmonary hypertension

In patients with acute pulmonary embolism, acute RV failure is present in 25 – 60% of cases. Its presence is a significant predictor of mortality, the risk of death being 2.4 – 3.5 times higher compared to patients without RV failure. The mortality rate at 30-days in these patients is between 5-10%. The presence of RV dysfunction is a marker of intermediate-risk in normotensive patients with PE.[3] In patients with cardiogenic shock (high-risk PE), present in 5% of PE patients, the mortality rate at 90-days is over 50%. The involvement of > 40% of the cross-sectional area of the pulmonary arterial bed significantly increases the pulmonary artery pressure and determines acute RV dysfunction in patients without previous pulmonary hypertension.

Acute RV myocardial infarction is another frequent cause of acute RV failure. In patients with acute inferior myocardial infarction, RV involvement is present in 30-50% of cases and increases the risk of shock, arrhythmias and death. It is usually due to the occlusion of the right coronary artery; the more proximal the occlusion, the more extensive the RV myocardial necrosis.[4]

Acute respiratory distress syndrome (ARDS) is accompanied by acute RV failure in 30-50% of cases. Predictors for the occurrence of acute RV failure in the setting of ARDS include pneumonia-induced ARDS, $pCO2 \geq 48$ mmHg, the ratio between $pO2/FiO2 < 150$ mmHg and plateau pressure – total positive end-expiratory pressure ≥ 18 cm $H2O$.[5] In patients with at least 2 of these predictors, routine echocardiography is recommended since the incidence of acute RV failure is higher than 20%.

Postoperative acute RV failure is a serious problem since it is associated with high mortality, longer hospitalization time and higher use of medical resources. Its incidence is related to the type of intervention: 0.1% after cardiotomy, 2-3% after heart transplantation, 10-20% after implantation of a left ventricular assist device.[6] In patients with LVAD implantation, RV failure can occur acutely or late. Acute RV failure is a

[3] Konstantinides SV, Torbicki A, Agnelli G et al. *Eur Heart J*. 2014, 35, 43, 3033 – 3069
[4] O'Rourke R, Dell'Italia JL. *Current Problems in Cardiology.* 2004, 29, 1, 6-47
[5] Mekontso Dessap A, Boissier F, Charron C et al. *Intensive Care Medicine.* 2016, 42, 5, 862 – 870
[6] Mekontso Dessap A, Boissier F, Charron C et al. *Intensive Care Medicine*. 2016, 42, 5, 862 – 870

cause or early morbidity and mortality and was found more frequently in patients with a history of chemotherapy compared with other forms of cardiomyopathies. Late RV failure (after discharge) is a complication found in 10% of patients, also associated with decreased quality of life and survival.[7] It is difficult to predict the occurrence of RV failure after LVAD implantation because risk prediction scores are unable to take into account intraoperative parameters such as mechanical ventilation, hypoxia or volume loading.

Both left and right valvular diseases may produce acute RV failure. The most frequent valvular disease involved in the pathogenesis of acute RV failure is tricuspid regurgitation. Acute RV failure may be a consequence of severe tricuspid regurgitation caused by tricuspid endocarditis which determines valvular destruction with RV overload and dilatation. Righ-heart endocarditis may occur on native valves, congenital heart defects, implanted devices or bioprosthetic valves and represents 5-10% of endocarditis cases.[8]

In patients with chronic pulmonary hypertension, an acute increase in pulmonary artery pressure can trigger an episode of acute RV failure. Such increases can be due to an episode of pulmonary embolism, pulmonary infections, supraventricular tachyarrhythmias.[9]

[7] Konstam MA, Kiernan MS, Bernstein D et al. *Circulation.* 2018, 137(20), 578-622
[8] Habib G, Lancellotti P, Antunes MJ et al. *Eur Heart J.* 2015, 36, 3075-3128.
[9] Harjola VP, Mebazaa A, Celutkiene J et al. *Eur J Heart Fail.* 2016, 18,226-241

CHAPTER 4

ASSESSMENT OF ACUTE RIGHT HEART FAILURE

IOAN RADU LALA

Patients with acute RV failure have various clinical presentations (Table 1) which depend on the underlying cause. This is why an initial thorough clinical history and physical examination should be performed as soon as possible. Specific etiologies that require specific treatment (such as pulmonary embolism or myocardial infarction) should be sought immediately because of their potential life-threatening features. Thus 12-lead electrocardiogram, arterial blood gases and lactate should be assessed routinely.

Electrocardiogram pathological findings

The general ECG criteria for acute right heart failure are: **electrical rotations** of the heart due to pressure or volume overload of the RV (most common orar rotation on the longitudinal axis as in **S1Q3** type), **specific ST-T segment repolarizations modifications** as in **ST depression or elevations** in the inferior and right leads due to RV ischemia, **minor or major right bundle branch block, a decrease in QRS amplitude** due to overstretching of the RV myocardial fibers, **diffuse anterior ischemia** due to RV- LV interdependency, a high likelihood of **arrhythmias** such as sinus tachycardia, atrial fibrillation and flutter or even ventricular tachycardias.

There are three types of acute right heart failure aspects visible on the ECG as follows:

1. The common type without right bundle branch block;
2. The type with right bundle branch block;
3. The type with diffuse ischemia;

Common type ECG without RBBB

In the limb leads, in D1 and aVL the QRS shape is of Rs, QR in D3 and aVF. Sometimes the S wave is more prominent in D1, sometimes the Q wave is more prominent in D3. The QRS amplitude can be reduced but is not mandatory. The ST-T segment can show an elevation in D3 and aVF with negative T wave and ST-T depression in D1 and aVL with positive T wave; the D2 lead describes ST horizontal depression with biphasic T wave.

In the thoracic leads, a common finding is the rSr' pattern, the small r' is an expression of the late depolarization of the dilated right ventricle. In V2-V3 there is an rS shape with a progressive rise of R wave towards the left anterolateral leads as in Rs shape. The ST segment can be elevated in V1 with negative T wave findings that can also be seen in the right precordial leads V3r, V4r. (Image 2, Image 3)

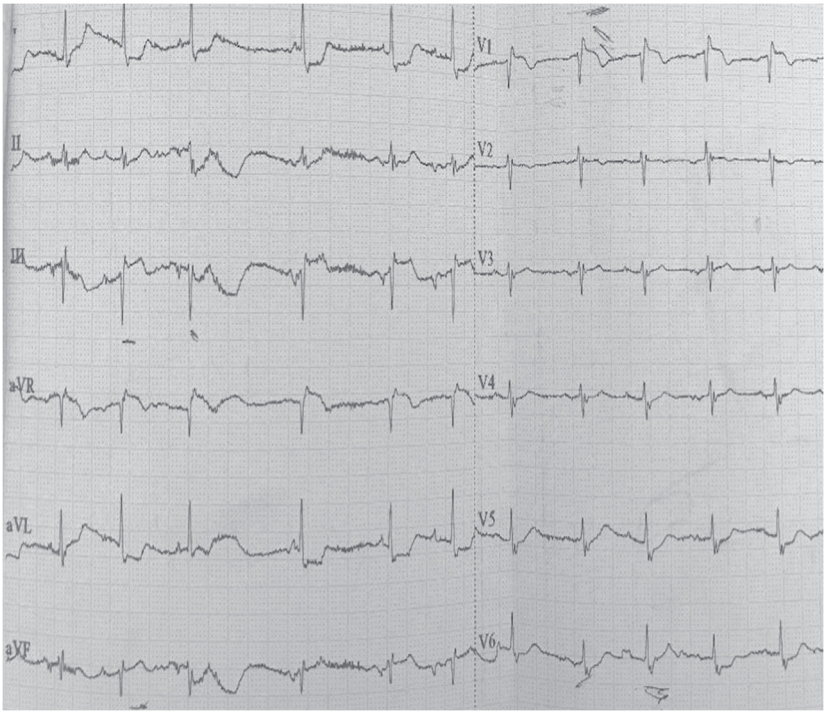

Image 2. Acute pulmonary embolism; common type without RBBB- right bundle branch block

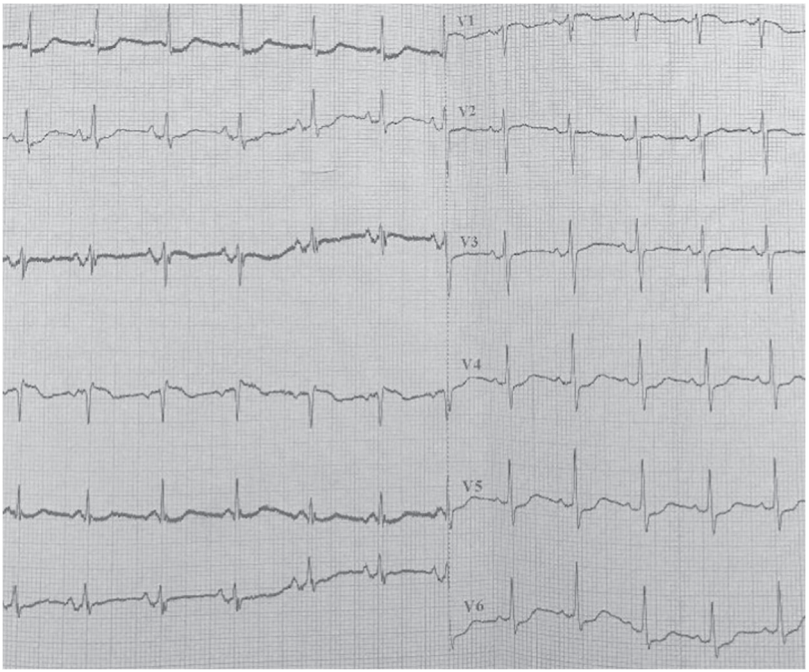

Image 3. Acute pulmonary embolism; common type without RBBB - right bundle branch block

Common type ECG with RBBB

In this case, we find a QRS length of over 0.12 s with a QRS shape of rsR' in V1, ST elevation and negative T wave in V1. (Image 4)

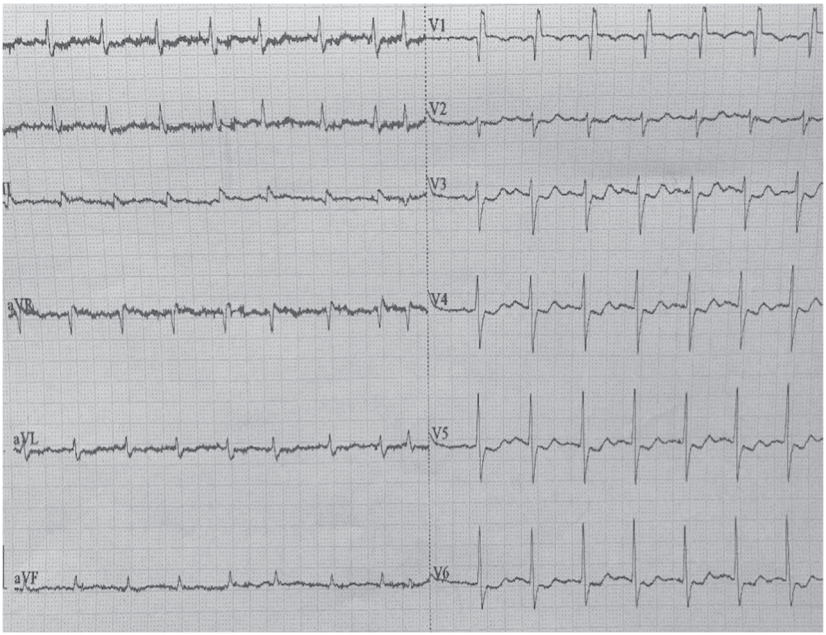

Image 4. Acute pulmonary embolism; common type with RBBB- right bundle branch block

Common type ECG with diffuse ischemia

The ECG recording is of anterior subendocardial ischemia with ST depression in V1-V6, the depression being more pronounced in V1-V4 and also present in the inferior leads D2, D3 and aVF. The T wave in the aforementioned leads is usually flattened or biphasic but can appear in certain situations as deep symmetric and negative in V1-V4 which can mimic an acute coronary syndrome (the Wellens Syndrome). The ECG pattern of acute right heart failure with diffuse ischemia is the result of the reduction of cardiac output and left main coronary artery hypoperfusion concordant with right ventricle overload. (Image 5, Image 6)

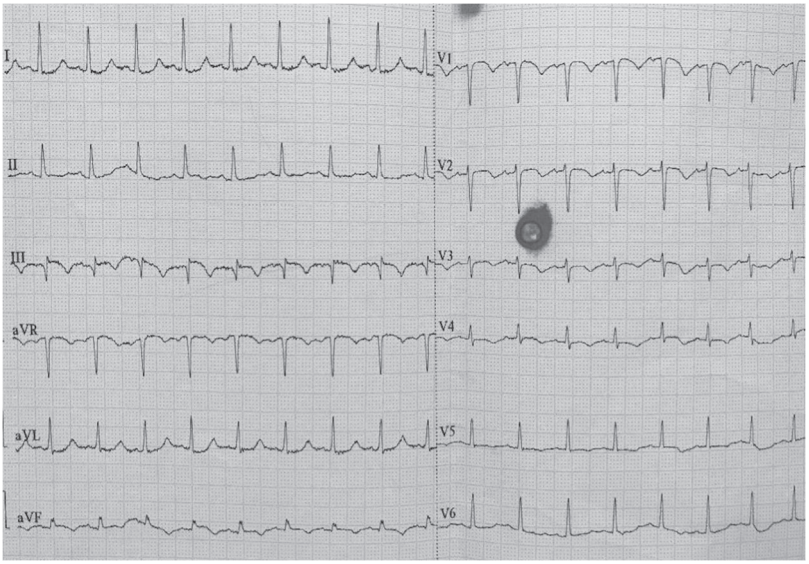

Image 5. Acute pulmonary embolism; common type with diffuse ischemia

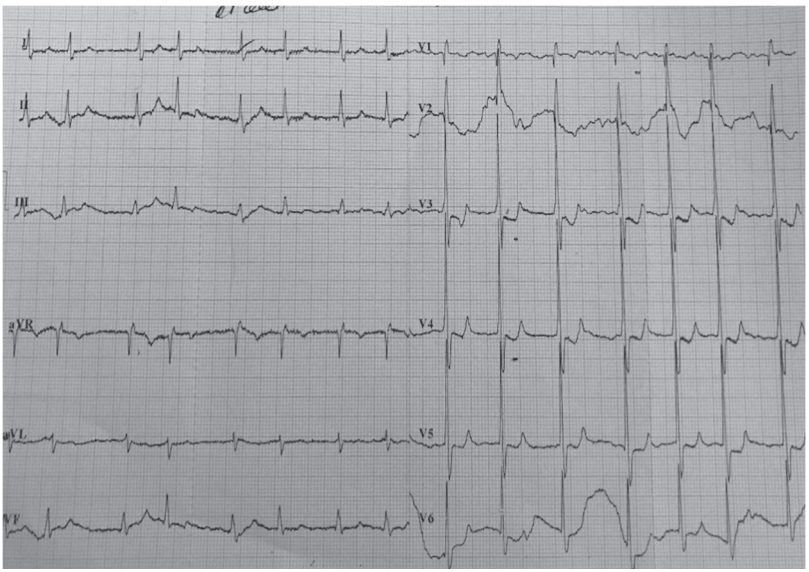

Image 6. Acute decompensated pulmonary hypertension – atrial fibrillation – right ventricular hypertrophy; common type with diffuse ischemia

Arrhythmias in acute right heart failure

Volume or pressure overload of the right ventricle will lead retrogradely to the overstretching of the right atrium causing acute paroxysmal supraventricular tachycardias such as atrial fibrillation or atrial flutter which will compromise the hemodynamic status. (Image 7)

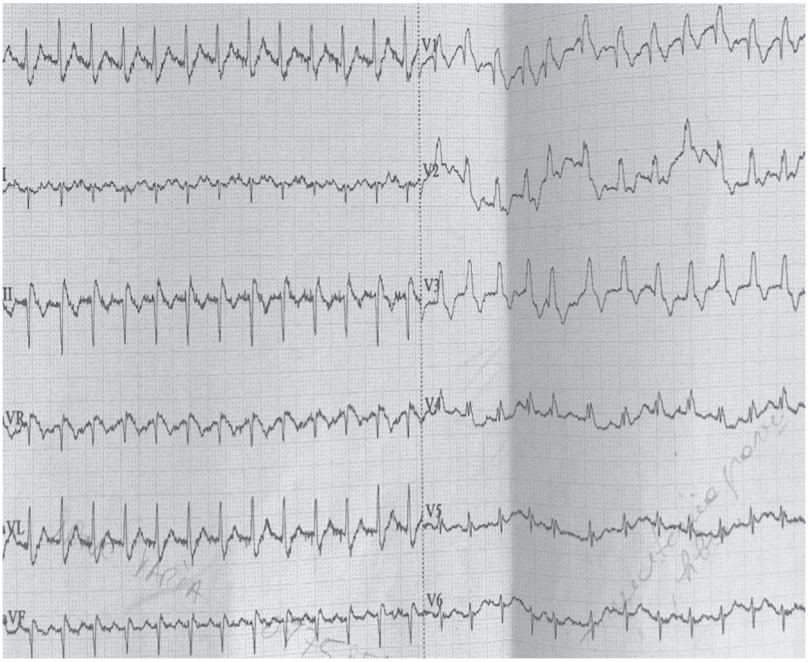

Image 7. Atrial flutter, RBBB – right bundle branch block

Arrhythmogenic right ventricular cardiomyopathy/dysplasia is a genetic heart disorder frequently seen in young people and athletes, manifested clinically by right ventricular electrical instability in the form of ventricular tachycardias (VT) or ventricular fibrillation (VF). Sustained or non/sustained VT in ARVC/D is characterized by a left bundle branch block (LBBB) pattern.

Inferior myocardial infarction with right ventricular involvement

Patients with inferior STEMI should all be checked for RV infarction especially if they are hemodynamically unstable with hypotension. These patients should undergo as soon as possible right-sided (V3R-V6R) ECG lead recordings. Right ventricular infarction should be suspected if the presence of ST elevation in V1, ST elevation in D3>D2 (D3 is a more right faceward lead than D2), ST elevation in V1>V2 or ST elevation in V1+ ST depression in V2. A direct confirmation of RV infarction is the presence of ST elevation in the right-sided leads (V3R-V6R). (Image 8, Image 9)

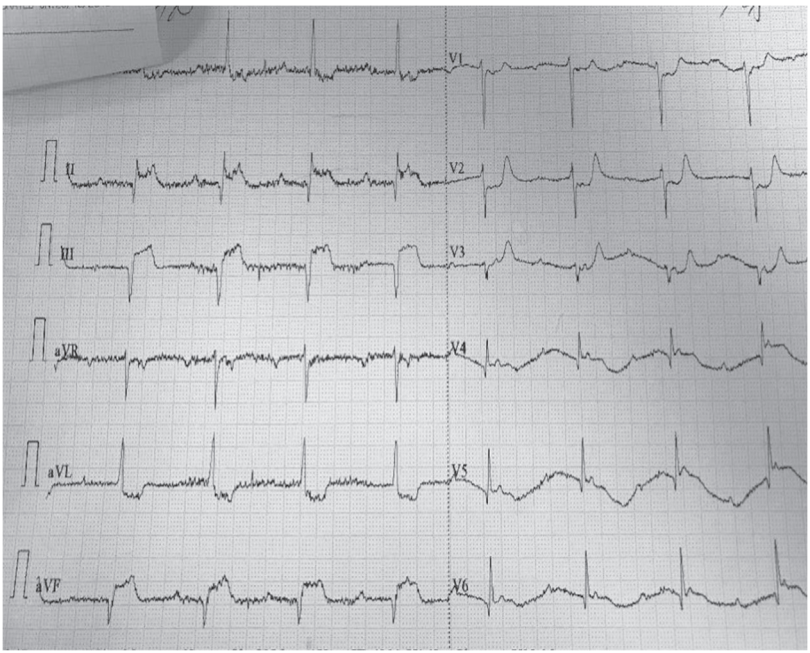

Image 8. Inferior - posterior myocardial infarction, total AV block

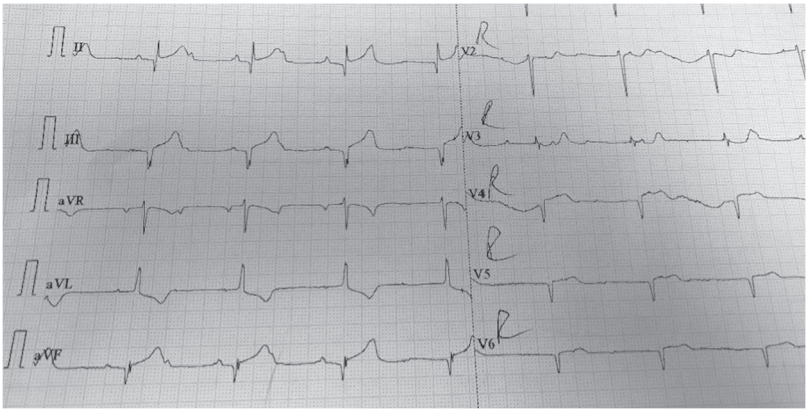

Image 9. Right ventricular myocardial infarction, total AV block

Cor pulmonale ECG changes

A typical finding is tall P waves in D2, D3 ("pulmonic P wave"), small P in D1, and biphasic P in V1. The QRS complex is characterized by small-amplitude with right axis deviation (+90*- +180*).

Limb leads modifications are of right ventricular hypertrophy: rS in D1, qR in D2, D3, aVF with QRS amplitude over 0.6mV; S1S2S3 pattern with predominant S con in cases with severe pulmonary emphysema; ST depression in D2, D3 and aVF, biphasic T wave.

Thoracic leads: dominant R wave in V1 with qR pattern, ST depression and negative T wave, R/S transition in V3, rS in V5-V6; deep S waves from V1 to V6 with poor R progression, R/S transition V5 or V6; negative QRS of W shape V1; QS V1-V3; right bundle branch block rsR' in V1; ST concave elevation V1-V6 with negative T wave V1-V3 which is positive in V5-V6 or ST depression V1-V3.

The Sokolow-Lyon index for right ventricular hypertrophy is only seen in 20-50% of patients and is caused by emphysema but right ventricular hypertrophy is responsible for ST-T left deviation and right axis deviation, which are very common findings. (Image 10)

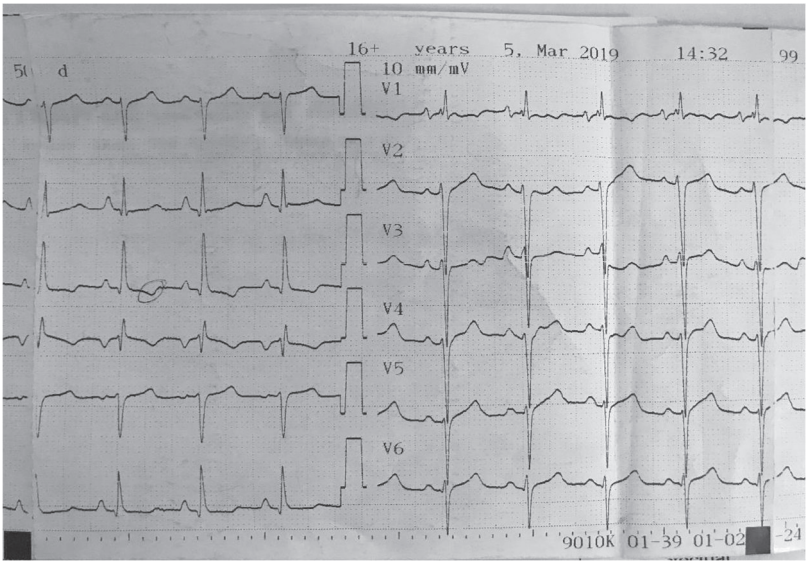

Image 10. Right axis deviation, right ventricular hypertrophy, chronic cor pulmonale

Table 1 - Physical examination

Clinical findings
Hypoxemia
Systemic congestion (jugular vein distension, hepato-jugular reflux, hepatomegaly, pericardial effusion, pleural effusion, peripheral edema, ascites, anasarca)
Signs of hypoperfusion: hypotension, oliguria, tachycardia, altered mental status
Cardiac examination: the presence of S3, tricuspid or mitral systolic murmur, hepatic pulsations, paradoxical pulse

Table 2 - Laboratory tests

Biochemistry
Increased lactate levels
Abnormal renal function (increased blood urea nitrogen and creatinine levels) **Abnormal liver function (increased liver enzymes, bilirubin; prolonged prothrombin time)**
High NT-ProBNP
High Troponin I or T
High D-dimer levels in case of pulmonary embolism

A routine chest X-ray is mandatory as it can reveal specific RV failure findings such as increased vascular pedicle width due to dilation of the superior vena cava, dilation of the azygos vein, and dilation of the right atrium. (Image 11)

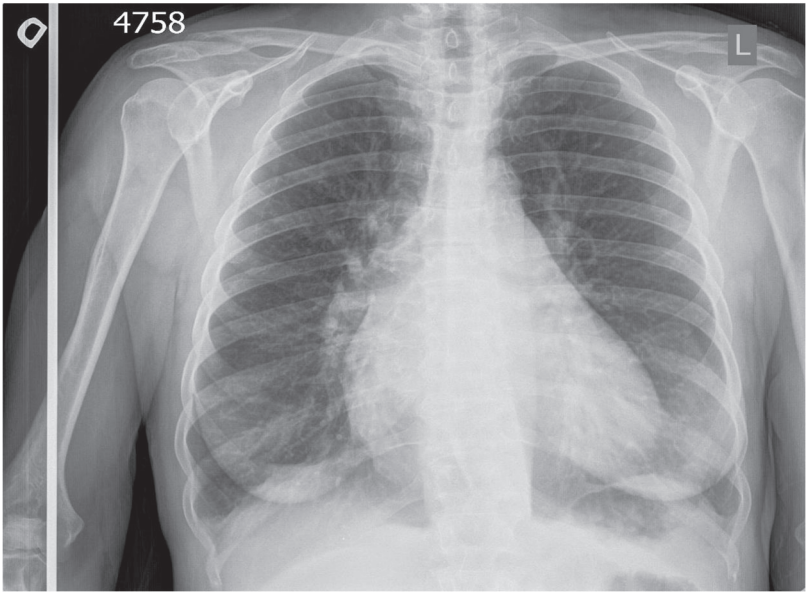

Image 11. Cardiomegaly, right atrium dilation, pulmonary hypertension

Imagistic assessment of right ventricular failure - Echocardiography

In the emergency department, bedside echocardiography is the first-line test to provide rapid information on RV structure, function and load. Due to its complex anatomy, it is often difficult to assess RV size and function but by qualitative 2D-echo evaluation, valuable information can be easily obtained.

Normally, the RV should be two thirds the size of the LV. This is the reason why its size must first be assessed. If in the parasternal long-axis view, the RV appears larger than the LV and the apical four-chamber view shares the apex with the LV, then RV dilatation is present.[1] (Image 12, Image 13)

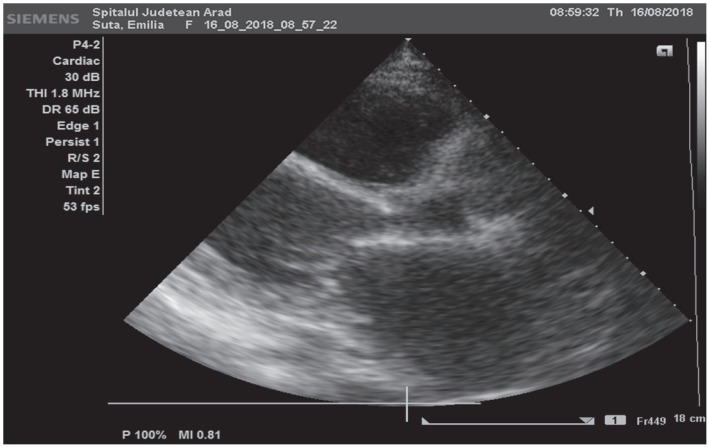

Image 12. Right ventricular dilatation

[1] Bleeker GB, Steendijk P, Holman ER et al. *Heart.* 2006;92(suppl 1):i19–i26.

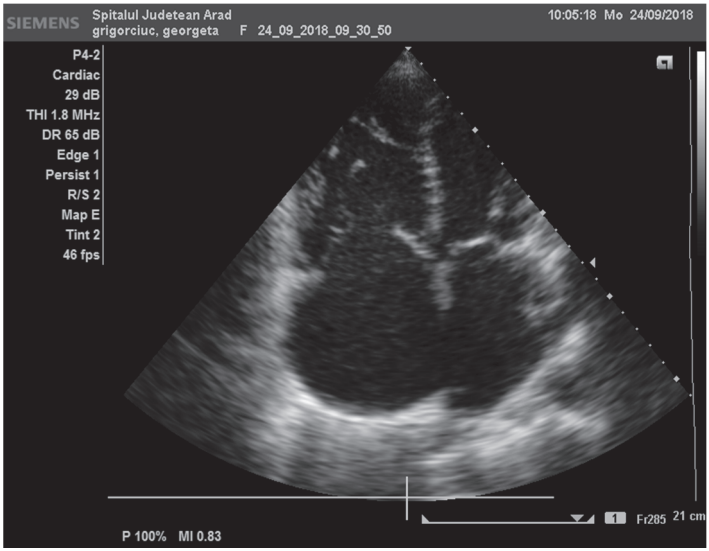

Image 13. Right ventricular dilatation

In the short parasternal view, if RV dilation is present, the LV forms a "D-shape" form instead of the normal circular geometry – this is due to the flattening of the interventricular septum. (Image 14)

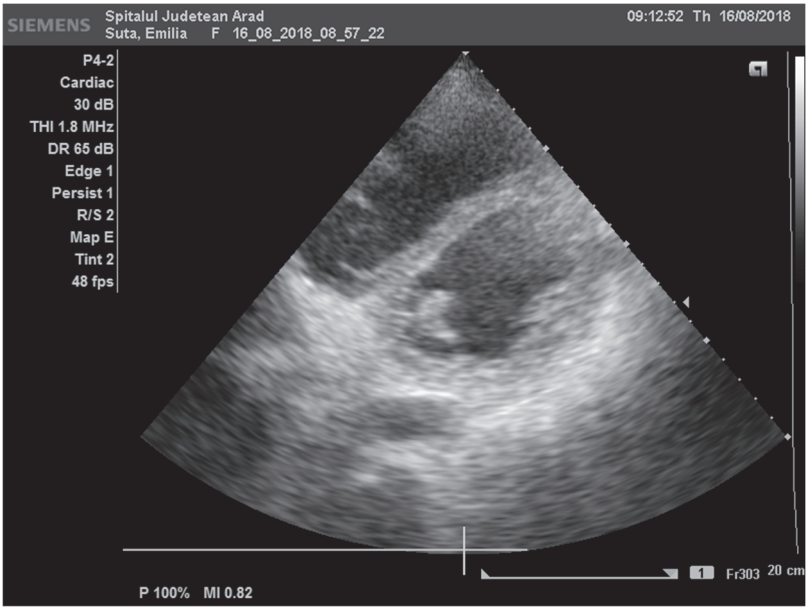

Image 14. D shaped septum due to right ventricular dilatation

A comparison between ventricles is the RV/LV ratio parameter that is determined by measuring basal diameters of both ventricles in end-diastole of the apical 4 chamber view. (Image 15)

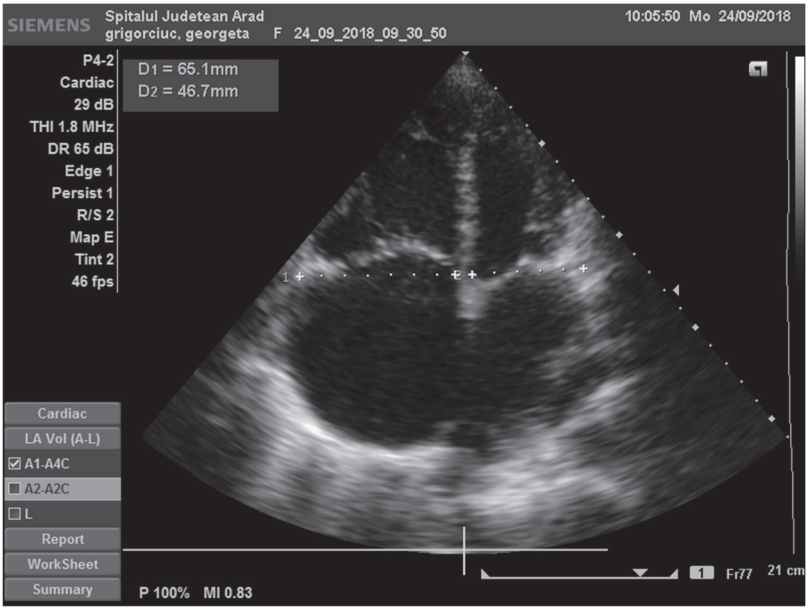

Image 15. Increased RVEDD/LVEDD ratio

A ratio of > 1 is suggestive of severe RV dilation.[2] The eccentricity LV index (which is the ratio between two perpendicular diameters of the LV – anteroposterior and septilateral – in the short parasternal axis view) is a quantitative measure of septal bowing in cases of increased RV pressure or volume overload. An index of > 1 is suggestive of RV pressure or volume overload.[3] [4]

A quantitative technique used to measure the RV size and function is the area-length method which traces the RV endocardial border in the 4-chamber view and the short parasternal view. (Image 16, Image 17)

[2] Krishnan S, Schmidt GA. *Chest*. 2015 147:835–846
[3] Ryan T, Petrovic O, Dillon JC, Feigenbaum H, Conley MJ, Armstrong WF. *J Am Coll Cardiol*. 1985; 5(4):918-927.
[4] Mekontso Dessap A, Charron C, Devaquet J, et al. *Intensive Care Med*. 2009;35(11):1850-1858.

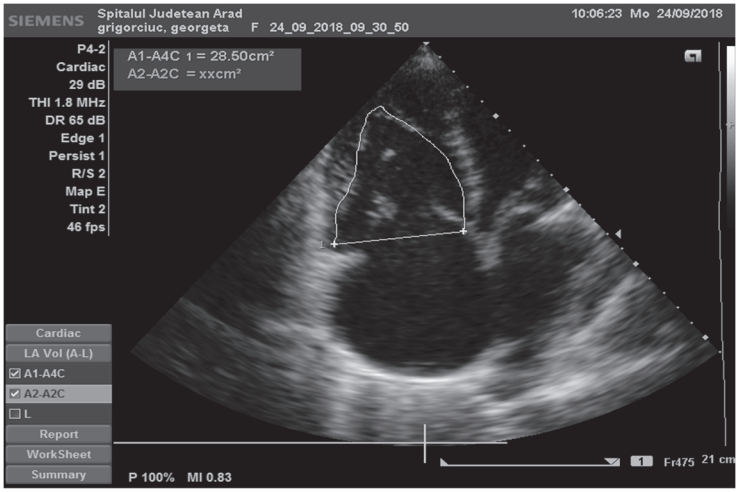

Image 16. Fractional area change right ventricle

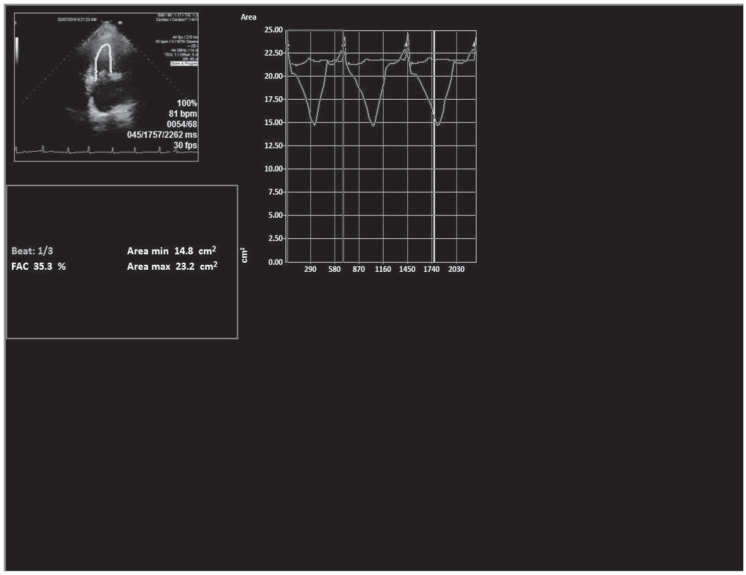

Image 17. Fractional area change right ventricle

Fractional area change of more than 35% is considered normal in adults.[5] FAC values under 17% are suggestive of decreased RV systolic function.[6] It was demonstrated that FAC correlates with the RV ejection fraction determined by MRI and has prognostic value in patients with myocardial infarction and PH.[7] [8] Due to the complex shape of the RV and patient anatomical structure (emphysema, obesity, thorax cage abnormalities), a large number of patients cannot be analyzed properly by lack of tracing the entire ventricle.[9] To obtain better views of the RV, intravenous contrast agents can be used, but still, this method is time-consuming and not the best choice in the emergency department.

A better and easier quantitative method to assess the function of the RV is the measurement of tricuspid annular plane systolic excursion (TAPSE). (Image 18)

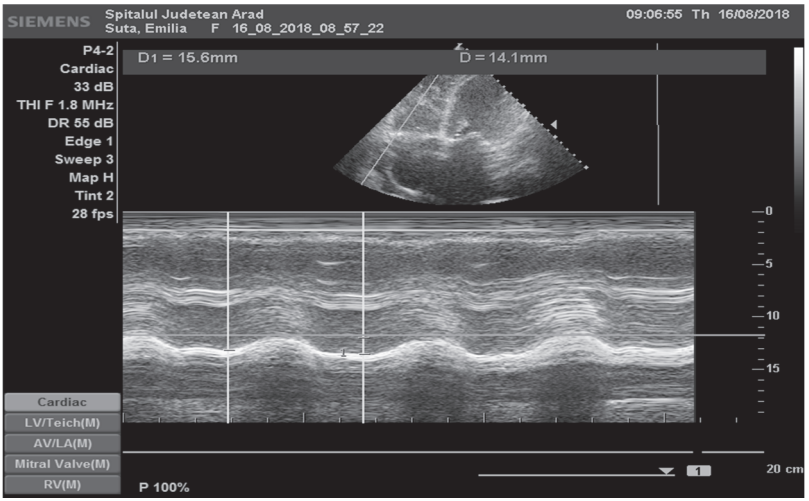

Image 18. Decreased tricuspid annular plane systolic excursion (TAPSE)

[5] Lopez-Candales A, Dohi K, Rajagopalan N, Edelman K, Gulyasy B, Bazaz R. *Postgrad Med J.* 2008; 84

[6] Rudski LG, Lai WW, Alalo J et al. *J Am Soc Echocardiogr.* 2010;23(7):685-713.

[7] Anavekar NS, Gerson D, Skali H, Kwong RY, Yucel EK, Solomon SD. *Echocardiography.* 2007; 24:452–456. [PubMed: 17456062]

[8] Anavekar NS, Skali H, Bourgoun M, et al. *Am J Cardiol.* 2008; 101

[9] Starling MR, Crawford MH, Sorensen SG, et al. *Circulation.* 1982;66:612–20.

This technique allows estimating the RV systolic function by measuring the systolic displacement of the tricuspid annular plane towards the apex in the apical four-chamber view. A good correlation between TAPSE and RV ejection fraction measured by angiography has been demonstrated.[10] [11] TAPSE with values below 16 mm is associated with increased mortality in patients with chronic right heart failure.[12] [13]

A useful echocardiographic parameter that can assess the RV function that is not affected by heart rate and loading condition is the Doppler index of myocardial performance (Tei index) and is expressed by the sum between isovolumic contraction time and isovolumic relaxation time ratio RV ejection time.

Tissue Doppler imaging (TDI) is a useful technique that permits assessing RV systolic and diastolic function by measuring the myocardial velocities. (Image 19)

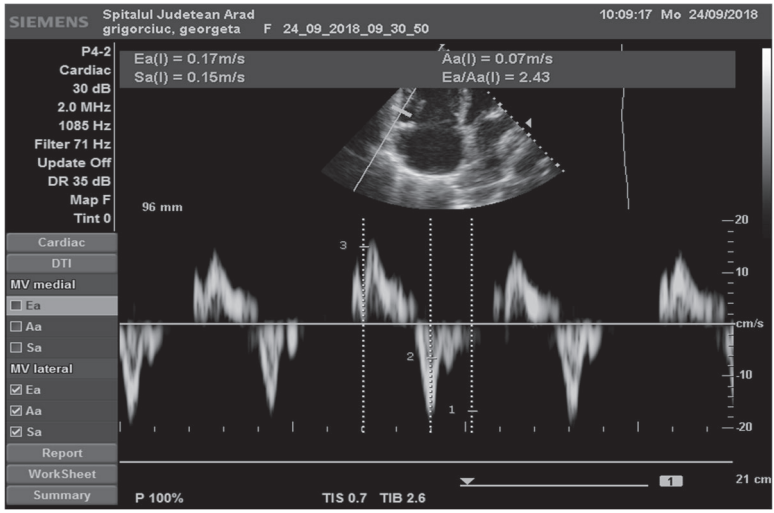

Image 19. Right myocardium velocities

[10] Kaul S, Tei C, Hopkins JM, et al. *Am Heart J*. 1984;107:526–31.
[11] Ghio S, Recusani F, Klersy C, et al. *Am J Cardiol.* 2000;85:837–42.
[12] Forfia PR, Fisher MR, Mathai SC et al. *Am J Respir Crit Care Med.* 2006;174(9):1034-1041.
[13] Damy T, Kallvikbacka-Bennett A, Goode K, et al. *J Card Fail*. 2012;18(3):216-225.

By Doppler TDI, one can measure the maximum systolic velocity of the lateral tricuspid annulus. Its normal values are over 12 cm/s, but they decrease with age.[14] Systolic velocities tend to decrease from the base towards the apex and are higher than mitral annulus velocities, a condition which is explained by different loading conditions of the RV with lower compliance and afterload, also the presence of predominant longitudinal myocardial fibers in the free RV wall.[15] A decrease by < 11cm/s of the systolic velocities correlates with an ejection fraction of < 45% with 90% sensitivity and 85% specificity.[16] It has been demonstrated that systolic velocities below 9.5 cm/s are a prognosis marker of worse outcomes in patients with chronic heart failure.[17] This parameter was proven useful by comparison with MRI.[18] Another TDI parameter that was studied regarding the RV involvement and estimating right atrial pressure is the E/ea ratio (ratio between early tricuspid inflow velocity determined by spectral Doppler and lateral tricuspid annular early diastolic velocity determined by tissue Doppler).[19] A ratio over 6 had a 79% sensitivity and 73% specificity in detecting mean right atrial filling pressures of over 10 mmHg.[79]

RV speckle tracking echocardiography

Because the RV has thinner walls compared to the LV, longitudinal myocardial shortening is the main driver of global RV contractility.[20] This is why speckle tracking is a useful technique in quantifying the regional and global deformation of the RV. Strain and strain rate are useful techniques to quantify regional and global RV function. Cut-off values for strain and strain rate (-25% respective -4s) have been proposed with a specificity of 88% in predicting RV ejection fraction over 50%.[21] (Image 20, Image 21)

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[14] Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, et al. *J Am Soc Echocardiogr*. 2011, vol. 24 (pg. 277-313)

[15] Kukulski T, Hubbert L, Arnold M, Wranne B, Hatle L, Sutherland GR. *J Am Soc Echocardiogr.* 2000; *13*: 194–204.

[16] Meluzin J, Spinarova L, Bakala J, Toman J, Krejci J, Hude P, Kara T, Soucek M. *Eur Heart J*. 2001;22:340 –348.

[17] Damy T, Viallet C, Lairez O, Deswarte G, Paulino A, Maison P, et al. *Eur J Heart Fail*, 2009, vol. 11 (pg. 818-24)

[18] Wahl A, Praz F, Schwerzmann M, Bonel H, Koestner S, Hullin R, et al. *Int J Cardiol*, 2010, vol. 151 (pg. 58-62)

[19] Nageh MF, Kopelen HA, Zoghbi WA, Quiñones MA, Nagueh SF. *Am J Cardiol.* 1999; *84*:1448–1451, A8

[20] Jamal F, Bergerot C, Argaud L, Loufouat J, Ovize M. *Am J Physiol Heart Circ Physiol*, 2003, vol. 285 (pg. H2842-7)

[21] Vitarelli A, Conde Y, Cimino E et al. *Eur Respir J*. 2006, vol. 27 (pg. 268-75)

The major advantages of speckle tracking compared to TDI are: it is a technique independent of the angle and is less dependent on loading. However, an important disadvantage of this technique is that it quantifies the deformation of RV only in 4-chamber which is not proper for assessing the global RV function. Be that as it may, measuring the global longitudinal strain of the RV with this technique is much more sensitive than using classical parameters such as TAPSE and FAC when evaluating RV dysfunction in different pathologies. In a study on 344 patients undergoing cardiac surgery, the prognostic role of RV dysfunction was evaluated by conventional measurement of TAPSE and FAC in comparison to global longitudinal strain by speckle tracking echocardiography.[22] Results showed that the rate of RV dysfunction detection was up to 61% with GLS compared to 20% with TAPSE and FAC.[117] The longitudinal strain of the RV free wall is considered to be an important predictor factor for RV performance in pulmonary hypertension.[23] Furthermore, it was pointed out that the longitudinal strain of the RV free wall and the mediobasal interventricular septum is reduced in pulmonary embolism.[24] Speckle tracking echocardiography allows it to appreciate the pattern of RV activation and evaluating RV dyssynchrony by determining the standard deviation of activation times of the RV 6 segments from the beginning of the QRS complex to the peak systolic myocardial deformation.[25] Speckle tracking was found useful in differentiating between pathological RV hypertrophy and physiological hypertrophy of athletes and hypertrophy cardiomyopathy patients. The latter group showed a reduced RV longitudinal strain compared to athletes' hearts.[26] A normal value for RV GLS was proposed in the range of -25.4±8.2%[27]

3D Echocardiography of the RV

Difficulties in correctly evaluating the RV function by 2D echocardiography derive from RV's asymmetric geometry, inner trabeculations,

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[22] Ternacle J, Berry M, Cognet T et al. *J Am Soc Echocardiogr.* 2013;26:721–6.
[23] Fukuda Y, Tanaka H, Sugiyama D et al. *J Am Soc Echocardiogr.* 2011; *24*:1101–1108
[24] Sugiura E, Dohi K, Onishi K et al. *J Am Soc Echocardiogr.* 2009, vol. 22 12(pg. 1353-1359)
[25]Platz E, Hassanein AH, Shah A, Goldhaber SZ, Solomon SD. *Echocardiography*. 2012, vol. 29 4(pg. 464-470)
[26] D'Andrea A, Caso P, Bossone E et al. *Eur J Echocardiogr.* 2010;11:492–500.
[27] Forsha D, Risum N, Kropf PA et al. *J Am Soc Echocardiogr.* 2014;27:413–22.

outflow and inflow tracts that can be evaluated only in different sections, the dependency of loading conditions, a low sensibility of echocardiographic parameters compared to invasive evaluation.[6] Although not a golden standard, 3D echocardiography is the method chosen when determining RV ejection fraction compared to 2D echocardiography because it offers a good correlation with volumes calculated by MRI; as volume measurements are independent on shape and size, it does not result in foreshortened images.[28] [29] The current evaluation of the RV involves 'full-volume' large-angle image acquisition from the 4 chamber apical view centered on the RV with the 3D probe. The images acquired will be then post-processed offline. The method is based on semiautomatic volumetric detection of the endocardium with manual adjustment of the correct contours thus permitting evaluation of telesistolic and telediastolic volumes. By using 3D echocardiography, one can analyze unique and different RV echo-slices after 3D reconstruction thus offering a better glimpse in understanding the pathology behind the failing RV: pulmonary hypertension, shunts, complex congenital heart disease or changes secondary to left heart valvulopathies.[124] [30] Data on normal reference values for volumes and ejection fraction of RV are scarce; however, there is one international multicentric study performed by Maffessanti et al. in which tried to determine these values. Gender and body surface were the sole independent factors to influence the shape and function of the RV. RV volumes according to gender differ consistently with higher values in favor of men (129±25ml) as compared to women (102±33ml).[31]

The evaluation of RV the volumes and ejection fraction represents important diagnostic and prognostic value in a wide range of cardiac diseases such as congenital heart disease, valvulopathies, pulmonary hypertension, heart failure.[32] 3D echocardiography has been already approved for quantifying RV volumes and ejection fraction in patients with pulmonary regurgitation, atrial septal defect, Fallot tetralogy, Ebstein

[28]Niemann PS, Pinho L, Balbach T et al. *J Am Coll Cardiol.* 2007, vol. 50 (pg. 1668-76)

[29] Amaki M, Nakatani S, Kanzaki H et al. *Hypertens Res* , 2009, vol. 32 (pg. 419-22)

[30] Badano LP, Ginghina C, Easaw J et al. *Eur J Echocardiogr.* 2010, vol. 11 (pg.27-37)

[31] Maffessanti F, Muraru D, Esposito R et al. *Circ Cardiovasc Imaging*. 2013, vol. 6 (pg. 700-710)

[32] Shiota T. *Curr Opin Cardiol*, 2009, vol. 24 (pg. 410-414)

anomaly and RV cardiomyopathy.[33] 3D echocardiography was also found useful in cardiac surgery for pre-operative detection of RV subclinical dysfunction which is known to be the most important cause for mortality after left heart valvulopathy correction and aorto-coronary by-pass.[34]

3D echocardiography has an important role in correctly evaluating the RV function and should be used whenever appropriate.

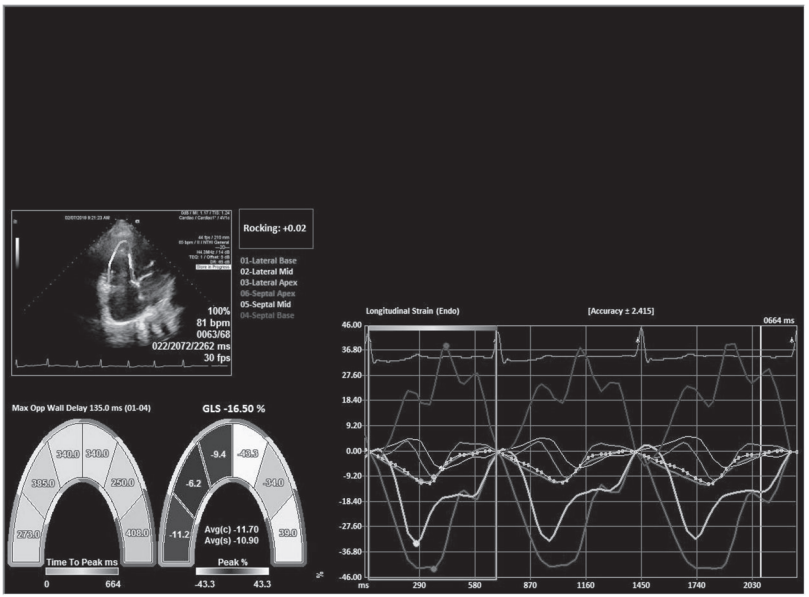

Image 20. Right myocardium longitudinal strain, decreased GLS – global longitudinal strain

[33] Grewal J, Majdalany D, Syed I, Pellikka P, Warnes CA. *J Am Soc Echocardiogr.* 2010; *23*:127–1333. doi: 10.1016/j.echo.2009.11.002

[34] Lang RM, Badano LP, Tsang W et al. *J Am Soc Echocardiogr.* 2012, vol. 25 (pg. 3-46)

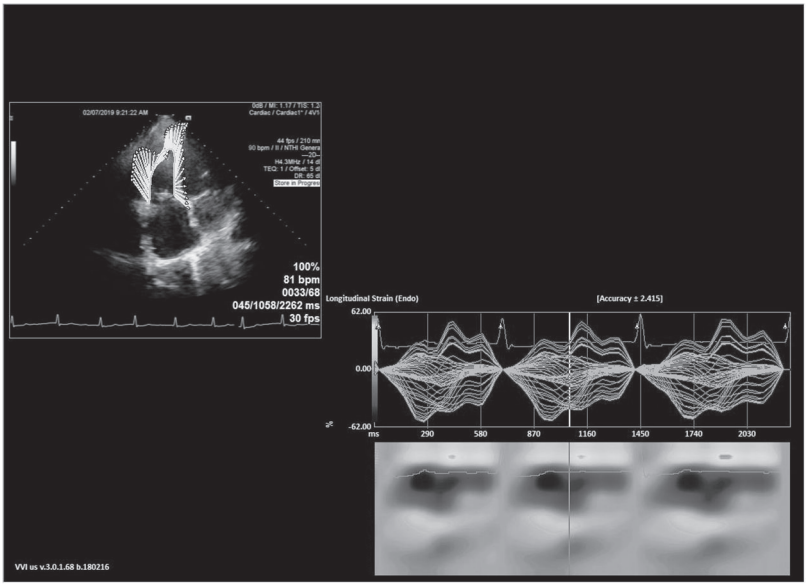

Image 21. Right myocardium longitudinal strain

Cardiac MRI and right ventricular assessment

Although not a very suitable technique in cases of the acute setting of right heart failure, cardiac MRI is a technique of excellent reproducibility in assessing RV function and volumes.[35] Furthermore, it can also show (through late gadolinium enhancement tissue characterization of the RV) where areas of scar tissue can appear, for instance cases of inferior myocardial infarction with RV involvement.[36] By the fat suppression technique, information on RV free wall fatty infiltrates can be provided when there is suspicion of arrhythmogenic right ventricular dysplasia or inflammation in the case of myocarditis.

When it comes to assessing accurate right ventricular function, cardiac magnetic resonance (CMR) is the method of choice as it gives the possibility of multiplanar imaging, as well as high spatial resolution and excellent endocardial definition.

The right ventricle is difficult to visualize with standard imaging such as transthoracic echocardiography while it can be easily visualized and

[35] Grothues F, Moon JC, Bellenger NG, et al. *Am Heart J.* 2004;147:218–23.
[36] Sato H, Murakami Y, Shimada T, et al. *Eur Heart J.* 1995;16:1195–9.

quantified with CMR. CMR provides highly reproducible volumes and systolic function assessment of the RV including in patients with congenital heart disease.[37] [38]

The gold standard to evaluate the right ventricular systolic function is ejection fraction. Besides function, CMR provides insight into tissue viability and its pathological patterns. Scars, edema, perfusions defects, fat infiltration or thrombus can be easily spotted and described in conditions that affect the RV, such as arrhythmogenic right ventricular cardiomyopathy, right ventricular infarction, sarcoidosis, Ebstein's disease, shunts and other complex congenital heart diseases.[39]

To correctly assess RV morphology by MRI, it is mandatory to be familiar with and recognize its distinguishable anatomical features. These special RV features are as following: cordal attachment of tricuspid septal leaflet to the interventricular septum; the presence of the moderator band which is a muscular structure that connects the interventricular septum to the RV free wall towards the apex; crista supraventricularis, which is a ridge that separates the inlet and outlet part; hypertrabeculated apical RV.[40] These features, especially the presence of the moderator band and tricuspid chordal attachment, are useful in distinguishing between RV and LV morphology in patients with congenital heart disease.

CMR is particularly useful in the recognition and assessment process of RV ischemia or myocardial infarction which is underappreciated in real life with conventional imagistic methods. Furthermore, RV involvement in ischemic heart disease is an independent factor for worse prognosis.[41] CMR studies have shown that RV ischemia can occur not only in patients with inferior myocardial infarction (with a proportion of 50%) but also in anterior myocardial infarction (with a proportion of 33%).[42] This argument is supported by the presence of typical necrosis patterns in the RV free anterolateral wall in patients with anterior LV myocardial infarction, while in the case of inferior myocardial infarction the typical necrosis pattern is seen in the posterior RV wall. (Image 22) The CMR approach in these patients is a combination of cine-stack images (for abnormal RV wall

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[37] Mooij CF, de Wit CJ, Graham DA, Powell AJ, Geva T. *J Magn Reson Imaging*. 2008 Jul;28(1):67-73.

[38] Clarke CJ, Gurka MJ, Norton PT, Kramer CM, Hoyer AW. *JACC Cardiovasc Imaging.* 2012 Jan;5(1):28-37

[39] Hendel RC, Patel MR, Kramer CM, et al. *J Am Coll Cardiol.* 2006 Oct 3;48(7):1475-97.

[40] Galea N, Carbone I, Cannata D et al. *Insights Imaging.* 4:213–223

[41] Goldstein JA. *J Am Coll Cardiol.* (2002) 40(5):841–853

[42] Masci PG, Francone M, Desmet W et al. *Circulation.* 2010, 122(14):1405–1412

motion – hypokinesia, akinesia, dyskinesia, paradoxical shift of the interventricular septum, RV dilation and tricuspid regurgitation), T2 weighted imaging (for spotting edema in the acute phase) and late gadolinium enhancement imaging (for spotting scarring and necrosis).[124]

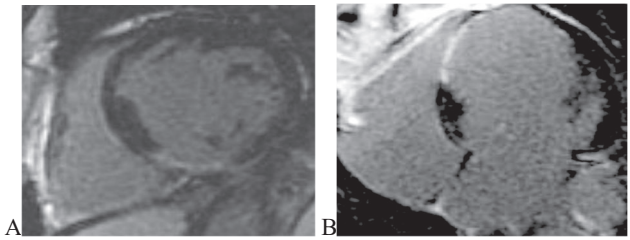

Image 22. A - LGE of LV inferior wall with inferolateral RV free wall involvement, B – LGE of LV septal wall with anterolateral RV free wall involvement

CMR is the gold standard test for the arrhythmogenic right ventricular cardiomyopathy/dysplasia diagnosis. The major magnetic resonance criteria for diagnosing ARVC are regional RV akinesia or dyskinesia or dyssynchronous RV contraction, a ratio of RV end-diastolic volume to body surface area over 110 ml/m2 (male) or 100 ml/m2 (female) and an RV ejection fraction under 40%.[43] The recommended sequence for obtaining all of these features is balanced state free-precession cine-MR sequence (b-SSFP cine-MR) in short axis, horizontal and vertical long-axis.[125] An additional MR feature that can be seen in ARVC is fibrofatty infiltration in the free and inferior RV wall. Now, fat infiltration in ARVC is described as extending from the epicardium towards the endocardium and the recommended sequences to describe this are: turbo spin-echo T1 weighted images (TSE-T1w) and fat suppression "black blood" turbo spin-echo T1 weighted images (fs-TSE-T1W).[125] Fat infiltration can also be found in the RV trabeculations, interventricular septum and the inferolateral LV wall. The LGE sequence is also useful especially in late stages to highlight fibrous replacement tissue in the diaphragmatic, apical and infundibular region of the RV ("RV triangle of dysplasia").[44]

CMR has also led to the description of RV involvement in hypertrophic cardiomyopathy (HCM) in up to 33% of patients affected by this disease (which was, interestingly, thought for a long time to spare the

[43] Marcus FI, McKenna WJ, Sherrill D et al. *Circulation*. 2010, 121 (13):1533–1541
[44] Murphy DT, Shine SC, Cradock A, Galvin JM, Keelan E, Murray JG. *Am J Roentgenol*. 2010, 194(4):W299–W306

RV).[45] This is particularly important as it may result in RV diastolic impaired filling with consequent development of right heart failure, tachyarrhythmias or sudden cardiac death. Patterns of HCM with RV involvement include diffuse RV hypertrophy, interventricular hypertrophy with right ventricular outflow obstruction, or regional apical RV hypertrophy.[46]

Cor pulmonale secondary to pulmonary hypertension is another condition that can be evaluated well with the help of CMR as it can encompass in the same examination MRI - angiography of the thoracic vessels. CMR can also reveal in these patients the potential presence of abnormal thoracic venous return which cannot be seen with conventional echocardiography.[47] Typical features of cor pulmonale seen at CMR are RV dilation and hypertrophy, D-shape RV with flattening of the interventricular septum and also late gadolinium enhancement at the septal insertion (typical junctional pattern of RV).[48]

CMR can provide useful information, especially in congenital heart disease with abnormal RV functions such as tetralogy of Fallot, pulmonary valve stenosis, transposition of the great arteries, shunts and Ebstein's disease. The most common indications for CMR in the tetralogy of Fallot are post-repair residual atrial and ventricular defects, akinesia or dyskinesia of the RV outflow tract, RV fibrosis and pulmonary artery stenosis.[130] The phase-contrast imaging technique by CMR can evaluate trans-valvular gradients, peak velocities, outflow volumes and regurgitant volumes.[49] In Ebstein's disease, CMR permits a good quantification of right chambers size regardless of how complicated the RV anatomy is.

With the help of CMR, the RV can be evaluated in numerous other conditions such as dilative cardiomyopathy, myocarditis, amyloidosis, sarcoidosis, storage diseases.

In conclusion, with CMR, measurements are highly reproducible and accurate for assessing an RV with abnormal function and load. Because CMR is a time consuming and expensive technique which is also dependent on experienced operators, it may not be suitable in the acute phase of right heart failure. Still, this technique should be used whenever there is doubt or inconclusive diagnosis in order to proceed with the management of the patient.

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[45] Maron MS, Hauser TH, Dubrow E et al. *Am J Cardiol.* 2007, 100 (8):1293–1298
[46] Mozaffarian D, Caldwell JH. *Clin Cardiol*. 2001, 24:2–8
[47] Shehata ML, Lossnitzer D, Skrok J et al. *Am J Roentgenol*. 2011, 196(1):87–94
[48] Méndez C, Soler R, Rodriguez E et al. *Insights Imaging*. 2011, 2:483–492
[49] Geva T. *J Cardiovasc Magn Reson.* 2011, 13:9

Cardiac CT and right ventricular assessment

Multi-detector computer tomography (MDCT) is an imaging technique that is not intended as a first-line examination for RV assessment mostly because of its high radiation level and exposure to the iodinated contrast agent. However, MDCT can be useful in certain pathologies, for instance when evaluating pulmonary embolism with RV dysfunction or inferior myocardial infarction with RV involvement.[50] MDCT can also be used to assess the RV in conditions such as COPD, congestive heart failure, cardiomyopathies and congenital heart disease.[51] [52]

Contrast-enhanced ECG-gated MDCT (prospective or retrospective) is the method of choice when assessing the RV function but non-ECG gated contrast-enhanced MDCT can still provide information about the RV such as volume overload by the presence of septal bowing or pressure overload by the dilation of the main pulmonary artery.[53] The increase in RV volume can be easily assessed with CT by measuring the RV to LV short-axis ratio. The ratio is determined by drawing the maximum diameter of each ventricle from the free ventricular wall to the interventricular septum and perpendicular to the long axis of the heart, where the tricuspid and mitral valve opening is the widest.[54] (Image 23) A ratio of over 1 has a good correlation with echocardiographic signs of RV dysfunction and also with worse prognosis in pulmonary embolism.[55]

[50] Ghaye B, Ghuysen A, Bruyere PJ, D'Orio V, Dondelinger RF. *RadioGraphics.* 2006; 26:23-39; discussion 39–40

[51] de Groote P, Millaire A, Foucher-Hossein C, et al. *J Am Coll Cardiol.* 1998; 32:948-954

[52] Andreini D, Pontone G, Pepi M, et al. *J Am Coll Cardiol* 2007; 49:2044-2050

[53] Dupont MlVM, Drägean CA, Coche EE. *AJR*. 2011, vol. 196 (pg. 77-86)

[54] Quiroz R, Kucher N, Schoepf UJ, et al. *Circulation* 2004; 109:2401-2404

[55] Lim KE, Chan CY, Chu PH, Hsu YY, Hsu WC. *Clin Imaging.* 2005; 29:16-21

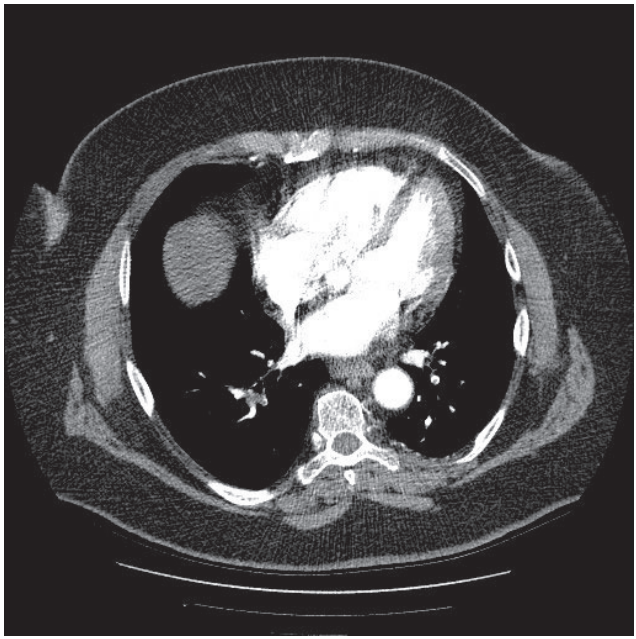

Image 23. RV dilation in massive pulmonary embolism by MDCT

A simple technique to assess the RV function and the global cardiac function is the right to left transit time which is the time of the contrast bolus to reach from one ventricle to another by obtaining a series of single level scans through the heart.[56] It shows a good correlation with cardiac output and a transit time longer than 10.5 s is diagnostic for heart failure. Although it is not a validated technique, it has its advantages and is easy to perform because the radiation exposure is minimal, it does not require ECG-gated CT and it can be performed within any thoracic and abdominal CT exam with contrast injection.[135] Other signs measurable with CT suggestive of RV volume or pressure overload are the diameter of the superior vena cava and the azygos which in the aforementioned situations should be increased. Also, certain studies pointed out a strong correlation between pulmonary embolism severity and the increased diameters of the superior vena cava and the azygos vein.[57]

[56] Vanhoenacker PK, Van Hoe LR. *Eur Radiol.* 2007; 17:2845-2851
[57] Ghaye B, Ghuysen A, Willems V, et al. *Radiology.* 2006; 239:884-891

A valuable sign seen at CT, suggestive of RV dysfunction is the reflux of the contrast agent in the inferior vena cava and hepatic veins.[139] The reflux can also be seen in tricuspid regurgitation and pulmonary hypertension.[58] Estimating the pulmonary artery pressure with CT can be done by measuring the diameter of the main pulmonary artery. A diameter over 29 mm is representative of pulmonary hypertension and is measured at the bifurcation of the pulmonary artery.[59] Two other indexes were proposed for pulmonary hypertension: a segmental artery to the bronchus ratio and the ratio of the main pulmonary artery to the aorta. Both are considered pathological at a ratio greater than 1.[60 61]

The main indication of MDCT remains for patients with lung disease that secondarily affects the RV. Simple measurements can be used even with non-gated ECG scans and can provide valuable information regarding the RV function.

[58] Yeh BM, Kurzman P, Foster E, Qayyum A, Joe B, Coakley F. *AJR.* 2004; 183:1227-1232

[59] Kuriyama K, Gamsu G, Stern RG, Cann CE, Herfkens RJ, Brundage BH. *Invest Radiol.* 1984; 19:16-22

[60] Tan RT, Kuzo R, Goodman LR, Siegel R, Haasler GB, Presberg KW. *Chest.* 1998; 113:1250-1256

[61] Ng CS, Wells AU, Padley SPA. *J Thorac Imaging.* 1999; 14:270-278

CHAPTER 5

CLINICAL SCENARIOS OF ACUTE RIGHT HEART FAILURE

IOAN RADU LALA

Acute pulmonary embolism

Acute pulmonary embolism is the most frequent cause of acute right heart failure.[60] RV failure is the main cause of mortality in the early stages of PE and is the result of pressure overload.[54] Up to 50% of patients with PE do not present hypotension or shock even though they have RV dysfunction.[1] [2] [3] Even so, by presenting RV dysfunction they are still at high risk of adverse events in the following days after admission.[4] Kucher et al. demonstrated that patients with PE and BP > 90 mmHg but with RV dysfunction had a 16.3% risk of death in the first 30 days from the event in comparison to those without RV dysfunction (9.4%).[86]

RV dysfunction is defined by imagistic signs and cardiac markers. As for cardiac markers in the context of PE, NT proBNP plasma levels are suggestive for hemodynamic instability and plasma troponin levels for myocardial injury. In meta-analyses, both NT proBNP and troponin plasma concentrations were found to be elevated in 50% of patients with PE and carried the risk of early in-hospital death and worse clinical outcome.[5] [6]

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[1] Goldhaber SZ, Visani L, De Rosa M. *Lancet*. 1999, vol. 353 (pg. 1386-1389)

[2] Logeart D, Lecuyer L, Thabut G, Tabet JY, Tartiere JM, Chavelas C, Bonnin F, Stievenart JL, Solal AC. *Intensive Care Med.* 2007; *33*: 286–292

[3] Kucher N, Rossi E, De Rosa M, Goldhaber SZ. Arch Intern Med. 2005; *165*: 1777–1781.

[4] Kasper W, Konstantinides S, Geibel A, Tiede N, Krause T, Just H. *Heart.* 1997; *77*: 346–349.

[5] Klok FA, Mos IC, Huisman MV. *Am J Respir Crit Care Med.* 2008;178(4):425 – 430.

[6] Becattini C, Vedovati MC, Agnelli G. *Circulation*. 2007;116(4):427 – 433.

Trials and metanalysis showed that hemodynamically unstable patients with massive PE (defined as hypotension, cardiogenic shock, syncope, cardiac arrest or respiratory failure) present overall hospital mortality of 32% and should receive thrombolytic therapy.[7] A 30 to 50% occlusion of the total cross-sectional area of the pulmonary artery bed given by thromboemboli will lead to an increase of pulmonary artery pressure.[8] The initial increase of pulmonary vascular resistance is also given by the release of vasoconstrictive factors such as thromboxane and serotonin.[9] The abrupt increase of pulmonary vascular resistance will determine RV dilation by pressure and volume overload leading to the increase of wall tension, myocardial stretch, neurohormonal activation and prolongation of the RV contraction time with interventricular desynchronization.[10] Consequently, a leftward bowing of the interventricular septum with LV impaired filling in early diastole will appear to generate a reduction of cardiac output and the appearance of hypotension and hemodynamic instability.[11]

The strategy for the management of patients with suspicion of high-risk PE with shock and hypotension is presented in the figures below. (Figure 2, Figure 3)

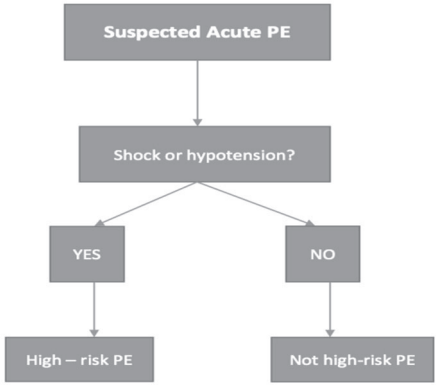

Figure 2.. Risk stratification

[7] Casazza F, Becattini C, Bongarzoni A. et al. *Thromb Res.* 2012; 130: 847-852.
[8] McIntyre KM, Sasahara AA. *Am J Cardiol.* 1971;28(3):288 – 294.
[9] Smulders YM. *Cardiovasc Res*. 2000;48(1):23 – 33.
[10] Molloy WD, Lee KY, Girling L, Schick U, Prewitt RM. *Am Rev Respir Dis.* 1984;130(5):870 – 874.
[11] Marcus JT, Gan CT, Zwanenburg JJ, Boonstra A, Allaart CP, Go¨tte MJ, Vonk-Noordegraaf A. *J Am Coll Cardiol.* 2008;51(7):750–757.

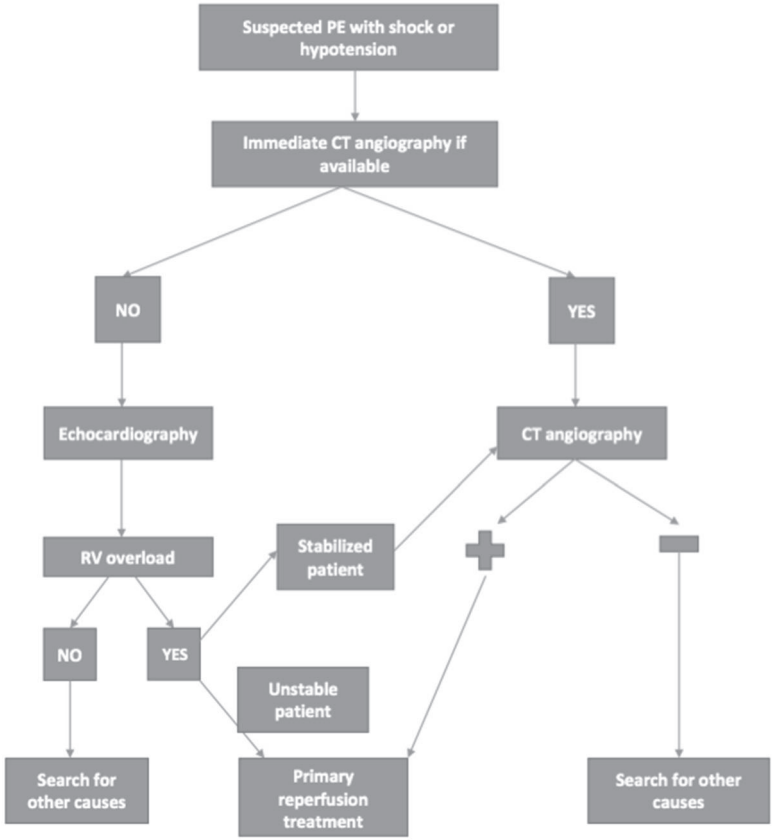

Figure 3. Management of high-risk PE

Differential diagnoses in patients with suspicion of high-risk PE should be done immediately to rule out the following: acute coronary syndrome, acute valvular dysfunction, aortic dissection and cardiac tamponade.[54] Immediate bedside echocardiography should be performed to evidence signs of RV dysfunction and if the patient is highly unstable, CT angiography can be by-passed in order to not delay life-saving thrombolytic treatment especially if PE probability is very high.[54] If the patient is rather stable and CT angiography is available, then it should be performed immediately for diagnosis confirmation. (Image 24, Image 25, Image 26)

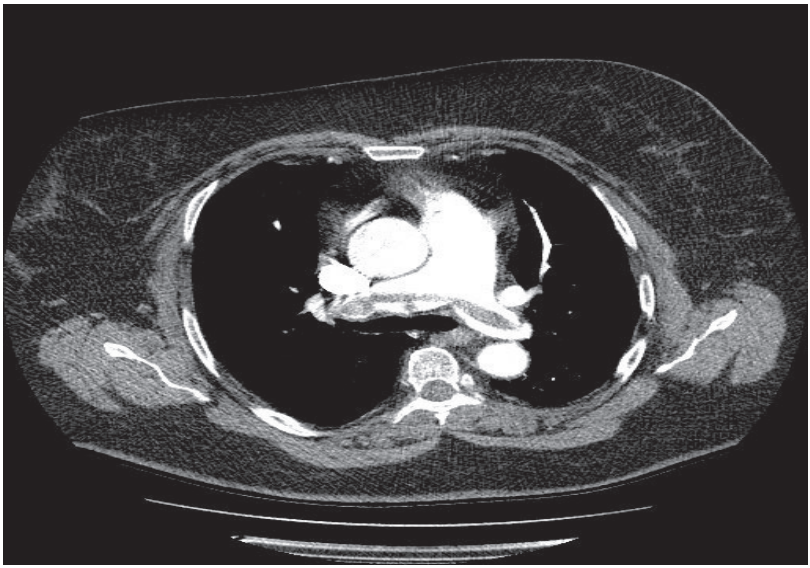

Image 24. Pulmonary embolus at the bifurcation of the main pulmonary artery

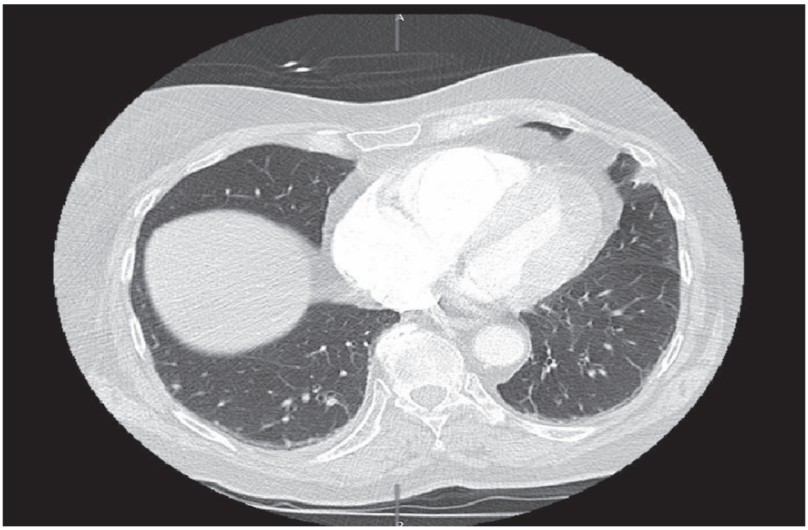

Image 25. Increased right ventricle diameter

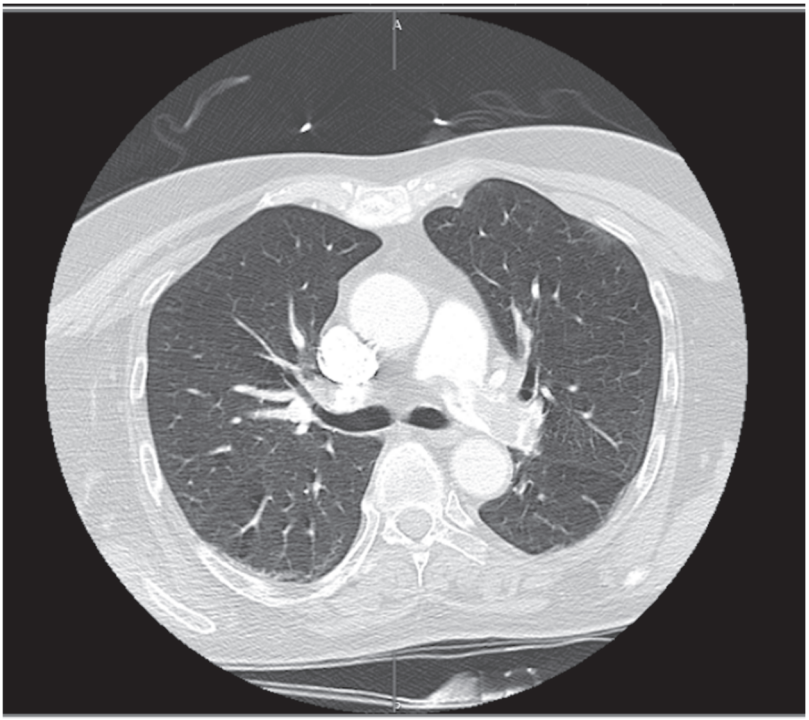

Image 26. Pulmonary thrombus on both right and left pulmonary artery

Thrombolytic therapy in acute high-risk PE restores pulmonary perfusion which leads to a prompt reduction in pulmonary vasculature resistance and improvement of the RV function. Over 90% of patients respond well in the first hours after thrombolytic treatment but some patients remain hemodynamically unstable in the first days, mainly due to myocardial injury; thus, they might require inotropic support.[12] [13] Although hemodynamic effects after thrombolytic treatment are limited in the first days, in surviving patients, these effects improve significantly after one week up to total resolution.[95] [96] The greatest benefit of thrombolytic treatment is seen in patients presenting to the hospital in the first 48 hours after symptom onset, but thrombolysis also remains useful in patients

[12] Becattini C, Agnelli G, Salvi A et al. *Thromb Res.* 2010;125(3): e82 – e86.
[13] Konstantinides S, Tiede N, Geibel A, Olschewski M, Just H, Kasper W. *Am J Cardiol.* 1998;82(8):966–970.

presenting after 6 to 14 days after symptom onset.[14] [15] The accelerated regimen with recombinant tissue plasminogen activator (rtPA) administered over 2 hours is of first choice (Table 3). rtPA, streptokinase and urokinase are the only thrombolytic agents approved for now in the treatment of acute PE with shock even though studies were performed with tenecteplase and reteplase showing similar beneficial effect as the ones aforementioned.[16] [17] Unfractionated heparin infusion should be given during the administration of rtPA and should be continued several hours after finishing thrombolytic treatment before switching to LWMH; however, it should be stopped during the administration of streptokinase and urokinase.[54]

Table 3 – Thrombolytic regimen

Approved thrombolytic regimens for pulmonary embolism
rtPA - 100mg over 2 hours or 0.6mg/kg over 15 min (maximum 50 mg)
Streptokinase – 250000 U as loading dose over 30 min, followed by 100000 U/h over 12-24 hours
Urokinase – 4400 U/kg as loading dose over 10 min, followed by 4400 U/kg/h over 12-24 hours

Administering thrombolytic therapy to patients with an intermediate-high risk of PE (PESI class III-IV, imagistic signs of RV dysfunction, positive cardiac biomarkers) remains controversial mainly because it carries the risk of major bleeding events such as intracranial hemorrhage.[18] Although PHEITO trial tested the efficacy of thrombolysis (tenecteplase) + heparin versus placebo + heparin in patients with high and intermediate-high risk of PE and showed a reduction in the rate of hemodynamic collapse and all-cause mortality in favor of the thrombolysis group, it also pointed out a 2% incidence of intracranial hemorrhage and a 6.3% incidence of major non-intracranial hemorrhage after thrombolysis in the intermediate high-risk PE group versus the placebo group.[19] Improving the safety of

[14] Meneveau N, Seronde MF, Blonde MC et al. *Chest.* 2006;129(4):1043 – 1050.
[15] Daniels LB, Parker JA, Patel SR, Grodstein F, Goldhaber SZ. *Am J Cardiol*. 1997;80(2):184–188.
[16] Tebbe U, Graf A, Kamke W, Zahn R, Forycki F, Kratzsch G, Berg G. *Am Heart J.* 1999;138(1 Pt 1):39 – 44.
[17] Tebbe U, Bramlage P, Graf A, Lechleitner P, Bode C, Riess FC, Clemens N, Al Rawi Y, Konstantinides S, Goldhaber SZ. *Thromb Haemost.* 2009;101(3):557 – 562.
[18] Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W. *N Engl J Med*. 2002, vol. 347 (pg. 1143-1150)
[19] Meyer G, Vicaut E, Danays T et al. *N Engl J Med.* 2014;370(15): 1402 – 1411.

thrombolytic therapy by acknowledging the contraindications, the presence of comorbidities, advanced age and even having in mind a reduced rtPA dose regimen in patients with moderate PE as suggested by Sharifi et al. is mandatory.[20] This is why patients with submassive PE, RV dysfunction (defined by echocardiography and cardiac biomarkers troponins, NTproBNP) and normotensive should only receive thrombolytic therapy after a thorough individual clinical evaluation and after showing signs of deterioration due to the risk of major intracranial bleeding associated with the therapy. In this type of situation, a useful parameter that can be easily assessed in daily practice is the Shock Index (HR/ SBP), where values >1 are associated with worse outcomes and should be treated by thrombolytic therapy.[21]

Right ventricular infarction

Acute RV infarction usually occurs in the context of acute inferior myocardial infarction due to proximal occlusion of the right coronary artery. It is considered as an independent short-term predictor of mortality.[22] [23] Up to 50% of patients with inferior MI present RV dysfunction but no complications such as hypotension or low cardiac output.[106] An infarcted RV may remain viable for several days after the acute event. These observations are supported by the fact that the RV is more tolerable to ischemia than the LV because of the dual anatomical supply from the right and left coronary arteries, lower oxygen demand, greater oxygen extraction capacity during stress and predisposition to acute collateral circulation development.[24] [25] Even so, between 25% and 50% of patients present hemodynamic compromise with severe hypotension and cardiogenic shock and high in-hospital mortality.[26]

Complications often associated with RV infarction are: bradycardia, total AV block, ventricular tachycardias and septum rupture.[60]

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[20]Sharifi M, Bay C, Skrocki L, Rahimi F, Mehdipour M. *Am J Cardiol.* 2013;111(2): 273 – 277.

[21] Sam A, Sanchez D, Gomez V et al. *Eur Respir J.* 2011; 37(4):762 – 766.

[22] Zehender M, Kasper W, Kauder E, Schonthaler M, Geibel A, Olschewski M, Just H. *N Engl J Med.* 1993; 328:981–988.

[23] Bueno H, Lopez-Palop R, Perez-David E, Garcia-Garcia J, Lopez-Sendon JL, Delcan JL. *Circulation.* 1998;98:1714–1720.

[24] Laster SB, Shelton TJ, Barzilai B, Goldstein JA. *Circulation.* 1993; 88:696–708.

[25] Laster SB, Ohnishi Y, Saftz JE, Goldstein JA. *Circulation.* 1994;90:1398–1409.

[26] Ondrus T, Kanovsky J, Novotny T, Andrsova I, Spinar J, Kala P. *Exp Clin Cardiol.* 2013; *18*:27–30.

Diagnosis is made by ECG where ST elevation > 1mm is seen in V1 and precordial leads V3r-V4r in a clinical context and the presence of inferior myocardial infarction. (Image 27) Actually, right precordial leads recordings should be done on a routine basis in the presence of inferior myocardial infarction; and an ST-elevation higher in D3 than D2 is pathognomonic for RV involvement.[109] Specific ECG tracings with findings such as hypotension, jugular vein distension and clear lungs on physical examination are suggestive of RV infarction.[109] Echocardiography may show RV dilation with global or regional RV free wall hypokinesia, reduced TAPSE and tricuspid annular myocardial systolic velocities. Of course, after vascularisation, RV involvement and lesions may be seen on cardiac magnetic resonance.

The most feared complication of RV infarction is cardiogenic shock, defined as persistent hypotension (<90mmHg) and signs of hypoperfusion despite adequate filling status. If transfer to a PCI center is estimated as > 120 min, then immediate thrombolysis is considered with afterward transfer to the PCI center and rapid angiography regardless of ST resolution upon arrival.[27] (Image 28) Inotropic support is often needed in un-responsive patients until catheterization. Sometimes patients with refractory hypotension and low cardiac output may benefit from intra-aortic balloon counterpulsation as it does not influence the RV performance but increases coronary perfusion pressure and consequently the RV function (especially if the RCA was opened).[28]

Special consideration should be sought in treatments that can compromise RV preload (nitrates or diuretics) which can be deleterious and potentially aggravate hypotension, the infarcted RV being very sensible to agents that reduce preload.[60] Furthermore, loading to increase RV filling should be done cautiously (250 ml of saline over 15 minutes) to prevent hemodynamic instability by myocardial overstretching.[60]

High-grade or total AV block usually responds promptly after reperfusion therapy but in refractory cases or cases accompanied by hemodynamic instability, temporary pacing is needed.[29] [30]

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[27] Ibanez B, James S, Agewall S et al. *Eur Heart J.* 2018;39:119–177.
[28] Goldstein JA. *J Am Coll Cardiol*. 2002;40:841–53.
[29] Goldstein JA, Barzilai B, Rosamond TL, Eisenberg PR, Jaffe AS. *Circulation* 1990;82:359 – 368.
[30] Topol EJ, Goldschlager N, Ports TA, Dicarlo LA, Jr, Schiller NB, Botvinick EH, Chatterjee K. Hemodynamic benefit of atrial pacing in right ventricular myocardial infarction. *Ann Intern Med* 1982;96:594–597.

Reperfusion is the only therapy that improves the outcome in RV infarction and the early complete reperfusion of the RCA or its branches will lead to the complete recovery of the RV function.

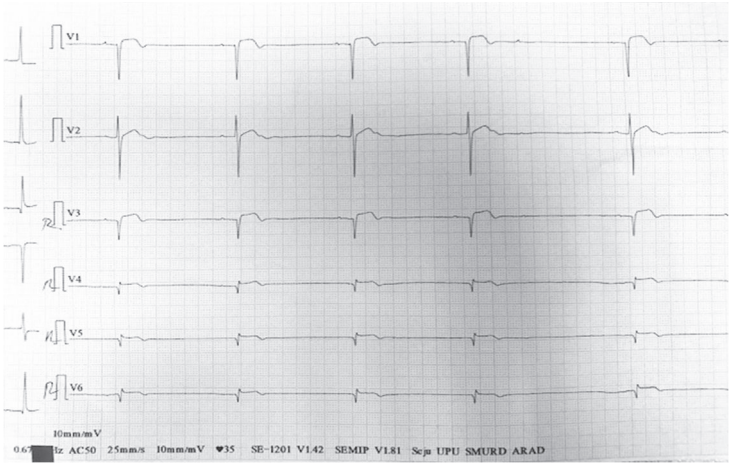

Image 27. RV infarction with ST elevation V1 and V3r-V6r

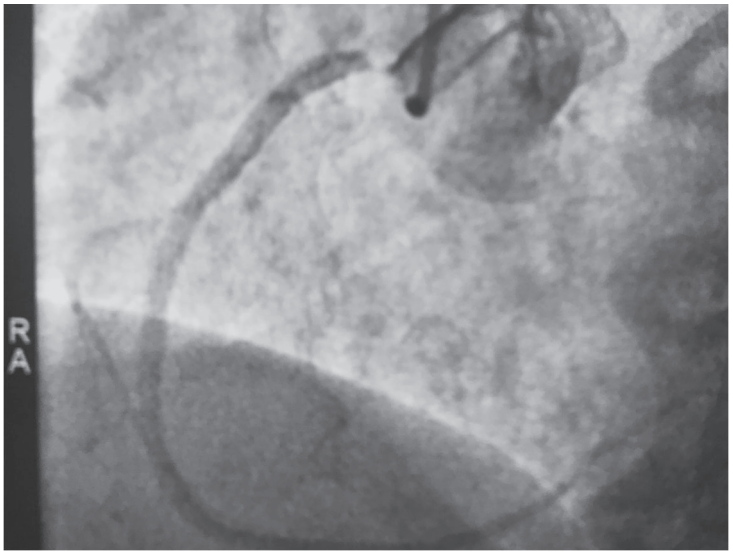

Image 28. Ostial 99% subocclusion of RCA

Pulmonary hypertension

Pulmonary hypertension is defined as an increase of > 25 mmHg of mean pulmonary artery pressure determined by right heart catheterization.[36] PAH is characterized by the presence of pre-capillary pulmonary hypertension with a measured pulmonary artery wedge pressure (PAWP) of < 15 mmHg and pulmonary vascular resistance (PVR) of > 3 Woods U in the absence of lung diseases, chronic thromboembolic pulmonary hypertension and other rare diseases.[36]

PAH falls in the Group 1 category of the comprehensive clinical classification of PH updated by Simonneau et al. In Group 1, the followings are described: idiopathic form, inherited form (BMPR2 mutation) and drug-induced and PAH associated to connective tissue disease (CTD), HIV infection, portal hypertension, congenital heart disease, schistosomiasis. Group 1 also describes two subgroups of PAH: pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis and persistent pulmonary hypertension of the newborn.[31] The prevalence and incidence of PAH in Europe are 15 to 60 patients per million population and 5 to 10 new patients each year per million population.[32]

The signs and symptoms of PAH are almost exclusively related to RV dysfunction: shortness of breath, fatigue, angina, syncope. Furthermore, in advanced stages with RV failure, the followings are preset: systemic congestion, peripheral edema, jugular vein distension, pansystolic murmur of tricuspid regurgitation, hepatomegaly, ascites, pleurisy. Due to the dilation of the pulmonary artery, hoarseness may appear because of the compression of the left recurrent laryngeal nerve, as well as wheezing because of bronchi compression and myocardial ischemia because of the left main coronary artery compression. A diagnosis algorithm is described in Figure 4. Image 29

[31] Simonneau G, Galie N, Rubin LJ et al. *J Am Coll Cardiol.* 2004;43(Suppl 1):S5–S12.
[32] Peacock AJ, Murphy NF, McMurray JJV, Caballero L, Stewart S. *Eur Respir J* 2007;30:104 – 109.

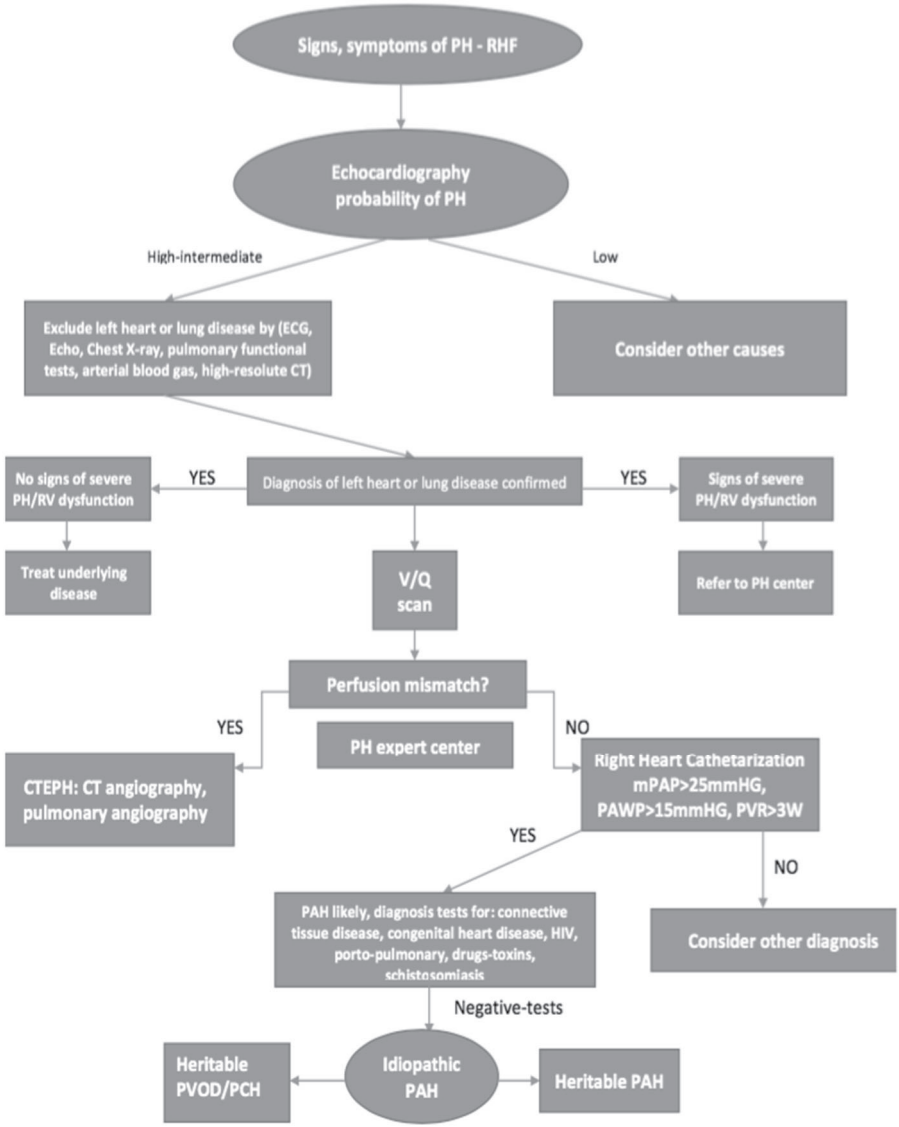

Figure 4. PAH diagnosis algorithm; PAH- pulmonary arterial hypertension

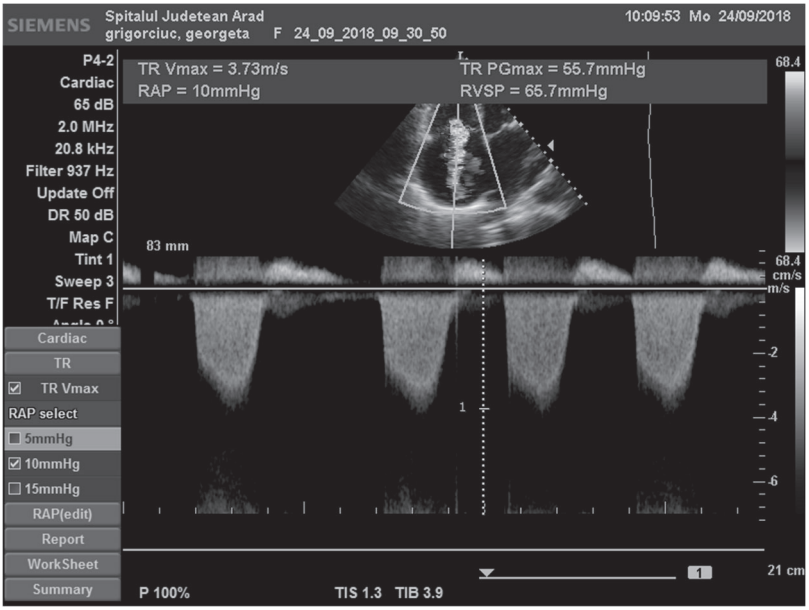

Image 29. Increased pulmonary systolic artery pressure (65 mmHg)

Pulmonary hypertension is a progressive disease leading to RV dysfunction and failure with very high mortality rates.[33] [34] Advanced PAH is characterized by impaired right ventricular filling and flow output with the occurrence of acute right heart failure.[60] Early recognition and management of RV dysfunction is crucial to improve the prognosis mainly because, in PAH patients, the survival is closely related to the RV's ability to adapt to increased afterload.[47] The pathophysiology of precapillary pulmonary hypertension is characterized in the early stages by pulmonary vasculature remodeling that will determine the alteration of the RV geometry and function first by concentric remodeling with preserved cardiac output and secondly in the final stages by eccentric remodeling with a decrease in cardiac output and hemodynamic compromise.[35] Usually, eccentric remodeling with dilation of right cavities is a maladaptive

[33] Humbert M, Sitbon O, Chaouat A, et al. *Circulation.* 2010; 122: 156–163.
[34] Benza RL, Miller DP, Gomberg-Maitland M, et al. *Circulation.* 2010; 122: 164–172.
[35] Savale L, Weatherald J, Jais X, et al. *Eur Respir Rev: Off J Eur Respir Soc*. 2017;26(146):1-12.

phenomenon describing end-stage pulmonary hypertension with clinical symptoms such as severe dyspnoea, hypotension, syncope and multi-organ failure. It is interesting to mention, that RV remodeling capacity differs from one individual to another and from one pulmonary hypertension etiology to another. For example, in scleroderma, a much more important alteration of the RV function is seen at lower pulmonary vasculature resistance than in Eisenmenger syndrome where higher pulmonary vasculature resistances are noted and the RV adapts by concentric hypertrophy.[36] [37] It seems that cytoskeleton reorganization at the molecular level might play a central role in compensatory RV remodeling and could be a target for future pharmaceutical or genetic approaches from the early stages of the disease.[38]

The acute decompensation of PAH is defined by a sudden worsening of clinical signs and symptoms of right heart failure with consequent systemic circulatory insufficiency and multi-organ failure.[118] This clinical scenario of acute right heart failure is usually a combination of systolic and diastolic RV impairment. Diastolic impairment leads to systemic congestion whilst systolic impairment determines a decrease in LV preload with a subsequent decrease in cardiac output and low peripheral tissue perfusion.[118] Multi-organ failure is the result of arterial vasoconstriction and venous congestion in acute right heart failure; in fact, the most frequent findings are acute kidney and liver injury leading to volume overload, hyponatremia, obnubilation, oliguria. In-hospital mortality rates in PAH-RHF range between 14% and 100% and depend on numerous factors such as renal dysfunction, hyponatremia, the use of vasopressors and inotropes, high BNP levels, severe tricuspid regurgitation, hypotension, mechanical ventilation and dialysis.[39] [40] [41]

The first step in the management of PAH – ARHF is identifying trigger factors of decompensations such as supraventricular arrhythmias, infections, thromboembolic events, patient non-compliance to diet and medication.[42] [43] [44]

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[36] Giusca S, Popa E, Amzulescu MS et al. *Echocardiography.* 2016; 33: 546–554.
[37] Argula RG, Karwa A, Lauer A et al. *Ann Am Thorac Soc.* 2017; 14: 682–689.
[38] Ryan JJ, Archer SL. *Circ Res.* 2014; 115: 176–188.
[39] Haddad F, Peterson T, Fuh E et al. *Circ Heart Fail.* 2011; 4: 692–699.
[40] Huynh TN, Weigt SS, Sugar CA et al. *J Crit Care.* 2012; 27: 739.e7–739.e13.
[41] Sztrymf B, Prat D, Jacobs FM et al. Respiration 2013; 85: 464–470.
[42] Green EM, Givertz MM. *Curr Heart Fail Rep.* 2012;9:228–235.
[43] Gayat E, Mebazaa A. *Curr Opin Crit Care.* 2011;17:439 – 448.
[44] Rajdev A, Garan H, Biviano A. *Prog Cardiovasc Dis.* 2012;55:180 – 186.

In supraventricular arrhythmias (atrial tachycardia, atrial flutter or atrial flutter), whenever possible, restoring the sinus rhythm should be an option as first-line therapy by electrical or pharmacological cardioversion with proper anticoagulation. If cardioversion is not considered due to potential thromboembolic events, then controlling the heart rate should be achieved with preferably the use of amiodarone. Drugs like beta-blockers or calcium-channel blockers should be avoided in the acute state due to their negative inotropic effect on the RV.[45] Infection as a trigger factor for decompensated PAH carries the worst prognosis which is why early detection and prompt management must be applied. Venous congestion leads to potential translocation of bacteria from the gut into the bloodstream with a systemic inflammatory response so controlling hypervolemia by increasing diuretics, and a salt-free diet in known PAH patients must be achieved to avoid infection.

The use of intravenous diuretics as first-line therapy to achieve hemodynamic optimization is recommended. Diuretics will reduce RV preload and tricuspid regurgitation, improve LV diastolic filling and reduce organ congestion.[118] It is important to monitor the central venous pressure in order to determine an optimal filling status of the RV and to hypovolemia by diuretics usage, which is also deleterious to the cardiac function. A bolus of IV furosemide 20-40 mg or twice the oral dose if the patient was on chronic diuretic therapy should be given in the first phase and afterward progressive titration of doses either fractioned bolus therapy or continuous perfusion therapy until euvolemia is achieved. All this should be done with careful monitoring of diuresis, fluid balance and RV filling pressures. Sometimes in severe cases of RV dysfunction, with hypotension adding an inotrope agent, it is necessary to improve the hemodynamic status.[60] The most commonly used inotropic agents are dobutamine, levosimendan and milrinone due to their capacity to improve ventricular-arterial coupling and cardiac output, as well as their capacity to reduce pulmonary vascular resistance.[46] [47] For patients with refractory hypotension, multi-organ failure and severely impaired RV function, the use of a vasopressor such as noradrenaline is recommended as first-line therapy.[48]

In PAH-ARHF, the main goal is to target the reduction in RV afterload with specific treatment for pulmonary hypertension. It is important to start the specific PH therapy whenever possible as it may be the only solution to recover from an acute right heart failure episode and by

[45] Provencher S, Herve P, Jais X et al. *Gastroenterology.* 2006; 130: 120–126.
[46] Kerbaul F, Rondelet B, Motte S et al. *Crit Care Med.* 2004; 32: 1035–1040.
[47] Price LC, Wort SJ, Finney SJ et al. *Crit Care.* 2010; 14: R169.
[48] Kerbaul F, Rondelet B, Demester J-P et al. *Care Med.* 2006; 34: 2814–2819.

chronically continuing it to prevent future recurrences. Specific therapy for the management of PAH targets all the signaling pathways involved in the disease's pathological process: the prostacyclin pathway (prostanoids), the endothelin pathway (ERA's) and NO pathway (PDE-5i, sGCs). Knowing the increased mortality in PAH, the initial approach should consider combination therapy with an emphasis on intravenous prostaglandin analog, but one should bear in mind that these agents cause systemic arterial hypotension and thus should be used cautiously, in small doses and carefully up titrated after restoring hemodynamics.[49] A recent meta-analysis on 858 patients with PAH, showed that specific combination therapy compared to the control group reduced clinical episodes of decompensation, mean PAP, RAP, PVR and improved exercise tolerance.[50] The recommendations for the use of PAH agents and their combinations are shown in tables 4 and 5 below.

Table 4 – Specific PAH pharmacological agents

Measure/Treatment	WHO-FC II	WHO-FC III	WHO-FC IV
Calcium channel blockers	IC	IC	-
Endothelin receptor antagonists			
Ambrisentan	IA	IA	IIbC
Bosentan	IA	IA	IIbC
Macitentan	IB	IB	IIbC
Phosphodiesterase type 5 – inhibitors			
Sildenafil	IA	IA	IIbC
Tadalafil	IB	IB	IIbC
Guanylate cyclase stimulators			
Riociguat	IB	IB	IIbC
Prostacyclin analogs			
Epoprostenol intravenous	-	IA	IA
Iloprost inhaled	-	IB	IIbC
Treprostinil subcutaneous	-	IB	IIbC

[49] Galie N, Humbert M, Vachiery JL et al. *Eur Heart J.* 2016;37:67–119.
[50] Galie N, Palazzini M, Manes A. *Eur Heart J.* 2010;31: 2080 – 2086.

Table 5 – Drug combination therapy for PAH

Measure/Treatment	WHO-FC II	WHO-FC III	WHO-FC IV
Ambrisentan + tadalafil	**IB**	**IB**	**IIbC**
Other ERA + PDE-5i	**IIaC**	**IIaC**	**IIbC**
Bosentan + Sildenafil + iv Epoprostenol	**-**	**IIaC**	**IIaC**
Bosentan + iv Epoprostenol	**-**	**IIaC**	**IIaC**
Other ERA or PDE-5i + sc Treprostinil	**-**	**IIbC**	**IIbC**
Other ERA or PDE-5i + other iv prostacyclin analogues	**-**	**IIbC**	**IIbC**

For PAH-ARHF associated with connective tissue disease, reports have shown a definite improvement after the use of corticosteroids or cyclophosphamide in combination with PAH specific agents.[51] [52] Patients with PAH due to pulmonary veno-occlusive disease do not respond well to PH specific agents which is why early lung transplantation should be sought as management.[53] Another specific approach appears in the case of chronic thromboembolic pulmonary hypertension where urgent surgical endarterectomy or pulmonary angioplasty in the case of distal lesions might be considered.[54] In patients with PAH and refractory right heart failure, despite maximal specific therapy or syncope, balloon atrial septostomy (BAS) should be considered for decompressing the right heart chambers. This technique should be avoided in patients presenting with RAP > 20mmHg and oxygen saturation < 85%.[132] [55]

For right heart failure secondary to pulmonary precapillary hypertension and refractory to optimal medical therapy, the only remaining solution is lung or heart-lung transplantation. Extracorporeal life support

[51] Jais X, Launay D, Yaici A, et al. *Arthritis Rheum.* 2008; 58: 521–531.
[52] Chen Y, Guo L, Li Y, et al. *Int J Rheum Dis.* 2015; 18: 331–335
[53] Montani D, Lau EM, Dorfmüller P, et al. *Eur Respir J.* 2016; 47: 1518–1534.
[54] Kim NH, Delcroix M, Jenkins DP, et al. *J Am Coll Cardiol.* 2013; 62: Suppl. 25, D92–D99.
[55] Sandoval J, Torbicki A. Atrial Septostomy. In Voelkel N, Schranz D. New York: Humana Press, Springer; 2015; p.419 – 437.

(ECLS) is an option as bridge therapy for the management of patients with refractory right heart failure undergoing transplantation.

Acute right heart failure in the intensive care setting

The most frequent cause of ARHF in the ICU (with a range between 25% and 50%) is ARDS.[56] [57] Positive pressure ventilation in ARDS is responsible for the uncoupling between pulmonary circulation and the RV with subsequent impairment of cardiac output.[60] Also, infection, hypercapnia, plateau pressure are predictors of RV failure in ARDS.[58] [59] The pathology of ARDS involves not only alveolar lesions but also pulmonary capillary lesions leading to pulmonary hypertension and eventually RV failure.[60] In other words, pulmonary hypertension in the setting of ARDS is the result of a combination of intrinsic factors (alveolar-capillary lesions) and extrinsic factors (mechanical ventilation strategy).[143] [61]

Pneumonia, a driving pressure > 18cmH2O, PaCO2 > 48cmH2O and PaO2/FiO2 ratio are risk factors for the setting of acute cor pulmonale in ARDS.[62] Driving pressure is the pressure that reflects tidal ventilation and is considered a surrogate for transpulmonary pressure in patients without significantly reduced chest wall compliance.[145] Transpulmonary pressure which represents alveolar pressure minus pleural pressure is usually low in normal spontaneous breathing conditions but is responsible in case of high values for RV dysfunction during tidal ventilation.[63]

RV failure incidence increases as there is a progression from acute lung injury to ARDS.[146]

The fundamental approach in reducing the risk of RV dysfunction is based on the following quote: “what is good for the RV is good for the lung”.[146] This is achieved with measures such as daily echocardiography monitoring of RV parameters and a ventilatory RV protective strategy: maintaining a plateau pressure < 27cmH2O, a PaCO2 < 60mmHg, adapting

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[56] Jardin F, Vieillard-Baron A. *Intensive Care Med.* 2007;33:444–447.
[57] Vieillard-Baron A, Schmitt JM, Augarde R, Fellahi JL, Prin S, Page B, Beauchet A, Jardin F. *Crit Care Med.* 2001;29:1551–1555.
[58] Boissier F, Katsahian S, Razazi K et al. *Intensive Care Med.* 2013;39:1725–1733.
[59] Lheritier G, Legras A, Caille A et al. *Intensive Care Med.* 2013;39:1734–1742.
[60] Zapol WM, Kobayashi K, Snider MT, Greene R, Laver MB. *Chest*. 1977;71(2 Sup- pl):306-7.
[61] Moloney ED, Evans TW. *Eur Respir J.* 2003;21:720-7.
[62] Repessé X, Vieillard-Baron A. *Ann Transl Med.* 2017;5:295.
[63] Repesse X, Charron C, Vieillard-Baron A. *Minerva Anestesiol.* 2012, 78: 941-948.

PEEP to RV function and considering a prone position for PaO2/FiO2 < 150mmHG.[64]

RV failure is considered the missing link responsible for high mortality rates in ARDS. The key for correcting ventricular-arterial uncoupling might be at the core of the safety mechanical ventilation strategy.

Acute cor pulmonale

Cor pulmonale (CP) is defined as an RV dysfunction/failure secondary to pulmonary hypertension that results from diseases which affect the structure/function of the lungs.[65]

Acute cor pulmonale (ACP) describes acute right heart failure as a result of a sudden increase in blood flow resistance in the pulmonary artery bed with hemodynamic instability. The most common causes of ACP are massive pulmonary embolism and ARDS, topics that have already been covered in the previous chapters.

Respiratory diseases associated with pulmonary hypertension and cor pulmonale are divided into three categories: obstructive lung diseases (COPD – chronic obstructive pulmonary disease, asthma, cystic fibrosis, bronchiectasis), restrictive lung diseases (neuromuscular diseases, kyphoscoliosis, sarcoidosis, connective tissue diseases, pneumoconiosis, idiopathic pulmonary fibrosis) and respiratory insufficiency of central origin (alveolar hypoventilation syndrome, obesity hypoventilation syndrome and sleep apnoea syndrome).[148] By far, the most common cause for cor pulmonale (with a frequency of 80-90%) is COPD.[148]Alveolar hypoxia is considered to be the leading cause of increased pulmonary vascular resistance in COPD. Acute hypoxia causes pulmonary vasoconstriction whereas sustained chronic hypoxia leads to precapillary pulmonary vascular remodeling.[66] Other causes of increased pulmonary vascular resistance include hypercapnic acidosis, hyperviscosity induced by polycythemia, loss of pulmonary vascular bed, compression of the arterioles and capillaries by the ongoing fibrotic process.[148]

Episodes of acute exacerbations of COPD are characterized by the worsening of hypoxemia and hypercapnia with a consequent increase in mean arterial pulmonary pressure and development of acute right heart

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[64] Vieillard-Baron A, Price LC, Matthay MA. *Intensive Care Med*. 2013;39:1836–1838.

[65] Weitzenblum E. *Heart.* 2003;89:225–230.

[66] Shujaat A, Minkin R, Eden E. *Int J Chron Obstruct Pulmon Dis*. 2007, 2 (3): 273-282.

failure.[67] [68] Episodes of severe oxygen desaturation and pulmonary hypertension are seen during sleep in patients with COPD due to alveolar hypoventilation, ventilation-perfusion mismatching or sleep apnoea associated syndrome.[69]

It should be highlighted that peripheral edema often seen in COPD does not always reflect right heart failure but rather secondary hyperaldosteronism induced by functional renal insufficiency due to hypercapnic acidosis and hypoxemia.[70] [71] That is why it is important to identify true heart failure which is characterized by jugular vein distension and raised natriuretic peptides.

The treatment of RHF in COPD patients involves mainly diuretic and oxygen therapy. Long term oxygen therapy has been shown to reduce pulmonary hypertension, improve hemodynamics and reduce episodes of RHF decompensation.[72] Vasodilator therapy such as inhaled nitric oxide, sildenafil, prostacyclins can be used for a short term in acute exacerbations to reduce the RV afterload but it is not suitable for the long term in COPD patients. Stone therapy in the acute phase remains the treatment of COPD exacerbation with bronchodilators, corticosteroids and antibiotherapy, whenever needed.

Acute right heart failure in patients with heart failure with preserved ejection fraction

According to Joseph et al., acute heart failure is classified into six syndromes, the sixth being right-sided acute heart failure, a syndrome that occurs in patients with postcapillary pulmonary hypertension due to left-heart failure.[73] The general clinical presentation of patients with right-sided AHF syndrome involves increased jugular venous pressure, hepatomegaly, edema, low-output syndrome and hypotension. It is now accepted that right ventricular dysfunction is considered to be an important factor of poor outcome in patients suffering from heart failure with reduced ejection fraction.[74] [15] Heart failure with preserved ejection fraction (HFpEF) is a

[67] Weitzenblum E, Apprill M, Oswald M et al. *Chest.* 1994;105:1377–82.
[68] Weitzenblum E, Apprill M, Oswald M et al. *Chest* 1994;105:1377–82.
[69] Fletcher EC, Levin DC. *Chest.* 1984;85:6–14.
[70] MacNee W. *Am J Respir Crit Care Med.* 1994;150:833–52; 1158–68.
[71] Richens JM, Howard P. Oedema in cor pulmonale. *Clin Sci.* 1982;62:255–9.
[72] Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med.* 1980;93:391–8.
[73] Joseph SM, Cedars AM, Ewald GA, Geltman EM, Mann DL. *Tex Heart Inst J.* 2009; 36:510–520.
[74] Ghio S, Gavazzi A, Campana C et al. *J Am Coll Cardiol.* 2001;37:183–188.

complex syndrome that has emerged in recent years with special attention given by clinicians due to its high prevalence, increased mortality rates and lack of specific treatment to improve survival.

It has been demonstrated that right ventricular dysfunction is not only frequent in HFpEF patients but also contributes to a poor prognosis.[75] In fact, Puwanant et al. showed a prevalence of HFpEF with RVD of nearly 50% by echocardiographic measurements.[76] Until recently, in European heart failure guidelines, cut-off values for ejection fraction varied from 40% to 50%, so the estimation of RV dysfunction prevalence might have been misleading due to the inclusion criteria. However, despite variable reports, a recent large meta-analysis showed at least one-fifth of RVD prevalence in HFpEF patients.[77] Studies also reported a 2.2 risk of all-cause mortality in HFpEF patients with RVD and 55% of deaths showed signs and symptoms of systemic congestion.[78]

The echocardiographic parameters TAPSE < 17 mm and FAC < 35% were the most frequently used to demonstrate RVD and showed a strong correlation with prognosis.[79] Right heart failure is the result of RVD progression in these patients, which manifests with structural and functional abnormalities such as RV remodeling, tricuspid annular dilation, functional tricuspid regurgitation and right atrial dysfunction. Gorter et al. proposed a staging system for RVD/RHF in HFpEF patients where stage 1 is characterized by the risk of RVD development, stage 2 by RVD without clinical signs and symptoms, stage 3 by RVD with clinical signs and symptoms of RHF and stage 4 by RVD with refractory signs and symptoms of RHF (jugular vein distension, hepatomegaly, peripheral edema).[160]

LV diastolic dysfunction and loss of atrial compliance is at the core of HFpEF pathophysiology. This leads to retrograde loading of the pulmonary venous system which eventually determines the appearance of pulmonary hypertension. It has been described that apart from increased pulmonary venous pressures, additional components such as endothelin-1 upregulation, decreased NO bioavailability, inflammation cells may also be

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[75] Gorter TM, Hoendermis ES, van Veldhuisen DJ et al. *Eur J Heart Fail.* 2016;18:1472–1487.

[76] Puwanant S, Priester TC, Mookadam F, Bruce CJ, Red eld MM, Chandrasekaran K. *Eur J Echocardiogr.* 2009;10:733 – 737.

[77] Gorter TM, van Veldhuisen DJ, Bauersachs J et al. *Eur J Heart Fail.* 2018;20:16–37.

[78] Melenovsky V, Hwang SJ, Lin G, Red eld MM, Borlaug BA. *Eur Heart J.* 2014;35:3452 – 3462.

[79] Lang RM, Badano LP, Mor-Avi Vet al. *Eur Heart J Cardiovasc Imaging.* 2015;16:233–270.

found in the pulmonary circuit causing pulmonary vascular vasoconstriction and remodeling with a further increase of pulmonary arterial pressure.[30] Severe PH (often seen in these patients) is sometimes hard to distinguish from primitive PAH and thus right heart catheterization may be needed. By hemodynamic assessment, the PH related to HFpEF is characterized as a mean PA > 25 mmHG, a PCWP > 15mmHG and a PVR < 3 W. These patients often present a pulmonary precapillary component besides the postcapillary component defined as PA > 25mmHg, PCWP > 15mmHG and PVR > 3 W.[132]

Pulmonary hypertension is the key link between HPpEF and RV dysfunction by exposing the RV to increased afterload that will lead to the activation of neurohormonal and molecular pathways such as: the RAAS and SNS system, cytokine and natriuretic peptides release. Besides the detrimental effect of the RV afterload, there are several non-cardiac comorbidities (commonly seen in HFpEF) like diabetes mellitus, obesity, or hypertension that will lead to endothelial dysfunction and RV myocyte remodeling via inflammatory pathways (oxidative stress and cytokine release).[80] Typical cardiac remodeling phenotype found in HFpEF with RVD is LV concentric hypertrophy and RV dilatation.

Despite the high prevalence and increased mortality in patients with HFpEF and acute right heart failure, the cornerstone in treating these patients remains on optimal volume management by reducing pulmonary and systemic congestion.[81] The depletion of excessive volume overload is mainly achieved by diuretic therapy and nitrates if high blood pressure is present. Evidence in reduction pulmonary pressures and RV afterload by specific PAH – drug therapy (targeting cGMP, NO and endothelin-1 pathways) is inconclusive with mixed results.[82] [83] Even detrimental effects have been reported with this therapy such as acute pulmonary edema due to rapid LV filling pressures, which is why current guidelines do not recommend the usage PAH - drug therapy in PH – HFpEF patients.[84] Another approach is the treatment of co-morbidities: controlling heart rate and rhythm in those with atrial fibrillation, blood pressure in those with hypertension, hyperglycemia in those with diabetes, hypoxemia and hypercapnia in those with COPD or sleep apnoea and promoting weight loss in obese patients.

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[80] Paulus WJ, Tschope C. *J Am Coll Cardiol.* 2013;62:263 – 271.

[81] Hoeper MM, Lam CS, Vachiery JL et al. *Eur Heart J.* 2016 Dec 23. https://doi.org/10.1093/eurheartj/ehw597 [Epub ahead of print].

[82] Guazzi M, Vicenzi M, Arena R, Guazzi MD. *Circulation.* 2011;124:164–174.

[83] Hoendermis ES, Liu LC, Hummel YM et al. *Eur Heart J* 2015;36:2565–2573.

[84] Koller B, Steringer-Mascherbauer R, Ebner CH et al. *Heart Lung Circ* 2017;26:433–441.

Current clinical trials with drugs that target pulmonary hemodynamics and RV function are ongoing and awaiting results.

Other clinical scenarios

Valvular disease

Tricuspid regurgitation is the most frequent cause of right-sided valvular heart disease responsible for RV failure and is associated with poor prognosis.[85] Functional tricuspid regurgitation due to the dilation of tricuspid annulus seen in cardiomyopathies is the most common etiology encountered in right heart valvular disease. The severity of tricuspid regurgitation will determine the appearance of hemodynamic consequences such as RV enlargement. (Image 30, Image 31)

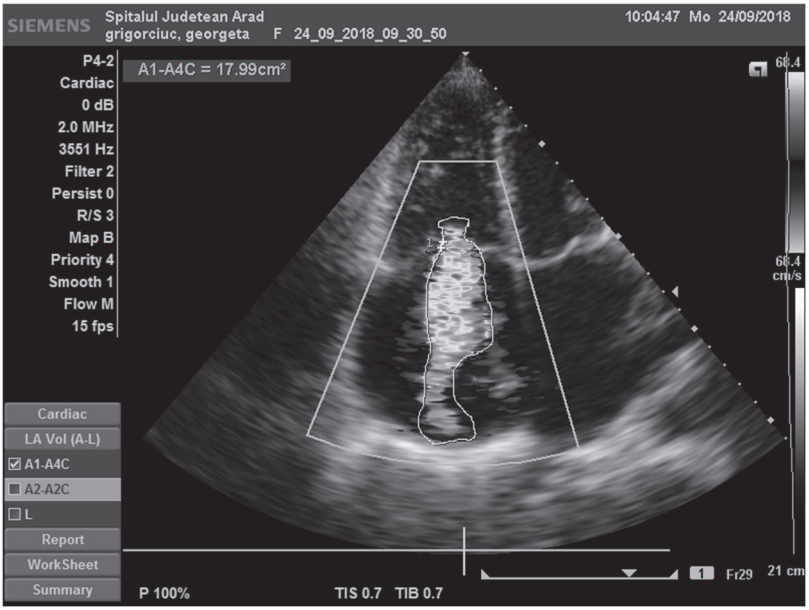

Image 30. Severe tricuspid regurgitation

[85] Lewis JF, Webber JD, Sutton LL, Chesoni S, Curry CL. *Am Coll Cardiol.* 1993;21:649–654.

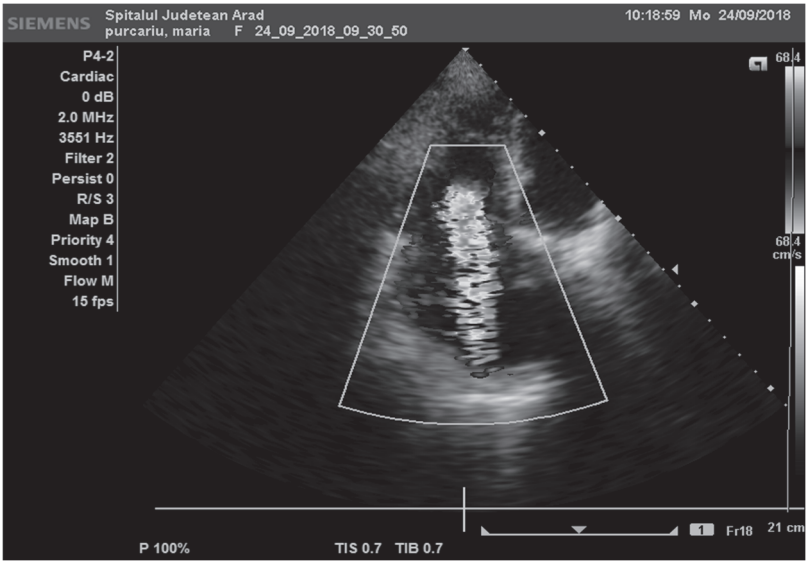

Image 31. Severe tricuspid regurgitation

Moderate to severe tricuspid regurgitation is responsible for worse survival rates despite the absence of pulmonary hypertension or even RV dysfunction.[86] Another cause of tricuspid regurgitation is infective endocarditis especially seen in intravenous drug abusers. According to current guidelines on valvular heart disease, severe secondary or primary tricuspid regurgitation in patients with marked symptomatology refractory to diuretic therapy or presence of RV dilatation/dysfunction, surgery by tricuspid valve repair or replacement is recommended.[87] Ring annuloplasty is the key surgery for secondary tricuspid regurgitation.[170]

Cardiac tamponade

Cardiac tamponade is a clinical syndrome characterized by rapid or progressive accumulation of fluid within the pericardial sack with symptoms like jugular vein distension, peripheral edema, dyspnoea, arterial hypotension or shock that mimics acute RV failure. It should be taken into

[86] Nath J, Foster E, Heidenreich PA. *J Am Coll Cardiol.* 2004;43:405–409.
[87] Baumgartner H, Falk V, Bax JJ et al. *Eur Heart J.* 2017;38:2739–2791.

account for differential diagnosis as treatment includes urgent percutaneous or surgical pericardial drainage.

Cardiac surgery

Acute RV failure during cardiac surgery can be caused by volume overload, myocardial ischemia, pre-existing RV dysfunction or arrhythmias.[88] [89] Several intraoperative factors that have been described as responsible for RV failure include suboptimal myocardial protection, myocardial stunning due to prolonged cardio pulmonary by-pass, air to the right coronary artery, and mechanical occlusion of the right coronary button.[90]

Measures such as combined anterograde or retrograde cardioplegia, avoidance of cardiopulmonary by-pass and liberal transfusions, maintenance of right atrial contraction and AV synchrony may provide RV myocardial protection.[91] [92] [93]

For patients at risk of RV failure, especially those with previous known PH or RV dysfunction, prolonged cardiopulmonary by-pass should be managed by a multidisciplinary team to ensure optimized medical care.

Acute right heart failure is the most feared complication in cardiac surgery especially after heart or heart-lung transplantation. In the 1960s, several deaths were reported early after heart transplant due to acute right heart failure.[94] The occurrence was seen in patients with pulmonary hypertension and the association between preoperative elevated pulmonary vascular resistance and the risk of right heart failure development after heart transplant was later confirmed.[95] This led to more strictness of inclusion criteria for transplantation by excluding patients with severe pulmonary hypertension.[237] What happens is that the donor's heart is not adapted to the afterload generated by the increased pulmonary vascular resistance and this results in right ventricular dilation, ischemia and the drop in cardiac output.

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[88] Haddad F, Couture P, Tousignant C, Denault AY. *Anesth Analg.* 2009;108:407–421.
[89] Haddad F, Couture P, Tousignant C, Denault AY. *Anesth Analg.* 2009;108:422 – 433.
[90] Candilio L, Malik A, Ariti C et al. *J Cardiothorac Surg.* 2014;9:1484.
[91] Pegg TJ, Selvanayagam JB, Karamitsos TD, Arnold RJ, Francis JM, Neubauer S, Taggart DP. *Circulation.* 2008; 117:2202 – 2210.
[92] Song HK, von HC, Jespersen CM et al. *Ann Thorac Surg.* 2014;97:1630 – 1635.
[93] Goldstein JA, Harada A, Yagi Y, Barzilai B, Cox JL. *J Am Coll Cardiol.* 1990;16:181 – 189.
[94] Guyton AC, Lindsey AW, Giully JJ. *Circ Res.* 1954;11:326–32.
[95] Griepp R, Stinson E, Dong E et al. *Am J Surg*. 1971;122:192–7.

It is important to diagnose pulmonary hypertension before heart transplant by cardiac catheterization. The majority of patients with chronic heart failure develop pulmonary hypertension by backward transmission to the pulmonary arteries of elevated left ventricular pressures, leading to pulmonary vasoconstriction. The increase in pulmonary vascular resistance is at first a reactive phenomenon, meaning that it can be lowered if the LV filling pressures are reduced by medical therapy.[96] However, at some point due to chronic increased pulmonary capillary wedge pressures, PVR can become irreversible due to structural changes in the pulmonary vasculature.[239] The onset of pulmonary hypertension in chronic heart failure depends on etiology but usually, it takes years to develop.

It is also important if the diagnosis of pulmonary hypertension was confirmed preoperatively, in order to distinguish whether PVR is reactive (reversible) or fixed (irreversible). These features can be tested during cardiac catheterization by administering provocative therapy with pulmonary vasodilators and measure baseline hemodynamic parameters such as PVR, PVR index, peak systolic pulmonary artery pressure and transpulmonary gradient.[97] Measuring these parameters is very useful when assessing risk for right heart failure development after cardiac transplantation. The patients with reversible parameters at provocatory therapy testing have a better prognosis and are least likely to develop right heart failure than those with fixed or irreversible pulmonary vascular resistance. The agents that are used to test pulmonary vasculature response are sodium nitroprusside, adenosine, prostacyclin and inhaled nitric oxide. Fixed pulmonary hypertension has been defined as visible in patients after provocative therapy with the following values: a PVR $\geq$ 4 WU, a PVRI $\geq$ 6 WU/m2, a systolic pulmonary artery pressure (SPAP) > 60 mmHg and a transpulmonary gradient (TPG) $\geq$ 15 mmHg.[98] [99] [100] Unfortunately, reactive or even normal PVR does not guarantee the probability of developing acute right heart failure after a cardiac transplant. Intraoperative factors or prolonged by-pass has been shown to increase PVR.[101]

Managing acute right heart failure after cardiac transplant is quite challenging but the key points for therapy of this high burden are to:

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[96] Dodson LA, Nathan NS, D'Ambra MN. *Curr Opin Anesth.* 1997;10:21–8.
[97] Stobierska B, Awad H, Michler RE. *J Am Coll Cardiol.* 2001; 38: 923–931.
[98] Chen JM, Michler RE. Kluwer Academic Publishers, 1997.
[99] Bhatia SJ, Kirshenbaum JM, Shemin RJ et al. Circulation 1987;76:819–26.
[100] Bauer J, Dapper F, Demirakca S et al. *J Heart Lung Transplant*. 1997;16:1238–47.
[101] Smith WJ, Murphy MP, Appleyard RF et al. *J Thorac Cardiovasc Surg.* 1994;107:800–6.

preserve coronary perfusion by maintaining systemic blood pressure, optimize right ventricular preload, reduce right ventricular afterload and to limit pulmonary vasculature vasoconstriction through ventilation with high inspired oxygen concentrations (FiO2 100%), increased tidal volume and optimal positive end-expiratory pressure ventilation (PEEP).[240] An important goal in treating RHF is pulmonary vasodilation to reduce PVR while maintaining systemic blood pressure.[240] Dobutamine and isoproterenol can be used to improve contractility and reduce RV afterload through their ability to produce pulmonary vasodilation, but their usage is limited due to their arrhythmogenic properties and an increase in myocardial consumption. A more suitable pulmonary vasodilator is inhaled, nitric oxide, which due to its rapid effect and pulmonary selectivity can reduce pulmonary vascular resistance without secondary effects such as systemic hypotension in comparison to other pulmonary vasodilators (prostaglandins, milrinone, adenosine, or phosphodiesterase inhibitors) which produce systemic hypotension. When RV failure is refractory to pharmacological therapies, the remaining solution is RV assist devices.

Unfortunately, acute right heart failure is not totally avoidable and the most viable solution to prevent this burden is by careful selection of the recipient.

LVAD and acute right heart failure

Left ventricular assist device is an important therapeutic option to improve quality of life, hemodynamics, organ dysfunction and survival in patients with end-stage heart failure.

Its primary indications are the bridge to transplant, bridge to candidacy, destination therapy and bridge to recovery.[102] However, despite its excellent results, over 20% of patients who undergo isolated left ventricular assist device, experience acute right heart failure, thus resulting in increased mortality rates.[103]

Right heart failure associated with LVAD may lead to decreased tissue perfusion and multi-organ failure.[104] There are several mechanisms potentially responsible for RV failure after LVAD surgery especially if there was a pre-existing RV dysfunction. One potential mechanism is that

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[102] Kormos RL, Teuteberg JJ, Pagani FD et al. *J orac Cardiovasc Surg.* 2010;139:1316-24.

[103] Argiriou M, Kolokotron SM, Sakellaridis T et al. *J Thorac Dis.* 2014;6 Suppl 1:S52-9.

[104] Kukucka M, Potapov E, Stepanenko A et al. *J Thorac Cardiovasc Surg.* 2011;141:1009-14.

increased cardiac output from LVAD determines the increase of venous return leading to the overload of an already dysfunctional RV with consequent ARHF.[105] Another potential mechanism is the left-ward shifting of the interventricular septum due to aggressive left ventricle decompression associated with continuous-flow LVADs.[106] [107] This will affect the contribution of the septum to the RV contraction. Also, with the increase of RV volume and tethering of the tricuspid leaflets secondary to left-ward interventricular septum, the shift will aggravate tricuspid regurgitation with a potential generation of right ventricle failure.[108]

Atrial tachyarrhythmias develop in over 20% of LVAD patients, thus increasing the risk of RV failure occurrence.[109] The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) characterized acute right heart failure after LVAD as documented elevated central venous pressure (right atrial pressure > 16 mmHg at right heart catheterization, dilated inferior vena cava without inspiratory variation on echocardiography, elevated jugular venous pressure), manifestations of elevated central venous pressure (peripheral edema, ascites or hepatomegaly, laboratory findings of hepatic and renal dysfunction – total bilirubin > 2.0mg/dl and creatinine level > 2 mg/dl).[110]

A severity scale of acute right heart failure associated with LVAD surgery was proposed as following: a moderate scale (criteria for right heart failure with the need for inotropes, inhaled nitric oxides or vasodilators up to 14 days after the implant), and a severe scale (criteria for right heart failure with the need for right ventricular assist device).[253] A severe scale can often result in death during hospitalization after the ventricular assist device procedure.

Taking into consideration the high incidence of right heart failure after the LVAD procedure, several risk scores have been proposed to predict the development of this condition. These risk scores could identify patients at high risk for right heart failure and thus improve selection to avoid this morbidity level after device implantation.

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[105] Farrar DJ, Compton PG, Hershon JJ et al. *World J. Surg*. 1985;9:89-102.
[106] Farrar DJ. *Semin Thorac Cardiovasc Surg.* 1994;6:163-8.
[107] Moon MR, Bolger AF, DeAnda A et al. *Circulation*. 1997;95:1320-7.
[108] Krishan K, Nair A, Pinney S et al. *Eur J Cardiothorac Surg.* 2012;41:213-7.
[109] Brisco M, Sundareswaran K, Milano et al. *J Card Surg.* 2014;29:572-80.
[110] Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). Appendix A: Adverse event definitions: adult and pediatric patients (2013). Available at http://www.uab.edu/medicine/ intermacs/appendices-4-0/appendix-a-4-0. Accessed September 23, 2014.

A various number of pre-operative risk factors were taken into account in the development of these scores: female gender, pre-operative mechanical support or intra-aortic balloon pump, presence of end-organ dysfunction (liver and renal dysfunction, coagulation abnormalities), increased natriuretic peptides and inflammatory markers, right ventricular dysfunction demonstrated by transthoracic echocardiography (reduced RV strain, increased RV end-diastolic diameter > 35mm, RV ejection fraction < 30%, TAPSE < 7.5mm, right atrial diameter > 50 mm, low RV fractional area change, severe tricuspid regurgitation), altered hemodynamic parameters measured by right heart catheterization (elevated central venous pressure > 15 mmHg, a CVP/PCWP index > 0.63, low right ventricular stroke index, elevated pulmonary vascular resistance), non-ischemic cardiomyopathy, reoperation.[246]

Some of the risk scores are as follows:

Matthews' score =4 (vasopressor requirement) +2 (if AST ≥ 80 IU/L) +2.5 (if bilirubin ≥2.0 mg/dL) + 3 (creatinine ≥ 2.3 mg/dL or renal replacement therapy).[111]

Fitzpatrick's score =18 (cardiac index <2.2 L/min) +18 (RV stroke work index ≤ 0.25 mmHg L/m2) +17 (creatinine ≥ 1.9 mg/dL) +16 (previous cardiac surgery) +16 (RV dysfunction) +13 (systolic blood pressure, ≤ 96 mmHg).[112]

Drakos' score =3.5 (destination therapy) +4 (intra-aortic balloon) +4 (pulmonary vascular resistance: 1 if PVR <1.7 Wood units, 2 if 1.8-2.7 Wood units, 3 if 2.8-4.2 Wood units, 4 if > 4.3 Wood units) +2.5 (inotrope dependency) +2 (obesity) +2.5 (angiotensin converting enzyme inhibitor and/or angiotensin II receptor blocker) +2 (β-blocker).[113]

Despite the wide range of risk factors included in these models and their potential benefit in identifying patients at risk to develop acute right heart failure, none of the models were validated for prospective studies. There are some major limitations regarding these risk scores such as: patients without risk factors still developed right heart failure, the lack of including intraoperative events that might jeopardize a previous normal

[111] Matthews JC, Koelling TM, Pagani FD et al. *J Am Coll Cardiol.* 2008;51:2163-72.
[112] Pettinari M, Jacobs S, Rega F et al. *Eur J Cardiothorac Surg*. 2012;42:621-6.
[113] Drakos SG, Janicki L, Horne BD et al. *Am J Cardiol.* 2010;105:1030-5.

right ventricle (blood transfusions, disruption of by-pass grafts or coronary arteries that supply the right ventricle and air embolism).[114]

However, there are optimal hemodynamic parameters accepted for RV function preoperatively that indicate a low likelihood to develop right heart failure: PCWP ≤18 mmHg; CVP/PCWP ≤0.66; PVR <2 wood units; RVSWI ≥400 mmHg mL/m_2.[246]

The management of right heart failure implies pre-operative, intraoperative and post-operative strategies. For example, patients with evidence of RV dysfunction should receive aggressive treatment pre-operatively to lower central venous pressure < 15 mmHg. Diuresis or ultrafiltration are two methods that can lower central venous pressure.[115] Decreasing systolic pulmonary artery pressure is another method used to stabilize a pressure overloaded right ventricle and can be achieved with inhaled nitric oxide, phosphodiesterase-5 inhibitors, intra-aortic balloon pumps and percutaneous temporary support devices.[116] [117] Intraoperative correction of tricuspid regurgitation by tricuspid valve repair or annuloplasty can improve RV function whenever moderate to severe tricuspid regurgitation is present or if a tricuspid annulus diameter of > 40mm is visible.[118] Other intraoperative strategies imply: transesophageal monitoring of RV function, maintenance of pump speed to keep the septum midline, maintaining the ventilator to avoid hypoxia, hypercarbia and acidosis, minimizing blood product use, minimizing cardiopulmonary bypass time and wean from cardiopulmonary bypass with pharmacological RV support.[257] Post-operative right ventricular assist device in case of acute right heart failure is a solution, but elective RVAD implant during LVAD implant has better survival rates.[119]

Right heart failure remains a common burden after LVAD procedure and limiting this event implies a better stratification of patients at risk or even biventricular support devices.

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[114] Lampert BC, Teuteberg JJ. J *Heart Lung Transplant.* 2015; *34*:1123–1130. doi: 10.1016/j.healun.2015.06.015.
[115] Feldman D, Pamboukian SV, Teuteberg JJ et al. *J Heart Lung Transplant.* 2013;32:157-87.
[116] Argenziano M, Choudhri AF, Moazami N. *Ann Thorac Surg* 1998;65:340-5.
[117] Tedford RJ, Hemnes AR, Russell SD et al. *Circ Heart Fail* 2008;1:213-9.
[118] Saeed D, Kidambi T, Shalli S et al. *J Heart Lung Transplant.* 2011;20:530-5.
[119] Morgan JA, John R, Lee BJ et al. *Ann Thorac Surg.* 2004;77:859-63.

Right heart failure and congenital heart disease

In congenital heart disease, the RV may serve either as the sub-pulmonary ventricle or as the systemic ventricle. The most common congenital pathologies that affect the RV are: atrial septal defect, Tetralogy of Fallot, pulmonary stenosis, Ebstein anomaly, arrhythmogenic right ventricular cardiomyopathy and pulmonary valve atresia. All of the aforementioned pathologies require timely corrective surgery or palliative surgery to prevent irreversible right heart failure.

Patients with congenital heart disease have both the systolic and diastolic RV function impaired. Tricuspid regurgitation and cardiac arrhythmias are important features of right heart failure secondary to congenital heart disease. Right heart failure in congenitals is a mixture of hemodynamic impairment, neurohormonal and inflammatory activation.[120]

Pressure overload, volume overload and intrinsic myocardial disease are the pathological mechanisms responsible for right heart failure in congenital heart disease.[263] Patients with Tetralogy of Fallot have a combination of pressure and volume overload that contribute to right heart failure development. Patients with congenital heart disease have often associated pulmonary artery hypertension and this is due to increased blood flow and pressure throughout the pulmonary vasculature.[121] This will lead to the development of endothelial dysfunction, hypertrophy and proliferation of smooth vasculature cells, the formation of plexiform lesions in the small arteries that will eventually increase pulmonary vascular resistance.[122] [123] For example, patients with Eisenmenger syndrome will develop systemic pressures in the pulmonary circulation.[124] However, patients with Eisenmenger syndrome or ventricular septal defect have a better right ventricular compensation and survival rate than patients with idiopathic pulmonary artery hypertension.[125] [126] Morphologically, those with Eisenmenger or ventricular septal defect have smaller and hypertrophied right ventricles compared to patients with idiopathic pulmonary hypertension

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[120] Guihaire J, Haddad F, Mercier O, Murphy DJ, Wu JC, Fadel E. *J Clin Exp Cardiol*. Jun 15 2012;8:1–11

[121] Simonneau G, Robbins IM, Beghetti M et al. *J Am Coll Cardiol.* 2009, 54: S43-54.

[122] Lowe BS, Therrien J, Ionescu-Ittu R et al. *J Am Coll Cardiol*. 2011, 58: 538-546.

[123] Engelfriet PM, Duffels MG, Moller T et al. *Heart.* 2007, 93: 682-687.

[124] Trojnarska O, Plaskota K. *Cardiol J*. 2009, 16: 500-506.

[125] Diller GP, Dimopoulos K, Broberg CS et al. *Eur Heart J.* 2006. 27: 1737-1742.

[126] Hopkins WE, Ochoa LL, Richardson GW, Trulock EP. *J Heart Lung Transplant.* 1996, 15: 100-105.

who have dilated and thinner right ventricles. These features were tested in experimental studies where the RV pressure overload was induced.[127] It was shown that for the same level of ventricular afterload obtained by mechanical pulmonary artery banding or by angioproliferative stimulus, a more severe form of right heart failure was seen in the latter group.[270] RV diastolic dysfunction has been described in patients with congenital heart disease and is manifested by increased right atrial filling pressures and restrictive right ventricle filling.[128]

The atrial septal defect is the most common congenital heart disease seen in adults that leads to right heart volume overload with consequent failure and complications such as arrhythmias, thromboembolic events and mortality.[129] RV dilation is seen in larger atrial septal defects with no restriction to intra-atrial flow where right atrial pressure equalizes left atrial pressures.[74] In the absence of other pulmonary or heart malformations, the magnitude of the left to right shunt correlates with the compliance of the two ventricles.[74] Also, in the absence of RV pathology, right ventricular ejection fraction correlates with pulmonary artery pressure.[130] This is why right heart failure is rarely seen in early life but rather in adulthood if no associated abnormalities are present.

The Ebstein anomaly is a heart malformation in which one or two leaflets are adherent to the RV wall leading to atrialization of an important portion of the RV and varying degrees of tricuspid regurgitation. The atrialized portion is responsible for RV dysfunction. The Ebstein anomaly is usually associated with various congenital heart defects like: atrial septal defect, ventricular septal defect, pulmonary atresia, mitral valve prolapse, subaortic stenosis or bicuspid aortic valve. Moreover, these patients may present preexcitation pathways that need often to be surgically interrupted. The severity of right heart failure depends on the degree of the RV hypoplasia and the success of tricuspid valve surgical repairement.[74]

Corrected transposition of the great arteries is a complex heart malformation in which the RV serves as the systemic ventricle and is coupled to the systemic circulation. It is usually associated with other cardiac malformations like a ventricular septal defect, pulmonary stenosis or Ebstein anomaly.[131] Right heart failure usually occurs in more than 50%

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[127] Bogaard HJ, Natarajan R, Henderson SC et al. *Circulation.* 2009, 120: 1951-1960.
[128] Davlouros PA, Niwa K, Webb G, Gatzoulis MA. *Heart*. 2006, 92: i27-38.
[129] Webb G, Gatzoulis MA. *Circulation*. 2006, 114: 1645-1653.
[130] Konstam MA, Idoine J,Wynne J et al. *Am J Cardiol*. 1983;51:1144–1148.
[131] Alonso-Gonzalez R, Dimopoulos K, Ho S, Oliver JM, Gatzoulis MA. *Rev Esp Cardiol.* 2010, 63: 1070-1086.

of patients with corrected transposition of the great arteries at mid-age and this risk increases as more heart defects are present.[132] Microvascular dysfunction contributes to RV dysfunction in this congenital pathology.[263] Complete transposition of the great arteries is not compatible with life if surgical repair is not performed from early infancy. The operation involves the arterial switch of both great arteries with translocation of the vessels to the opposite roots thus recreating ventriculo-arterial concordance.

Pulmonary valve stenosis is responsible for 12% of all congenital heart diseases in adults.[133] It exposes the right ventricle to chronic pressure overload that leads to adaptive remodeling characterized by RV hypertrophy without dilatation. Right heart failure usually appears late in the course of the disease or if associated with pulmonary valve insufficiency.

The appropriate management of patients with congenital heart disease involves finding the right moment for corrective surgery. Correct timing allows functional and structural recovery of the RV. On the other hand, when corrective surgery is delayed, the only remaining option to minimize right ventricular failure complications like cachexia or protein enteropathy is palliative surgery.[263] After corrective surgery the RV has the ability to fully recover and this was shown after lung transplant in patients with severe pulmonary artery hypertension or after atrial septal defect closure.[272] RV recovery is better seen in patients with hypertrophy secondary to right ventricular outflow obstruction than in patients with RV dilation secondary to atrial septal defect and late closure.[134] Studies have demonstrated that RV end-diastolic volumes higher than 200ml/m2 are representative of limited reverse remodeling after surgery.[263]

When it comes to medical therapy, the neurohormonal blockade has not been proven from clinical studies to be efficient in improving outcome in patients with right ventricular failure secondary to congenital heart disease, despite its fundamental role in systemic left heart failure.[135] The only success in this population was seen from the introduction of pulmonary vasodilators in those patients with severe pulmonary artery hypertension.[136] The biggest concern in using these agents was worsening the right to left shunt, which is why they were tested in small case studies where actually there was an improvement in hemodynamics, arterial oxygen

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[132] Graham TP Jr, Bernard YD, Mellen BG et al. *J Am Coll Cardiol*. 2000;36:255–261.

[133] Brickner ME, Hillis LD, Lange RA. *N Engl J Med*. 2000, 342: 256-263.

[134] Salehian O, Horlick E, Schwerzmann M et al. *J Am Coll Cardiol.* 2005, 45: 499-504.

[135] Dore A, Houde C, Chan KL et al. *Circulation.* 2005 112: 2411-2416.

[136] Schulze-Neick I, Hartenstein P, Li J et al. *Circulation.* 2003, 108: II167-173.

saturation and exercise tolerance. The biggest trial to test pulmonary vasodilators in adults with Eisenmenger syndrome was BREATHE-5 (The Bosentan Randomized Trial of Endothelin Antagonist THErapy-5) which showed not only the safety usage of the agents but also improvement in symptomatology and hemodynamics.[137] All being said, these agents should be used cautiously and only in specialized centers for pulmonary artery hypertension.

Right heart failure and arrhythmogenic right ventricle cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a disease caused by the dysfunction of cardiac myocyte desmosomes.[138] This disease was first described in the 1970s when several patients underwent surgery for drug-resistant ventricular tachycardia; during the surgical intervention changes such as right ventricular enlargement, late potentials by epicardial mapping and fibrofatty infiltrations from biopsy specimens were observed.[139] All these findings proved the right ventricular origins of the tachycardias.

The diagnosis of ARVC is quite challenging due to its wide expressivity and incomplete penetrance in family members. However, the diagnostic criteria from 2010 based on ECG data, histological studies and multimodality cardiac imaging improved the diagnostic specificity.[140]

The main pathological characteristic of this disease is the replacement of myocytes with fibrous or fibro-fatty tissue in the right ventricular free wall.[141] As previously mentioned, ARVC is caused by desmosomal impairment. Desmosomes are intercellular junctions that assure cell adhesion. Desmosomal impairment is caused by mutations in desmosomal proteins like plakophilin and desmoplakin which determine the loss in the ability of the myocytes to tolerate mechanical stress and eventually detach from one another with consequent cell death.[142] This

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[137] Galie N, Beghetti M, Gatzoulis MA et al. *Circulation.* 2006, 114: 48-54.

[138] Corrado D, Link MS, Calkins H. *N Engl J Med*. 2017;376:61–72. doi: 10.1056/NEJMra1509267.

[139] Fontaine G, Guiraudon G, Frank R et al. Lancaster, PA: MTP Press. 1977:334–50.

[140] Marcus FI, McKenna WJ, Sherrill D et al. *Eur Heart J.* 2010;31:806–14.

[141] Gandjbakhch E, Redheuil A, Pousset F, Charron P, Frank R. *J Am Coll Cardiol.* 72 (2018), pp. 784-804

[142] Sen-Chowdhry S, Syrris P, McKenna WJ. *J Cardiovasc Electrophysiol*. 2005;16:927–935. doi: 10.1111/j.1540-8167.2005.40842.x.

process is accompanied by local inflammation and fibro-fatty infiltration that replace the death of the myocytes.[285] As a result, right ventricular dysfunction develops and is the most common ventricular irritability that predisposes to ventricular arrhythmias. Usually, the lesions extend from the epicardium towards the endocardium and affect the area between the pulmonary infundibulum, the apex and the infero-posterior wall, also referred to as the "triangle of dysplasia".[284] Also, the lesions are mostly focal or segmental and do not affect the interventricular septum.[284] From a histological point of view, fat infiltration is not required for diagnostic criteria due to its lack of specificity demonstrated on myocardial biopsies studies.[143] However fibrous infiltration and myocyte loss are mandatory diagnostic criteria.[283] Also, quite frequent lymphocytic-histiocytic infiltrates, necrosis and apoptosis are seen in myocardial biopsies making it hard to distinguish from myocarditis.[144]

The revised diagnostic criteria for ARVC are a combination of major and minor criteria depending on all the available diagnostic tools. A comprehensive guide for the diagnosis of this disease is not included in the subject of this book, which is why we will focus only on major criteria. A better understanding of the disease and other information can be found in the state of the art position papers and guidelines on ARVC.

The electrocardiographic diagnostic criteria for ARVC are divided into: repolarization abnormalities and depolarization/conduction abnormalities. Major repolarization abnormalities involve inverted T waves in the right precordial leads (V1, V2, V3) or beyond in individuals over 14 years of age and in the absence of complete right bundle branch block QRS>120ms. Major depolarization/conduction abnormalities involve the presence of the epsilon wave in the right precordial leads (V1, V2, V3).[283] (Image 32)

[143] Basso C, Ronco F, Marcus F et al. *Eur Heart J.* 2008;29:2760–71.
[144] Asimaki A, Saffitz JE. *J Cardiovasc Electrophysiol.* 2011;22:111–7.

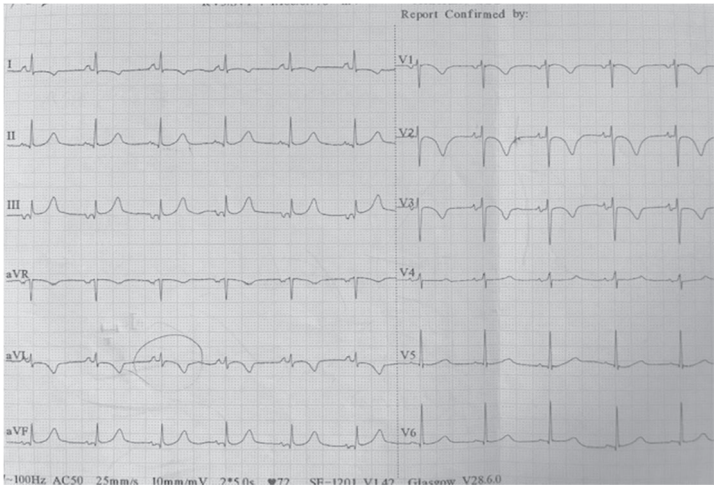

Image 32. ARVC – inverted T waves in right precordial leads V1-V3

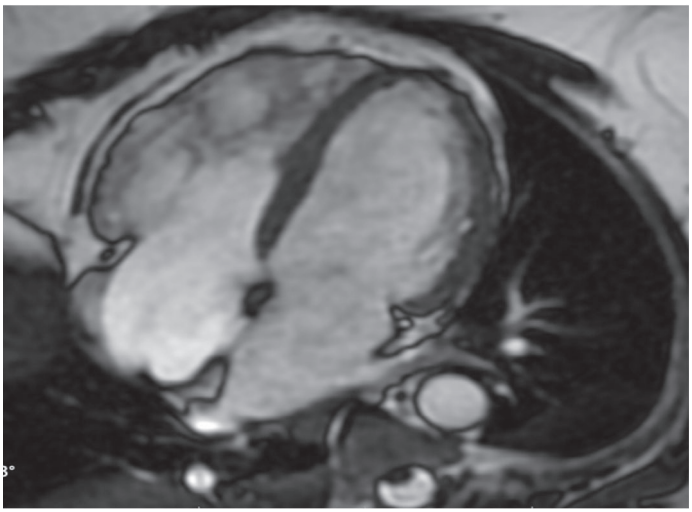

Image 33. ARVC – cardiac MRI – dilated RV with free wall bulging

An indirect diagnostic criterion for ARVC is the presence of RV global or regional dysfunction with structural alterations which can be demonstrated by 2D echocardiography, MRI and RV angiography. (Image 33) Major echocardiographic findings are RV akinesia, dyskinesia or

aneurysm. At least one of the following end-diastole measurements is required: a right ventricular outflow tract (RVOT) measured in parasternal long-axis view of ≥ 32 mm (≥ 19mm/m2 body surface area), in parasternal short axis view of ≥ 36 mm (≥ 21mm/m2 body surface area) or a fractional area change ≤ 33%. MRI can be appreciated very well RV akinesia, dyskinesia, dyssynchronous contraction as well as the measurement of RV end-diastolic volume (≥ 110 ml/m2 – males, ≥ 100 ml/m2 – females) and RV ejection fraction ≤ 40%.[283]

The histology study by endomyocardial biopsy offers a good characterization of the RV free wall tissue, where the presence of myocytes < 60% with the replacement of fibrous tissue in at least one sample pleads for ARVC.[283]

Suggestive ventricular arrhythmias for this condition are nonsustained or sustained ventricular tachycardia of left bundle branch block morphology with a superior axis (negative or indeterminate QRS in leads II, III, aVF and positive in lead aVL). Another important criterion for ARVC/D is the family history of this condition that should be confirmed in a first-degree relative.[283] (Image 34)

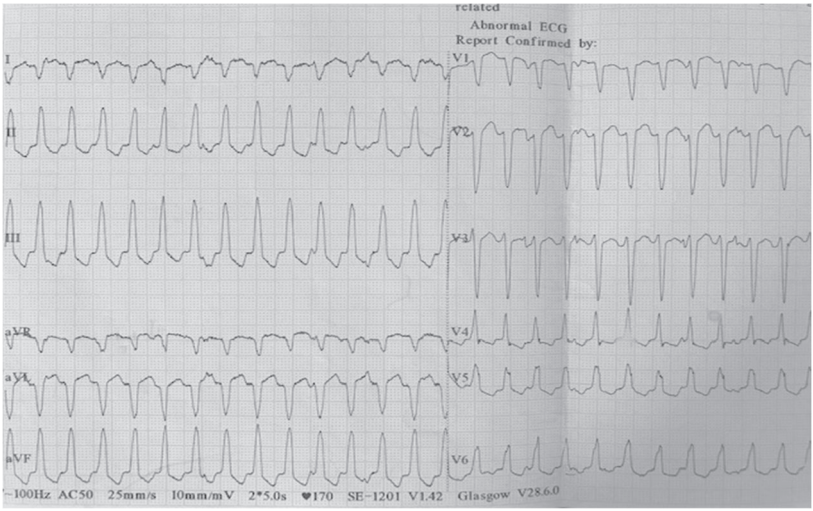

Image 34. Sustained VT of LBBB morphology

Although ARVC/D is characterized by RV enlargement with wall motion abnormalities, right heart failure is not very common in this population, ventricular arrhythmias being the predominant presentation.

However, right heart failure will develop in the late stages of the disease. Protonotarius et al. were among the first to reveal in a group of 73 patients with ARVC/D the presence of right heart failure symptoms in 14 patients of which 2 had these symptoms at presentation.[145] Another study from the North American registry on 108 patients with ARVC/D has shown a prevalence of right heart failure symptoms in only 5 patients.[146] The largest study so far on the prevalence of right heart failure in ARVC/D population was performed by Gilotra et al. which showed the presence of RHF symptoms in nearly half (49%) from a total number of 289 patients with ARVC/D.[147] Of these patients, 29 also had left ventricular involvement and 31 presented RHF clinical symptomatology before the ARVC/D diagnosis.[290] Also, it was shown that those patients with heart failure symptoms at presentation have lower ventricular arrhythmic events.[290] The disproportionate prevalence between studies could have been the revised 2010 criteria for diagnosing ARVC/D where RV volume overload was included as new criteria and used in the aforementioned study.

ARVC/D is an autosomal dominant genetical disorder that is more frequent in men than in women.[148]

The management of ARVC/D relies on preventing sudden cardiac death by using ICD's, electrophysiological ablation and antiarrhythmic therapy. However, patients that present signs and symptoms of right heart failure should undergo medical therapy with diuretics for volume unloading or the use of ACE inhibitors if there is left ventricle involvement. With the improvement of survival with the use of ICD's most of the patients are at risk of developing right heart failure and even become candidates for heart transplantation.

Acute right heart failure and tachyarrhythmias

Right heart failure is associated with a greater risk for arrhythmias and is also considered responsible for decompensation episodes, especially in patients with PAH etiology.[149]

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[145] Protonotarios N, Anastasakis A, Antoniades L et al. *Eur Heart J*. 2011;32:1097–1104. doi: 10.1093/ eurheartj/ehr043.

[146] Marcus FI, Zareba W, Calkins H et al. *Heart Rhythm*. 2009;6:984–992. doi: 10.1016/j.hrthm.2009.03.013.

[147] Gilotra NA, Bhonsale A, James CA et al. *Circ Heart Fail.* 2017;10:e003819.

[148] Bauce B, Frigo G, Marcus FI et al. *Am J Cardiol*. 2008;102:1252–1257. doi: 10.1016/j.amjcard.2008.06.054.

[149] Folino AF, Bobbo F, Schiraldi C et al. *Lung.* 2003;181:321–8.

Chronic pressure or volume overload in chronic right heart failure is responsible for the right atrium and right ventricular structural remodeling. This will determine the formation of an arrhythmogenic substrate. Numerous other mechanisms responsible for the unstable arrhythmic substrate are described: excessive extracellular matrix, ion channels remodeling, the presence of scars, dilatation and stretch, neurohormonal activation, delayed cardiac repolarization that will eventually result in the enhancement of QT dispersion.[150] An important role for promoting arrhythmic activity was attributed to autonomic system modulation.[292] The increase in pulmonary pressure and the drop in cardiac output stimulates autonomic activity with an increase in the sympathetic drive which is considered to be pro-arrhythmic.[151] Enhanced QT dispersion is considered not only a predictor of tachyarrhythmias but also of all-cause mortality and was shown to correlate with mean pulmonary artery pressure in patients with PAH.[152] Right ventricular ischemia is an important pathophysiological mechanism in severe pulmonary artery hypertension that aggravates RV failure and is thought to be a key promoter of ventricular arrhythmias.[295]

Right ventricle electrical remodeling is characterized by a series of changes like: down-regulation of transient outward potassium current (Ito), up-regulation of Ca2+ inward current, impaired Ca2+ current inactivation, the increase in late sodium currents, reduction in transient outward potassium currents, abnormal handling of intracellular Ca2+ with consequent cytosolic overload that predisposes to abnormal triggered activity and automaticity.[153] [154] [155] [156] All of the aforementioned electrophysiological abnormalities together with structural changes predispose to heterogenous prolongation of action potential duration with consequent repolarization dispersion that generates electrical instability and the appearance of supraventricular, ventricular arrhythmias and even sudden cardiac death.

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[150] Janse MJ, van Capelle FJ, Morsink H et al. *Circ Res.* 1980;47:151–65.
[151] Rajdev A, Garan H, Biviano A. P*rog Cardiovasc Dis.* 2012;55:180–6.
[152] Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J. *Circulation.* 839 1991;83:1888–94.
[153] Kääb S, Nuss HB, Chiamvimonvat N et al. *Circ Res.* 865 1996;78:262–73.
[154] Houser SR, Piacentino 3rd V, Weisser J. *J Mol Cell Cardiol.* 2000;32:1595–607.
[155] Wang Y, Tandan S, Cheng J et al. *J Biol Chem.* 2008; 283:25524–32.
[156] Undrovinas AI, Maltsev VA, Sabbah HN. *Cell Mol Life Sci.* 1999;55:494–505.

The main electrophysiological mechanisms responsible for tachyarrhythmias in right heart failure are increased automaticity, triggered activity and re-entry phenomenon.[157]

Supraventricular tachyarrhythmias

Supraventricular arrhythmias as atrial fibrillation, atrial flutter are some of the main reasons for chronic right heart failure decompensation in patients with pulmonary artery hypertension. Their occurrence is mainly due to chronic pressure overload and increased automatic tone of the atrium. Increased right atrium pressure and size along with chronic hypoxia promote fibrosis development and tissue inhomogenity thus predisposing the appearance of atrial fibrillation, flutter or tachycardias.[158] Their deleterious effects resonate in hemodynamic instability on an already malfunctioning right ventricle due to loss of atrial function, impaired ventricular fillings and increased myocardial oxygen consumption.

The incidence of supraventricular arrhythmias in patients with right heart failure varies between 10 to 25% of which 82% are considered responsible for the clinical worsening of RV failure.[159] The distribution between atrial fibrillation and atrial flutter is the same (42.8%) among patients with RHF.[302] Supraventricular tachycardias like atrial fibrillation are usually a marker of advanced heart disease but can also contribute to disease progression or episodes of decompensation. Tongers et al. showed, on a population with PAH, that 84% of atrial arrhythmias were responsible for episodes of acute right heart failure.[302] They also pointed out that in patients to whom the restoration of rhythm control was intended, PAH improved significantly compared to those with refractory supraventricular arrhythmias where mortality reached up to 82% during a period of 11 months from diagnosis.[302] In another study by Olsson et al. in patients with pulmonary hypertension, 97.5% of patients with atrial arrhythmias developed clinical deterioration or acute right heart failure.[160]

Atrial arrhythmias are poorly tolerated by patients with RV dysfunction and PAH or chronic left heart failure with pulmonary hypertension. In these patients, RV clinical stability by maintaining or

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[157] Zipes DP, Jalife J.Cardiac electrophysiology. From cell to bedside. 3rd ed. Philadelphia: WB Saunders; 2000. p. 345–56.

[158] Grapsa J, Gibbs JS, Cabrita IZ et al. *Eur Heart J Cardiovasc Imaging* 2012;13:666–72. DOI: 10.1093/ehjci/jes003; PMID: 22294683.

[159] Tongers J, Schwerdtfeger B, Klein G et al. *Am Heart J.* 2007;153:127–32.

[160] Olsson KM, Nickel NP, Tongers J, Hoeper MM. *Int J Cardiol.* 2013;167:2300–5.

restoring sinus rhythm strategy is mandatory to avoid episodes of acute right heart failure.[161] Due to significantly worse prognosis associated with atrial tachyarrhythmias in this population, most of the observational studies report an initial attempt of the rhythm control strategy.[303] [162] In acute right heart failure, rate-control agents like beta-blockers or calcium channel blockers should be avoided because of their negative inotrope effects. For patients with right heart failure secondary to PAH, both the European Cardiology Society and the European Respiratory Society guidelines recommend the management of atrial tachyarrhythmias by restoring sinus rhythm.[132]

In the acute setting of atrial fibrillation for patients with RV failure secondary to left-sided heart failure, urgent electrical cardioversion is indicated if atrial fibrillation is thought to be contributing to the patient's hemodynamic compromise in order to improve the patient's clinical condition as a class I-C recommendation. Also, the European Cardiology Society guidelines recommend for patients with acute heart failure NYHA class IV, in addition to conventional heart failure treatment, administration of an intravenous bolus of amiodarone or digoxin which should be considered to reduce the ventricular rate as class II B recommendation.[163]

Regarding rhythm vs rate control strategy, the biggest trial so far - The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) - evaluated 4060 patients with atrial fibrillation at risk for stroke or death. They concluded that the outcome after 3.5 years of follow-up was not significantly different between groups with a mortality rate of 23.8% in the rhythm-control group and 21.3% in the rate control group.[164] A substudy of this trial showed that digoxin use was associated with the increase of all-cause mortality, although another substudy found no association and rejected this hypothesis.[165] [166] Be that as it may, current guidelines on pulmonary artery hypertension recommend the possibility of using digoxin to slow ventricular rate in patients with atrial tachyarrhythmias.[132] A study performed by Rich et al. even showed improvement of cardiac output in

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[161] Wanamaker, B, Cascino, T, McLaughlin et al. *Arrhythmia Electrophysiol Rev* 2018; 7: 43.

[162] Cannillo M, Grosso Marra W, Gili S et al. *Am J Cardiol* 2015;116:1883–9. DOI: 10.1016/j. amjcard.2015.09.03; PMID: 26522342.

[163] Ponikowski P, Voors AA, Anker SD et al. *Eur Heart J.* 2016; *37*:2129–2200. doi: 10.1093/eurheartj/ehw128.

[164] Wyse DG, Waldo AL, DiMarco JP et al. *N Engl J Med.* 2002;347:1825–33.

[165] Whitbeck MG, Charnigo RJ, Khairy P et al. *Eur Heart J.* 2013;34:1481–98.

[166] Gheorghiade M, Fonarow GC, van Veldhuisen DJ et al. *Eur Heart J.* 2013;34:1489–97.

patients with right ventricular dysfunction and PAH.[132] It is commonly known that calcium channel blockers like verapamil or diltiazem should be avoided or used cautiously in patients with acute heart failure because of their negative inotrope effects. However, there is a subpopulation with vasoreactive PAH to calcium channel blockers and might respond to lower heart rate but they need to be tested for vasodilator therapy responsiveness at cardiac catheterization. In other words, the only agents that can be used in the acute setting to slow heart rate for hemodynamically unstable patients or with reduced cardiac output are digoxin or amiodarone. When it comes to antiarrhythmic agents for pharmacological conversion in acute right heart failure, the preferred drug remains amiodarone. It should be noted that chronic use of amiodarone for the maintenance of sinus rhythm could be deleterious for patients with right ventricular dysfunction secondary to PAH due to its potential toxic side effects and development of pneumonitis/fibrosis thus aggravating pulmonary hypertension. Furthermore, as amiodarone is a CYP2C9 inhibitor, it can increase bosentan plasma levels in patients with PAH treated with this endothelin antagonist drug.[132]

For pharmacological cardioversion, amiodarone should be administered intravenously: 5-7 mg/kg over 1-2 hours as the first dose with a follow-up dose of 50 mg/hour to a maximum of 1 g over 24 hours. Intravenous anticoagulation (unfractionated heparin or low molecular weight heparins) should be administered to all patients before cardioversion therapy.

All patients with right heart failure and atrial fibrillation or flutter should be considered for chronic oral anticoagulation therapy to prevent systemic thromboembolism. One should balance the benefit of anticoagulation with the risk of bleeding by assessing the CHADSVASC score and the HASBLED score. A major proportion of patients with right heart failure present renal and hepatic dysfunctions due to systemic congestion and low cardiac output and this will only increase the risk of bleeding HASBLED score > 3. The increase in HASBLED score could discourage the physician to administer anticoagulant therapy but needless to say, these patients have an increased CHADSVASC score also due to associated comorbidities and the high risk of stroke. This is why rather than avoiding anticoagulant therapy one should consider adjusting the dose according to glomerular filtration rate or retrieving drugs that in combination with anticoagulants increase the risk of hemorrhage. Novel oral anticoagulants (NOAC's) are preferred for patients with right heart failure and non-valvular atrial fibrillation in expense to antivitamin K antagonists due to their more effective and safer (less intracranial hemorrhage) profile. In patients with mechanical valves or severe mitral

stenosis antivitamin K antagonists are the drugs of choice to prevent thromboembolism. The dosage of NOAC's should be adjusted according to age and renal function. For example patients older than 80 years with creatinine clearance < 50ml/L should have a reduction in doses of dabigatran (110 mg twice daily), rivaroxaban (15 mg once daily) or apixaban (2.5 mg twice daily).

The management of atrial tachyarrhythmias such as cavotricuspid isthmus dependent atrial flutter or atrio-ventricular nodal re-entrant tachycardia in patients with RHF and PAH, catheter ablation should be the first-line approach to improve outcome.[304]

Ventricular tachyarrhythmias

Sudden cardiac death accounts for 28% of patients with RV failure and PAH.[167] [168] Despite the statistical facts, ventricular tachyarrhythmias are quite rare in this population compared to patients with advanced left heart failure. Ventricular tachyarrhythmias originating from the right ventricle usually affect young persons whose pathogenesis of appearance implies genetic disorders such as: arrhythmogenic right ventricular cardiomyopathy, Brugada syndrome, right ventricular outflow tract ventricular tachycardia and ventricular tachycardias related to congenital heart disease.[169] Patients with RHF secondary to CHD present quite often ventricular ectopy and non-sustained ventricular tachycardias.[170] Sustained ventricular tachycardias in CHD patients can be monomorphic, polymorphic or ventricular fibrillation.[171] Sustained ventricular tachycardias appear more often among patients with Tetralogy of Fallot, transposition of the great vessels, systemic right ventricle and left ventricular outflow tract obstructive lesions.[313] Sudden cardiac death due to ventricular arrhythmias is seen in up to 20-25% of patients with CHD and the risk is even higher if systemic ejection fraction < 35% or biventricular dysfunction.[172] The risk for ventricular tachycardia in Tetralogy of Fallot is given by: left ventricular systolic dysfunction, a QRS > 180ms, extensive right ventricular scarring, non-sustained ventricular tachycardia.[313] The management of these patients implies the implantation

[167] Tateno S, Niwa K, Nakazawa M et al. *Int J Cardiol.* 2006;106:373–81. 1063
[168] Humbert M. Presse Med. 2010;39 Suppl 1:1S41–5.
[169] Capulzini L, Brugada P, Brugada J, Brugada R. *Rev Esp Cardiol.* 2010 Aug;63(8):963–983.
[170] Hernandez-Madrid A, Paul T, Abrams D et al. *Europace.* 2018;20(11):1719–1753.
[171] Khairy P, Harris L, Landzberg MJ et al. *Circulation.* 2008; 117:363–70.
[172] Koyak Z, Harris L, de Groot JR et al. *Circulation.* 2012;126: 1944–54.

of an ICD or, if monomorphic ventricular tachycardia is present, catheter ablation can be considered.[313]

It is recommended, for the management of ventricular arrhythmias in right heart failure, to correct potential aggravating/precipitating factors like low serum potassium, magnesium or ongoing ischemia. Amiodarone can be used to suppress initial symptomatic ventricular tachycardia but its routinely use in order to prevent future events is not recommended due to safety concerns (worsening heart failure, proarrhythmia and death).[173]

Ventricular arrhythmias are more often seen in advanced forms of cardiomyopathies and heart failure. This is given by maladaptive cardiac remodeling, fibrosis, hypertrophy, dyssynchrony.[174] Ventricular arrhythmias with their forms of presentation (frequent premature ventricular beats, non-sustained ventricular tachycardias, sustained ventricular tachycardias or ventricular fibrillation) contribute to disease progression with the risk of recurrent hemodynamic decompensation over time. In the COMPANION study, the investigators showed on ambulatory patients with advanced heart failure NYHA III/IV class carriers of ICD, that appropriate shocks received for sustained ventricular tachycardia were associated with increased mortality.[175] The question that arose from this study was whether appropriate ICD shocks for ventricular tachycardias are a marker for heart failure progression or the shock itself can potentially aggravate heart failure.[318] The puzzle was solved in the ALTITUDE study which demonstrated that appropriate shocks for ventricular tachycardias were indeed associated with increased mortality and disease progression whereas no risk for mortality was seen after inappropriate shocks for noise artifacts or supraventricular arrhythmias.[176] The mechanism behind ventricular arrhythmias leading to aggravation of heart failure is a depletion of metabolic energy through myocardial stunning. In advanced heart failure, there are already limited lipid and energy stores with the use instead of ketones as substrate energy.[317]

When it comes to the management of ventricular arrhythmias with the use of antiarrhythmic drugs, data are not encouraging. In a meta-analysis on 2268 patients with heart failure and ventricular arrhythmias where the benefit of class III antiarrhythmic drugs was tested, the authors concluded that there was a 34% reduction in ventricular arrhythmic episodes with ICD shocks compared to the control group.[177] However, despite a reduction in

[173] Bardy GH, Lee KL, Mark DB et al. *Engl J Med.* 2005;352:225 – 237.
[174] Santangeli P., Rame J.E., Birati E.Y., Marchlinski F.E. *J Am Coll Cardiol.* 2017, 69:1842–1860
[175] Saxon LA, Bristow MR, Boehmer J et al. *Circulation*. 2006;114:2766–72.
[176] Powell BD, Saxon LA, Boehmer JP et al. *J Am Coll Cardiol.* 2013; 62:1674–9.
[177] Santangeli P, Muser D, Maeda S et al. *Heart Rhythm.* 2016;13:1552–9.

ventricular arrhythmias, this did not lead to a reduction in all-cause mortality.[320] In a subgroup analysis of this trial amiodarone was associated with increased all cause-mortality and probably due to its organ toxicity.[178] There is evidence that intravenous lidocaine due to its short-half life and safety profile can be given as the first drug of choice.[179] Also intravenous amiodarone is recommended as first-line therapy especially if the patient is not on oral chronic therapy with amiodarone. Whenever possible, after the acute event, for recurrent ventricular tachycardias to prevent heart failure progression, it is recommended to try catheter ablation.[317] It is known, that for patients with left heart failure, the best ways to reduce or prevent ventricular tachycardias are: ACE-inhibitors, mineralocorticoids and beta-blocker therapy. This conventional therapy is not suitable for lone right ventricular failure and few data are available on their efficacy in this context, however the right heart failure profile secondary to left-sided disease may respond to this therapy. Advanced right heart failure with recurrent ventricular tachycardias clinical presentation is a common feature among patients with arrhythmogenic right ventricular cardiomyopathy. The management of this category of patients is rather challenging because of the limited efficacy of antiarrhythmic drugs. The only suitable solutions in these cases are ICD implantation to prevent sudden cardiac death or catheter endo-epicardial ablation to prevent recurrent ventricular episodes and right heart failure progression.[180] [181] Studies on catheter ablation in patients with arrhythmogenic right ventricular cardiomyopathy showed a rate of 71% cases free of ventricular tachycardias episodes.[182]

Catheter ablation is a viable solution even during acute episodes of heart failure. Santangeli et al. proposed an algorithm for the management of patients with advanced heart failure and refractory to pharmacological therapy ventricular tachyarrhytmias:[317]

If the patient is hemodynamically unstable and presents signs of low cardiac output, cool extremities, low blood pressure, weak peripheral pulse, elevated jugular venous pressure, rales, dyspnea at rest then the

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[178] Santangeli P, Di Biase L, Burkhardt JD et al. *Expert Opin Drug Saf.* 2012;11:191–214.
[179] Rademaker AW, Kellen J, Tam YK et al. *Clin Pharmacol Ther.* 1986;40:71–80.
[180] Bai R, Di Biase L, Shivkumar K et al. *Circ Arrhythm Electrophysiol.* 2011;4:478–85.
[181] Philips B, Madhavan S, James C et al. *Circ Arrhythm Electrophysiol.* 2012;5:499–505.
[182] Santangeli P, Zado ES, Supple GE, et al. *Circ Arrhythm Electrophysiol.* 2015;8:1413–21.

patient should undergo right heart catheterization to determine which type of hemodynamic support should be used (ECMO or LVAD) during catheter ablation therapy. ECMO is the preferred choice for biventricular failure and signs of elevated central venous pressure. After successful radiofrequency ablation, the attempt to wean of the patient from temporary circulatory support should be intended. If the patient cannot be weaned of circulatory support and there is a need for inotropic and vasopressor support, the patient should be considered a candidate for a heart transplant or continuous LVAD support. In case the patient is relatively stable with no active signs of low cardiac output and there is no need for temporary circulatory support, then radiofrequency ablation can be done with close monitoring after the procedure. No matter how compensated the patient is, if ejection fraction is severely reduced (< 25%) then the candidate should be evaluated for possible need for hemodynamic support during radiofrequency ablation.[317]

Clearly, the management of ventricular arrhythmias in the context of acute heart failure in any form (even acute right heart failure) is challenging and remains of low survival rates, thus future larger trials should test hybrid therapy such as the combination of interventional ablation of arrhythmias concomitant with circulatory hemodynamic support.

CHAPTER 6

MANAGEMENT IN THE ACUTE SETTING

IOAN RADU LALA

The initial triage and the assessment of potential patients with acute right heart failure have to be performed rapidly and by skilled multidisciplinary medical staff in order to manage the patient by the clinical scenario. The main focus is to support the RV function by optimizing preload, afterload and contractility and to ameliorate symptomatology (shortness of breath, edema, anxiety). (Figure 5)

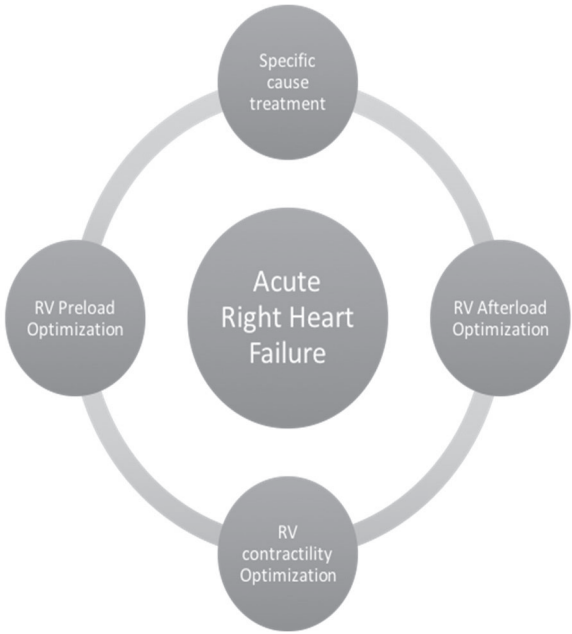

Figure 5. Essential points in ARHF management

Preload optimization

Critically ill patients with RV failure may be preload-dependent due to volume loss, decreased vascular tone, sepsis and positive pressure ventilation. However, volume loading has to be done cautiously due to the potential of over-distending the RV with a consequent increase in wall tension, decrease in contractility and tricuspid regurgitation aggravation, as well as increase of interventricular interdependency which leads to the impairment of the LV function and reduced cardiac output.[1] [60] Therefore it is recommended that volume loading be guided by central venous pressure monitoring if low blood pressure and filling pressures are present.[60]

Another easy way is to measure the inferior vena cava (IVC) diameter and its respiratory collapse, which in case of a diameter of >21 mm and a reduced respiratory collapse of < 50% usually denotes increased right atrial (RA) pressure. (Image 35)

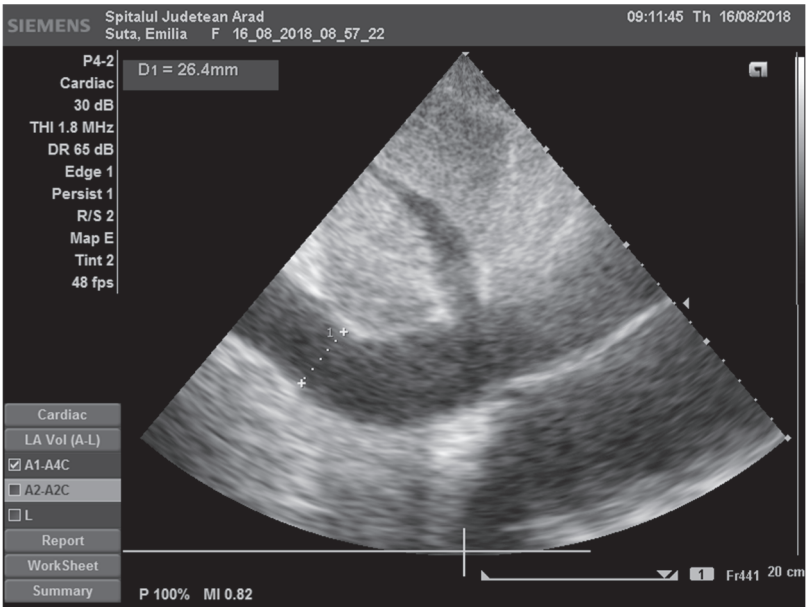

Image 35. Dilated inferior vena cava

[1] Mehmood M, Frank TA. *E-Journal of Cardiology Practice*. Vol 14, No.33. 19 Dec 2016

Most RV failures are caused or aggravated by volume overload and therefore diuretics are the first-line of choice if signs of venous congestion and maintained blood pressure are present.[60] It is recommended that optimal filling pressure in case of RV failure be within the range of 8-12 mmHg.[177] Right-sided filling pressures and oxygen delivery can be determined by inserting a central venous line and having access to the superior vena cava oxygen saturation (Svo2) and central venous pressure.[2] Svo2 values lower than 70-80% with normal arterial oxygenation could indicate reduced cardiac output.[178] Thus, by reducing preload via diuresis, there is a decrease in RV free wall tension and this minimizes ischemia with contractility improvement.

RV preload optimization differs based on afterload conditions. For example, if there is increased RV afterload, volume loading can lead to the displacement of the septum towards the LV with impaired diastolic filling. On the other hand, when RV failure with reduced or normal afterload is present, such in the case of RV myocardial infarction, the RV end-diastolic pressures need to be increased above normal to maintain cardiac output.[178]

Afterload optimization

Optimizing RV afterload can be achieved with general measures such as correcting conditions that increase pulmonary vasculature resistance (hypoxia, acidosis, hypercapnia) or with pharmacotherapy (pulmonary vasodilators, thrombolytic therapy).[3]

Guided use of mild hyperventilation is an effective way to improve afterload. By using a lower but effective plateau pressure, tidal volume, positive end-expiratory pressure when non-invasively or invasively ventilating a patient, RV afterload and preload optimization can be achieved.[179] It is known that a reduction of arterial pCO2 from 50 mmHg to 30 mmHg will reduce pulmonary vasculature resistance.[4] To reduce airway and pulmonary vasculature resistance, it is crucial to treat underlying pathologies such as COPD and thus attenuate pulmonary hypertension.[5] Therefore, in patients with exacerbated COPD, bronchodilatory therapy (B-agonists, anticholinergic agents, methylxanthines) given by nebulization is known to be effective in reducing pulmonary vascular resistance and improve RV contractility.[6]

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[2] Ventetuolo CE, Klinger JR. *Ann Am Thorac Soc.* 2014;11:811 – 822.
[3] Vieillard-Baron A, Jardin F. *Curr Opin Crit Care.* 2003;9:15-21.
[4] Fullerton DA, McIntyre RC, Kirson LE et al. *Ann Thorac Surg*. 61: 696–701, 1996.
[5] Anzueto A. *Eur Respir Rev.* 2010;19:113–118.
[6] Matthay RA, Berger HJ. *Clin Chest Med.* 1983, 4:269–295

In sepsis, several vasoactive factors such as endothelin, thromboxane, serotonin and IL-6 are overexpressed and incremented to be involved in the pathogenesis of pulmonary vascular resistance via suppression of nitric oxide synthesis.[7] [8]

With a short half-life and rapid onset, inhaled nitric oxide is a potent vasodilator that has been used off-label in critically ill patients in the attempt to unload the RV.[9] Inhaled nitric oxide although without any benefits on the outcome, has been shown to improve RV hemodynamics and mixed venous oxygen saturation in patients with acute RV failure.[10] [11] However, pulmonary vasodilators such as prostacycline derivates and phosphodiesterase 5 inhibitors should be used only in case of right heart failure secondary to pulmonary arterial hypertension and not in critically ill patients due to their potential to cause systemic hypotension and worsen ventilation-perfusion matching.

Contractility optimization

Reduced RV contractility is mainly driven by: RV free wall mechanical overstretching due to altered preload or afterload, deranged myocyte metabolism due to acidosis, hypoxia, the generation of reactive oxygen species, inflammatory cytokines and last but not least oxygen delivery mismatch due to decreased coronary artery perfusion.[178]

The first step is to control the heart rate or restore sinus rhythm (electrical or pharmacological cardioversion) in case of tachyarrhythmias (atrial fibrillation, atrial flutter, atrial tachycardia) as it may compromise the cardiac function and output.[177] Another situation is the case of chronotropic incompetence or AV blocks where atrio-ventricular sequential pacing can improve cardiac output if RHF is present.

In life-threatening situations, particularly RHF with hemodynamic instability, vasopressors and/or inotropes are ofirst choice when restoring systemic blood pressure and improving organ perfusion. There are situations where RHF is associated with increased pulmonary systolic artery

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[7] Pittet JF, Morel DR, Hemsen A, Gunning K, Lacroix JS, Suter PM, Lundberg JM. *Ann Surg*. 1991;213:261–264.

[8] Sibbald W, Peters S, Lindsay RM. *Crit Care Med.* 1980;8: 490–494.

[9] Walmrath D, Schermuly R, Pilch J, Grimminger F, Seeger W. *Eur Respir J* 1997;10:1084–1092.

[10] Rossaint R, Slama K, Steudel W, Gerlach H, Pappert D, Veit S, Falke K. *Intensive Care Med.* 1995;21:197–203.

[11] Bhorade S, Christenson J, O'connor M, Lavoie A, Pohlman A, Hall JB. *Am J Respir Crit Care Med.* 1999;159:571–579.

pressure that may exceed the systemic blood pressure. In this type of scenario, a primary goal would be vasopressor therapy to restore systemic blood pressure to levels above pulmonary systolic artery pressure.[178]

An ideal vasopressor to be used in acute RHF with hypotension or shock would be an agent that increases RV contractility and systemic arterial pressure without raising pulmonary vascular resistance. *Norepinephrine* would fall in this category as it improves ventricular systolic interaction and coronary perfusion without changing pulmonary vascular resistance.[12] It is an agent with a predominant alpha 1 receptor activity that produces vasoconstriction and slight beta- 1 receptor activity. However, it has been demonstrated on animals with RV dysfunction that noradrenaline improved pulmonary artery/RV coupling by its contractility effects.[13] Noradrenaline is given intravenously by continuous perfusion with adjustments of *0.2-1 ug/kg/min* to maintain arterial pressure.

When it comes to inotropes, in normotensive or hypotensive non-tachycardiac patients, *dobutamine (inodilator)* would be the agent of choice as it restores RV/pulmonary artery coupling and cardiac output by improving RV contractility and compliance and thus reducing RV wall stress and right diastolic systolic pressures.[14] Dobutamine can be titrated between *2-20 ug/kg/min* by continuous IV perfusion, but in doses up to *5 ug/kg/min* it can reduce pulmonary artery resistance and thus RV afterload.[15]

Levosimendan (calcium sensitizer) was proved to be a more effective and superior agent than dobutamine by favoring RV inotropy and pulmonary vasodilatation.[131] Working with patients with ARDS and RV failure treated with levosimendan, Morelli et al. demonstrated its beneficial role by its capacity to induce pulmonary vasculature vasodilation and hence reduce RV afterload.[16] It has also been shown that it can improve RV contractility without the expense of myocardial oxygen consumption and myocardial diastolic impairment.[17] [18] [19] *0.1-0.2 ug/kg/min* can be administered by continuous IV perfusion or by IV bolus *6-12 ug/kg/min over 10 minutes* (not recommended if SBP < 90 mmHg). Due to its positive

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[12] Ghignone M, Girling L, Prewitt RM. *Anesthesiology.* 1984;60:132–135.
[13] Schreuder WO, Schneider AJ, Groeneveld AB, Thijs LG. *Chest.* 1989 Jun;95(6):1282-8.
[14] Vincent JL, Reuse C, Kahn RJ. *Crit Care Med*. 1988, 16:659–662
[15] Leier CV, Binkley PF. *Prog Cardiovasc Dis.* 1998;41:207–224.
[16] Morelli A, Teboul JL, Maggiore SM et al. *Crit Care Med.* 2006, 34(9):2287–2293
[17] Slawsky MT, Colucci WS, Gottlieb SS et al. *Circulation.* 2000;102:2222–2227.
[18] Innes CA, Wagstaff AJ. *Drugs.* 2003;63:2651–2671.
[19] Sonntag S, Sundberg S, Lehtonen LA, Kleber FX. *J Am Coll Cardiol.* 2004; 43:2177–82

inotropic effects and pulmonary vasodilatory properties, levosimendan appears to be the preferred drug of choice in the intensive care unit for inotropic support.

Milrinone (phosphodiesterase 3 – inhibitor) enhances RV contractility while it simultaneously lowers the systolic pulmonary artery pressure.[20] [21] Nevertheless, this agent should be used cautiously due to its potential of aggravating systemic arterial hypotension, as well as on normotensive patients with pulmonary hypertension secondary to left heart failure and on chronic beta-blocker therapy.[177] However, there are some studies where inhaled milrinone administration was tested for RHF management and was proved to be beneficial in increasing cardiac output and lowering pulmonary artery systolic pressure, with no systemic hypotension side effects, yet neither improved outcome.[22] [23]

The aforementioned inotropic agents, whenever needed and also because of the systemic hypotension side effect, should be given alongside noradrenaline. Levosimendan or milrinone are also the preferred agents over dobutamine in RV failure with pulmonary hypertension secondary to left heart failure.[60]

Mechanical circulatory support

Whenever medical therapy in the context of acute RHF is proved to be inefficient in the intensive care unit, mechanical circulatory support should be considered. Acute mechanical support of the RV should be sought or required in the following clinical situations: RV myocardial infarction with cardiogenic shock, acute pulmonary embolism with shock, after left ventricular assist device implantation, graft rejection after heart transplantation.[60]

Several studies which provide data on the successful use of extracorporeal life support (such as venovenous and venoarterial extracorporeal membrane oxygenation - ECMO - in patients with acute RHF secondary to massive pulmonary embolism, chronic thromboembolic pulmonary artery hypertension or pulmonary arterial hypertension) but

[20] Hollenberg SM. *Am J Respir Crit Care Med.* 2011;183:847–855.
[21] Chen EP, Bittner HB, Davis RD Jr, Van Trigt P III. *Ann Thorac Surg.* 1997;63:814–821
[22] Singh R, Choudhury M, Saxena A, Kapoor PM, Juneja R, Kiran U. *J Cardiothorac Vasc Anesth.* 2010;24:797–801.
[23] Haraldsson s A, Kieler-Jensen N, Ricksten SE. *Anesth Analg.* 2001;93:1439–1445.

usually as a bridge to thromboendarterectomy or lung transplantation.[24] [25] [26] [27] Usually, ECMO should be used no more than 5 to 10 days as bridging therapy for surgery or long-term device implantation because of potential complications associated with this technique (local or general infections, thrombus formation around the cannulae, limb hypoperfusion).[60] [28] Right ventricular assist devices have been approved for usage for up to four weeks.[29] Data has shown functional recovery after right ventricular assist device (RVAD) in 42-75% of cases but decreased LV function predicts worse outcomes in terms of isolated RVAD.[30] [31] In the case of refractory RV failure, the only remaining option is the cardiac transplant.

Right ventricular assist devices ar superior to pulmonary artery counterpulsation pumps with better clinical outcomes in acute right heart failure. RVADs are surgical pumps that deliver rotational kinetic energy into the circulation. The major determinants of the device flow for the pumps are the rotations per minute of the impeller and the pressure gradient (or pressure head) which represents the pressure between the inlet (preload) and outlet (afterload) of the impeller. Practically, through the cannulation of these pumps, blood is drawn from the right atrium and pumped into the pulmonary artery. For RVADs, the pressure gradient is determined by pulmonary artery pressure and right atrial pressure. The variations inflow generated by RVADs are usually smaller than those generated by LVADs because of lesser pressure variations in the right heart cavities than in the left heart cavities. Depending on the severity and etiology of the right heart failure, device flow can be either high or low. For example, in patients with RV failure secondary to myocardial infarction the pressure gradient is low and device flow is high. For patients with RV failure secondary to acute decompensated pulmonary hypertension, the pressure gradient is high while the device flow is low.

Most RVADs that are used are extracorporeal centrifugal-flow pumps that are placed by thoracotomy or open sternotomy. Mechanical circulatory support devices used for right ventricular failure can be

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[24] Maggio P, Hemmila M, Haft J, Bartlett R. *J Trauma.* 2007;62:570–576.
[25] Olsson KM, Simon A, Strueber M et al. *Am J Transpla*nt. 2010;10:2173–2178.
[26] de Perrot M, Granton JT, McRae K et al. *J Heart Lung Transplant* 2011;30:997–1002.
[27] Berman M, Tsui S, Vuylsteke A et al. *Ann Thorac Surg*. 2008;86:1261–1267.
[28] Keogh AM, Mayer E, Benza RL et al. *J Am Coll Cardiol.* 2009;54(1 Suppl):S67–S77.
[29] Grif th KE, Jenkins E, Stulak J et al. *Perfusion.* 2012;27:65–70.
[30] Kapur NK, Paruchuri V, Jagannathan A et al. *JACC Heart Fail.* 2013;1:127–134.
[31] Cheung AW, White CW, Davis MK, Freed DH. *J Heart Lung Transplant.* 2014;33:794–799.

classified according to their mechanism of action that is by direct or indirect right ventricular by-pass systems. The direct systems such as TandemHeart, Impella RP displace blood from the right atrium to the pulmonary artery thus bypassing the right ventricle. The indirect system such as venoarterial extracorporeal membrane oxygenation pump (VA-ECMO) displaces and oxygenates blood from the right atrium to the femoral artery. The effects of the direct RV by-pass systems in the case of isolated ARHF are: reducing right atrium pressure, increasing mean pulmonary artery pressure and increasing left ventricular afterload. As a consequence, if the left de function is preserved, cardiac output will increase while left ventricular filling pressures will increase and left ventricular afterload will remain the same. The effects of the indirect RV by-pass systems in case of isolated ARHF are: reducing right atrium and pulmonary artery pressures, the decrease in left ventricular preload. Consequently, if the left side function is normal, cardiac output will remain the same or even decrease in the presence of increased left ventricular afterload.

The Impella RP is a microaxial flow catheter that uses an impeller attached to it and delivers blood from the right atrium towards the pulmonary artery. The first prospective trial that studied this device was RE-COVER RIGHT and was performed on patients with refractory right heart failure secondary to myocardial infarction or after cardiac surgery. The results showed 30-day survival rates of 73%, reduction of central venous pressure, improvement of cardiac index and weaning of inotrope and vasopressor support. The most common side effects were bleeding or hemolysis while thromboembolic events were not reported.

Mechanical ventilation

Mechanical positive pressure ventilation determines the increase of RV afterload by increasing transpulmonary pressures which can lead to the deterioration of the RV function.[32] Whenever possible, positive pressure ventilation should be avoided especially if RV failure is present; however, if mechanical ventilation is needed then the applied pressures should be controlled in such a manner that plateau pressure within the airways does not exceed 27cm H2O, and tidal volumes are kept low (6(-8)mL/kg, including low PEEP (8-12cm H2O).[33] [34]

[32] Jardin F, Delorme G, Hardy A, Auvert B, Beauchet A, Bourdarias J. *Anesthesiology* 721990966970

[33] Amato MB, Barbas CS, Medeiros DM et al. *N Engl J Med.* 1998, 338:347–354

[34] Zamanian RT, Haddad F, Doyle RL, Weinacker AB. *Crit Care Med.* 2007;35:2037–2050.

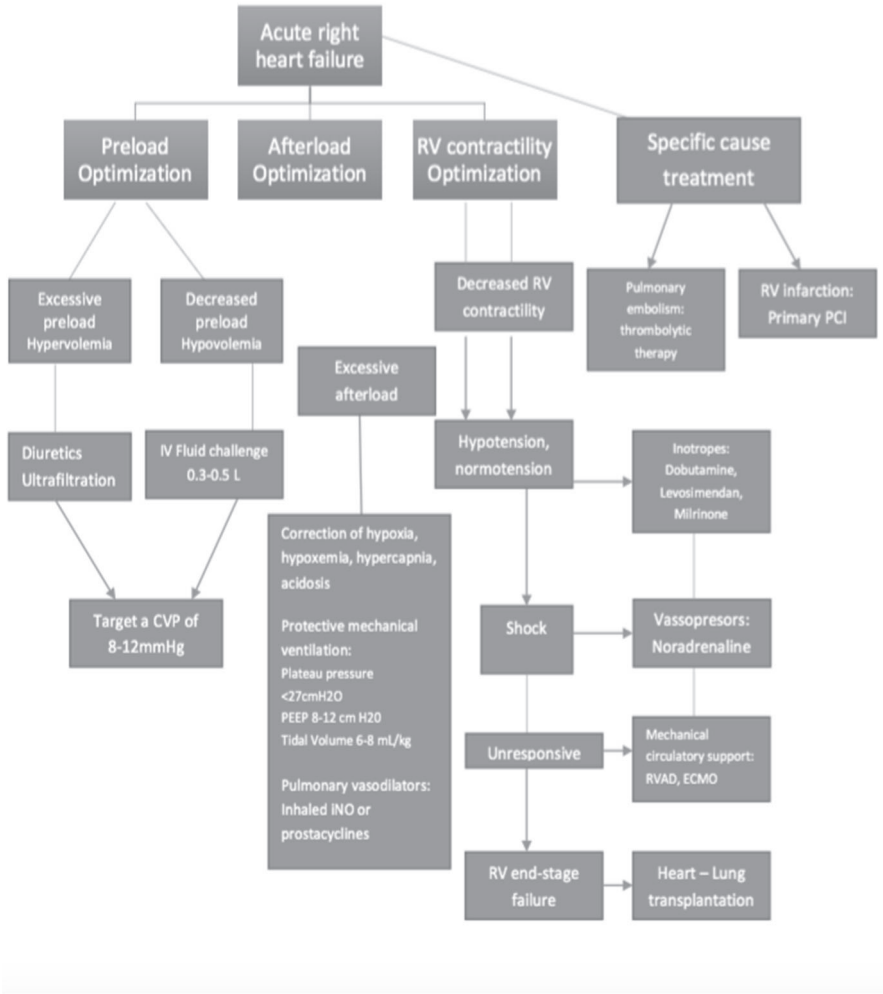

Figure 6. Management of ARHF

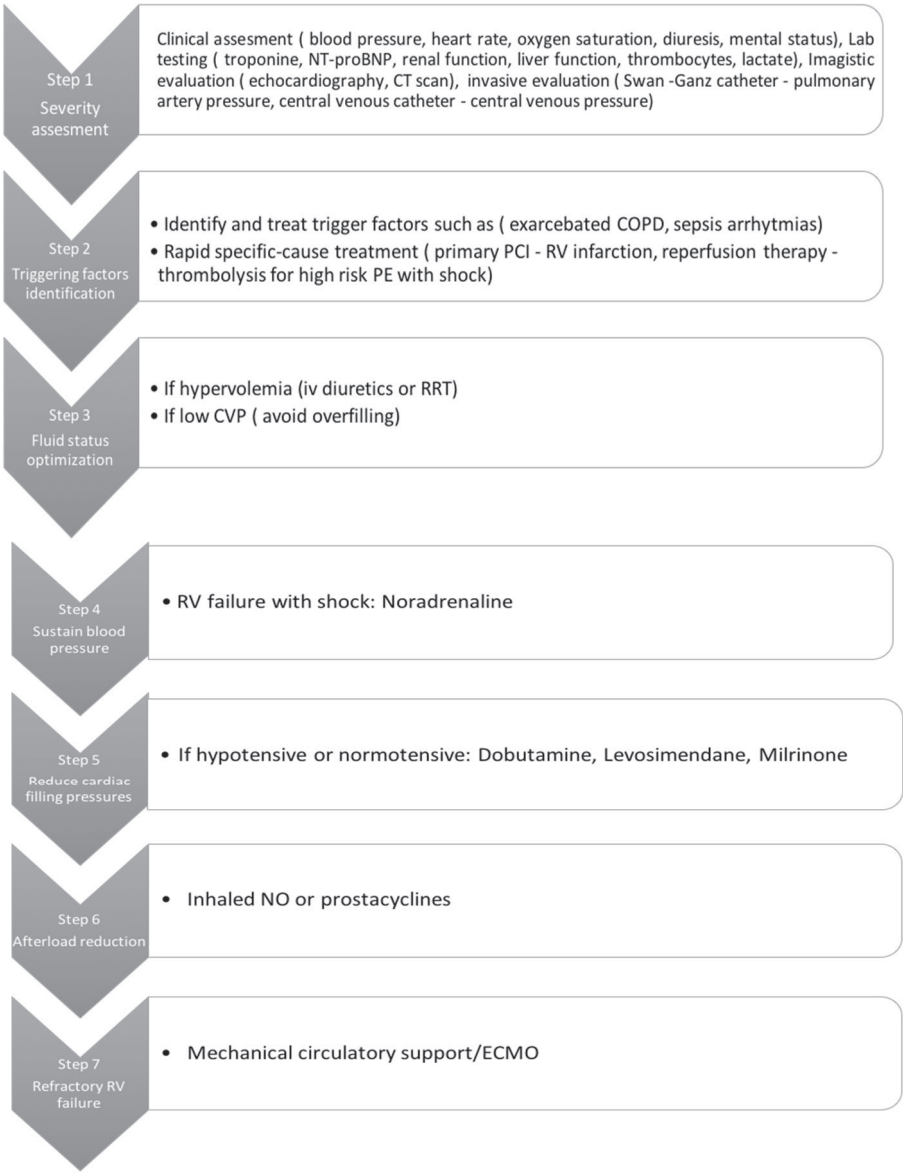

Figure 7. Stepwise approach to the management of ARHF

Table 6 – ARHF therapy

Agents	Properties	Side effects
Volume optimization ***Saline or ringer lactate (250 - 500mL – 15-30 min)***	RV failure with hypotension and normal CVP	Overdistension of the RV
Loop diuretics ***Iv furosemide (20 – 40 mg IV bolus, those on chronic diuretic therapy twice or equivalent the oral dose)***	RV failure with hypervolemia, sign and symptoms of congestion	Hypokalemia and worsening renal failure
Vasopressors ***Noradrenaline (0.2-1 ug/kg/min)***	Increase of systemic blood pressure (alpha 1 ++), RV inotropy (Beta 1 +), positive ventricle interactions, restoring of coronary grading perfusion	Excessive vasoconstriction with tissue hypoperfusion
Inotropes ***Dobutamine (2-20ug/kg/min)***	RV inotropy increasement (Beta 1 ++), lowers pulmonary vasculature resistance (Beta 2 +), lowers ventricular filling pressures	Risk of aggravating hypotension, arrhythmias
Levosimendane (0.1-0.2ug/kg/min)	Increases RV inotropy, pulmonary vasodilatation, improves RV/PA coupling	Hypotension arrhythmias
Mechanical circulatory support ***ECMO***	Short-term use, bridging therapy for transplantation	Local or generalized infections, thrombus formation
RVAD	Longer term use, bridging therapy for transplantation	

Oxygen therapy

Pathologies such as COPD, ARDS, PE, and interstitial pulmonary diseases manifest with arteria hypoxemia leading to the increase of pulmonary vasculature resistance and thus RV afterload impairment. In this case, oxygen therapy will lead to pulmonary artery vasodilation and lower the RV afterload.[35]

[35] Timms RM, Khaja FU, Williams GW. *Ann Intern Med.*1985;102:29-36

CHAPTER 7

CLINICAL CASES

MARIA PUSCHITA, IOAN RADU LALA

A curious case of Dr. Jekyll and Mr. Hyde

A 59-year-old male patient arrived in the emergency room complaining of persistent dyspnoea while resting with sudden onset two days before. His medical history showed that he was a chronic smoker, he had arterial hypertension grade II and that two weeks before he underwent a right knee arthroscopy intervention. The patient also remembered that 5 days before he had a swollen right calf that remitted by itself 3 days before, approximately at the time when the symptoms of dyspnoea started.

The physical examination showed a general influenced state, pale teguments, arrhythmic central pulse, a heart rate of 100 beats per minute, a blood pressure (BP) of 90/65mmHg, weak peripheral pulse, respiration rate of 22 per minute, normal lung sounds and blood saturation oxygen of 89%. The ECG showed atrial fibrillation with left axis deviation and non-specific repolarization abnormalities.

Because the patient arrived with persistent hypotension and was in an obvious life-threatening situation, the clinical probability of acute pulmonary embolism with high-risk was very likely. The rapid differential diagnosis had to be done to exclude cardiac tamponade, acute coronary syndrome, acute valvular dysfunction and acute aortic dissection. Immediate bedside echocardiography was performed showing: normal volume and wall motion of left cavities, right ventricle overloading with hypokinesia of the free wall (McConnell sign present), mild tricuspid regurgitation, mild pulmonary hypertension and a very striking mobile right atrium thrombus.

Blood samples showed raised troponin levels (0.207 ng/ml), increased D-dimers (>5 Ug/mL), acute liver and kidney injury with elevated liver enzymes (ALT = 158 U/L, AST=166 U/L) and creatinine levels (2.04 mg/dl).

Peripheral venous ultrasonography was also performed but showed no signs of deep vein thrombosis.

After the patient's rapid clinical and paraclinical assessment, the diagnosis of acute pulmonary embolism with acute right heart failure was very clear. According to the guidelines of the European Society of Cardiology (ESC)[54] because the patient had persistent hypotension, had an sPESI score of 2, showed signs of RV dysfunction on imaging test and elevated cardiac laboratory biomarkers, he presented a high early mortality risk.

The ESC guidelines also clearly state that the management of high-risk acute pulmonary embolism involves primary reperfusion treatment and that thrombolytic therapy is recommended as a first-class level of evidence B.[54] So we have a primary indication of pharmacological reperfusion but the question that comes to mind is: "according to what?" Because the ESC guidelines' only statements on pulmonary embolism with right heart thrombi are: therapeutic benefits of thrombolysis in these patients remain controversial and short-term mortality rates after this approach exceed 20%.[54]

And yet what does the literature say? Right heart thrombi were observed in only 4% to 18% of the cases with acute pulmonary embolism.[1] They are the result of either detachment from the lower limb deep vein system (in case of thrombosis) or in situ formation in cases of atrial fibrillation with persistent patent foramen ovale. The mortality of these treated patients is up to 28% and 100% in the case of untreated patients.[2] The European Working Group on Echocardiography described three patterns of right heart thrombi:

- Type A thrombi, which present a serpiginous shape, are highly mobile and are usually associated with deep vein thrombosis (they embolize from the large vein and are captured in transit by echocardiography), as well as pulmonary embolism;
- Type B thrombi, which are non-mobile, formed in situ under pre-existing cardiac abnormalities such as atrial fibrillation and persistent patent foramen ovale;
- Type C thrombi, which are quite rare, very mobile and show a high resemblance to cardiac myxoma.[3]

[1] Ferrari E, Benhamou M, Berthier F et al. *Chest.* 2005;121:1051-3.
[2] Rose PS, Punjabi NM, Pearse DB. *Chest*. 2002;121:806-14.
[3] Kronik G. *Eur Heart J.* 1989;10:1046-59.

Treatment in this situation involves three choices: lone parenteral anticoagulation, thrombolysis therapy or surgical embolectomy. What do clinical studies say about the treatment? There is no clinical randomized trial to compare and show the efficacy of these methods. Still, in one study performed on 160 patients with right heart thrombemboli, Rose et al. showed that the mortality rates of patients who underwent thrombolysis were quite low (11.3%) as compared to those who underwent heparin treatment (28.6%) or surgery (23.8%).[213] Athappan et al. demonstrated in a pooled analysis when comparing the efficacy of different therapies, that patients with right heart thrombi in transit and who are hemodynamically unstable present a better outcome when treated with thrombolytics (favorable odds 4.83(95%CI 1.52 -15.36)) than those treated with heparin alone or surgical embolectomy.[4] On the other hand, in a study in patients with right heart thrombi and pulmonary embolism, Torbiki et al. showed no difference in the mortality rates at 14 days and 3 months regardless of the treatment of choice: heparin, thrombolysis or surgery.[5]

Returning to our patient in the emergency room, we decided to administer him thrombolytic therapy (Alteplase 100 mg within 2 hours) concomitant with unfractionated heparin (80UI/kg iv bolus) and dobutamine (4ug/kg/min continuous perfusion to increase RV contractility). Six hours after the thrombolysis, BP was 128/75mmHG and the heart rate was 80 beats per minute with sinus rhythm (spontaneous conversion of atrial fibrillation) and normal peripheral pulse. The echocardiography showed the resolution of the thrombus in the right atrium, the systolic pulmonary artery pressure being 25 mmHG and the ejection fraction 60%. After the thrombolytic treatment, intravenous unfractionated heparin perfusion (18UI/kg with aPTT daily monitoring) was continued for 7 days and dobutamine was discontinued after 6 hours. The laboratory samples at 5 days after the thrombolytic therapy showed a decrease in liver enzymes (AST=42 U/L, ALT=45U/L) and creatinine levels (1.26mg/dl). During hospitalization, the patient underwent transoesophageal echocardiography (TEE) to check for patent foramen ovale (FOP) but was not detected. After 7 days, the patient was released home on oral therapy 2 x 5mg apixaban per day for 6 months.

The particularity of the case was that even though two scenarios were possible at the time of presentation in the emergency room (atrial fibrillation with FOP and thrombus formation or deep vein thrombosis - DVT with thrombus embolization), it turned out that the latter was the only

[4] Athappan G, Sengodan P, Chacko P, Gandhi S. *Vasc Med.* 2015;20:131–138
[5] Torbicki A, Galie N, Covezzoli A et al. *J Am Coll Cardiol.* 2003;41:2245-51.

culprit despite lack of signs of DVT. In favor of this mechanism was not only the undetected FOP at TEE but also the clinical history where the patient mentioned that he had recent knee intervention with calf swelling that had disappeared right about the time of the onset of the acute symptoms which could have been probably the moment of embolization and thus no thrombus was found on vascular venous Doppler. The patient was not known with atrial fibrillation so the mechanism of this arrhythmia might have been the increasing pressures in the right atrium secondary to an acute rise in afterload due to pulmonary embolism. Despite the hidden multi-faces (just as a type of "Mr. Hyde") of this particular diseases' presentation and lack of randomized controlled trials to test the efficacy of treatment, thrombolysis remains the handiest therapy in patients with high-risk pulmonary embolism and right heart thrombi in transit.

A contemporary case play of Hamlet

A 79-year-old male patient arrived in the emergency room with the following symptoms: acute onset of dyspnoea at rest and chest pain. The patient's history showed that he was known to have primary immune thrombocytopenia (for which he was taking azathioprine 100mg three times a day), autoimmune hemolytic anemia, deep vein thrombosis and left bundle branch block.

Physical examination showed: general influenced state, obnubilation, pale teguments, tachypnea, low blood pressure (80/50 mmHg), tachycardia (150 beats per minute), weak peripheral pulse, normal lung sounds, low saturation of oxygen (88%). The ECG depicted the left bundle branch block and atrial flutter with conduction 2:1. Fast bedside echocardiography revealed an overloaded right ventricle with hypokinesia of the free wall (positive McConnell sign), mild tricuspid regurgitation, a D shaped septum with normal volume and kinetics of the left ventricle, and an ejection fraction of 50%.

After the initial clinical evaluation, and excluding other diseases such as acute coronary syndrome, acute aortic dissection and cardiac tamponade, the primary diagnosis was clearly in favor of acute high-risk pulmonary embolism. Because of immediate availability, the patient underwent thoracic CT angiography which confirmed the diagnosis of pulmonary embolism (thrombus that extends from the bifurcation of the main pulmonary artery towards the main left and right pulmonary arteries and finally to the lobar pulmonary arteries). (Image 36) Blood samples also showed: raised troponin levels (0.242ng/ml), elevated D-dimers (>5

Ug/mL), a hemoglobin level of 11.8g%, 140.000/mm3 thrombocytes and creatinine levels of 1.77 mg/dl.

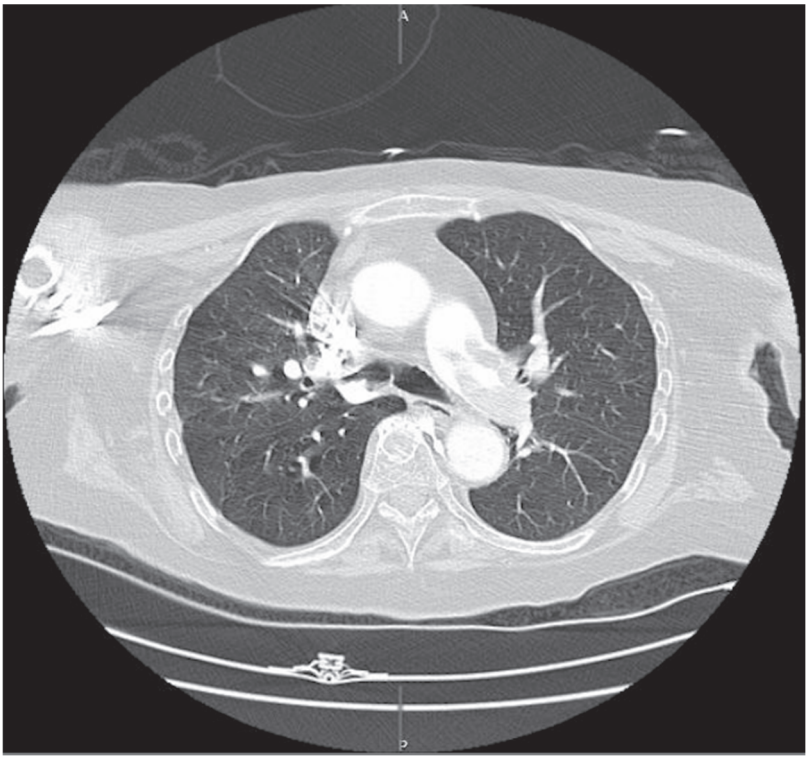

Image 36 – pulmonary thrombus at the main pulmonary artery bifurcation

According to the ESC guidelines and risk-adjustment, the definitive diagnosis was that of high-risk acute pulmonary embolism with cardiogenic shock and with a primary indication of reperfusion therapy.[54] Thrombolysis, according to the same guidelines, is considered as first-line therapy in cases of pulmonary embolism with hypotension or shock. Considering the patient's age and after carefully evaluating the contraindications of thrombolytic therapy, one thing came into attention: known bleeding risk or known bleeding diathesis which is an absolute contraindication of thrombolysis. But what is bleeding diathesis or what does it refer to? Bleeding diathesis is the existing susceptibility to bleed due to hypercoagulability in the context of a coagulopathy. Thrombocytopenia, a

condition the patient was known to have, seems to have fallen in this category of bleeding diathesis.

Having in mind the patient's bleeding risk and the fact that without reperfusion therapy, mortality could reach a rate of 100%, it was a situation of "to be or not to be"? An interdisciplinary approach was considered, so there was thorough consulting between the cardiologist, hematologist, emergency physician and anesthesiologist. Finally, the decision was made to administer thrombolytic therapy with careful monitoring of vital signs and blood count.

The patient was administered 100 mg of IV perfusion with alteplase for 2 hours concomitant with bolus IV of Heparin (80Ui/kg) and Noradrenaline 1ug/kg/min to maintain blood pressure. Atrial flutter converted spontaneously into sinus rhythm before starting thrombolytic therapy. Four hours after thrombolysis, the blood pressure was 130/70mmHg, the heart rate was 80 b/min and vasopressor therapy was discontinued. No hemorrhagic events were observed in the first 24 hours, repeated blood samples showed 135.000 mm3 thrombocytes, and the hemoglobin level was 11.5 mg/dl. One day after thrombolysis, repeated echocardiography revealed the right cavities of normal volume and kinetics. So everything turned out well, everybody made it so far but what to do next, considering that the patient needs to continue with parenteral anticoagulation for at least 5 more days? Takagi et al. proposed a treatment algorithm for anticoagulation in patients with a risk of thromboembolism and concomitant immune thrombocytopenia.[6] For patients with immune thrombocytopenia requiring anticoagulation who have current mild or no bleeding and with platelet counts > 50.000 mm3, anticoagulation therapy should be started as soon as possible with the regular therapeutic dose. If platelet counts < 50.000 mm3, anticoagulation therapy should be started but with half the therapeutic dose of unfractionated heparin or low molecular weight heparin. On the other hand, for patients with immune thrombocytopenia and current severe bleeding, anticoagulation is contraindicated.[217]

Therefore, parenteral anticoagulation with unfractionated heparin was continued for 5 days with daily monitoring of full blood count. The patient was released home with chronic oral anticoagulation Apixaban 5 mg twice a day. At discharge, the patient had the thrombocyte count of 284.000 mm3, the hemoglobin level of 12.2 g% and serum creatinine of 1.24 mg/dl.

Clearly, the particularity of this case stands in the massive pulmonary embolism with cardiogenic shock associated with bleeding

[6] Takagi S, Suzuki I, Watanabe S. *J Hematol Thrombo.* 2015, Dis 3: 185. doi:10.4172/2329-8790.1000185

diathesis. It was an "on edge situation" where rapid clinical judgment and experience overcame guideline recommendations. Most often, a multidisciplinary medical team is required to carefully assess such a patient, to evaluate the risks and benefits of the therapy, as well as for hemodynamic monitoring and decision making.

It should be noted that recent studies suggested the association between immune thrombocytopenia and the risk of thrombosis. Aledort et al. were the first to report 18 thromboembolic events in 186 patients with chronic immune thrombocytopenia.[7] Severinsen et al., in a matched controlled study from the Danish National Registry, reported on a cohort of 391 patients with immune thrombocytopenia, a twofold risk for venous thromboembolism compared with the general population.[8] The mechanisms behind paradoxical thrombosis events in immune thrombocytopenia are vague. It has been shown that antiphospholipid bodies increase in immune thrombocytes and might be the cause of thrombosis.[9] Several studies are indicating that patients with immune thrombocytopenia and increased antiphospholipid antibodies are more prone to develop thromboembolic events.[220] Additional factors that may be responsible for thrombosis in immune thrombocytopenia include the presence of high levels of prothrombotic platelet-derived microparticles and complement activation on antibody-coated platelets.[10]

Has anybody seen the spleen?

A 45-year-old patient was presented at the emergency room with the following complaints: dyspnoea at small exertion, fatigue, chest pain and cough. The symptoms debuted 2 weeks prior and had aggravated in the past 48 hours. The patient's history showed that he was a former smoker who quit smoking 5 years ago, who had no personal or family history of cardiovascular disease and who underwent splenectomy after a car accident. Clinical physical examination showed a general influenced state, a blood pressure of 130/80mmHg, a heart rate of 100b/min, normal lung sounds, no added heart sounds, jugular vein distension, hepatomegaly, oxygen saturation of 92 % and normal weight. ECG findings were: right axis deviation, right

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[8] Severinsen MT, Engebjerg MC, Farkas DK et al. *Br J Haematol*. 2011; 152(3):360–362.
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ventricle hypertrophy, right atrium hypertrophy, ST depression in D2, D3, aVF and V1-V3 (all signs of right heart overloading).

The first step was to assess the probability of pulmonary embolism by calculating Wells (1.5 points) and Geneva (5 points) scores which showed an intermediate clinical probability. The next step, according to the pulmonary embolism diagnostic algorithm was to measure D-dimers which resulted in being positive. Finally, the patient underwent thoracic CT angiography which ruled out pulmonary embolism and any parenchymal lung lesions.

Blood samples showed a normal troponin level, hypercholesterolemia, hyperuricemia and elevated NTproBNP (800 pg/ml). Echocardiography revealed dilated right cavities, normal left cavities, the paradoxical motion of the interventricular septum, diastolic dysfunction of the left ventricle, decreased tricuspid annulus plane systolic excursion (11 mm), mild tricuspid regurgitation with severely increased systolic pulmonary artery pressure (70 mmHg) with a preserved ejection fraction of 50%.

The patient was admitted to the Cardiology unit with the diagnosis of acute right heart failure. He was immediately put on intravenous diuretics to reduce preload, small doses of non-dihidropiridinic calcium channel blockers to reduce afterload and ACE inhibitors for further prevention of cardiac remodeling.

Thus far, all the findings led to arterial pulmonary hypertension, the decompensated form. Based on the ESC Pulmonary Artery Hypertension guidelines, further investigations were carried out in order to see what type of PAH was involved so that specific PAH-treatment could be started as soon as possible.[132] The CT angiography already ruled out chronic thromboembolic pulmonary hypertension. Spirometry was carried out to rule out COPD which showed normal pulmonary function tests. Other tests such as liver function, thyroid function, HIV antibodies, and connective tissue disease antibodies were all normal.

Cardiac catheterization was performed to measure mean arterial pulmonary pressure. The results from cardiac catheterization revealed the following: systemic oxygen desaturation of 90%, maximum pulmonary artery pressure 78 mmHg, mean pulmonary artery pressure of 47mmHg, PCWP of 8mmHg and pulmonary vascular resistance of 11 U Woods. The diagnosis of idiopathic PAH was confirmed and the patient was started on an endothelin receptor antagonist, Macitentan 10 mg once a day. After 7 days of treatment, his functional class improved significantly from WHO-FC II to WHO-FC I, the 6-minute walk test was 97 % normal, NT proBNP levels decreased to 250 pg/ml and systolic pulmonary artery pressure at echocardiography was 40 mmHg.

The question which arose at this point was the following: was it really idiopathic pulmonary artery hypertension (as there was no family history of this disease) or did we forget to rule out something? When looking more closely at the PAH classification, group 5 (PAH from unclear or multifactorial mechanisms) mentions hematological disorders, more exactly splenectomy. The patient's history showed that he had splenectomy after a car accident. Could this specific clue be the missing piece of the puzzle?

The initial connection between splenectomy and pulmonary hypertension was observed in patients with thalassemia and hereditary stomatocytosis.[11] [12] [13] The time range estimated between splenectomy and the development of pulmonary hypertension is long (2 to 35 years) and in the presented case the time of onset was 8 years.[14] [15] Over 50% of splenectomized patients with thalassemia showed at autopsy microthrombemboli in the pulmonary vasculature. In a study in patients with pulmonary hypertension, 8% of those believed to have CTPH had a history of splenectomy and 2.5% in those with IPAH.[226] An increased incidence of pulmonary hypertension was described in patients with splenectomy after trauma.[225] As splenectomy is associated with venous thrombosis in general due to reactive thrombocytosis, it was postulated that pulmonary hypertension might occur through the thromboembolism of the pulmonary microvasculature.[16] Persistent thrombocytosis after splenectomy predisposes patients to pulmonary hypertension.[17] Also, it was demonstrated that patients who undergo splenectomy have increased levels of anion phospholipids which might explain thrombogenicity in splenectomized patients.[18] Anion phospholipids promote the delay of thrombus resolution and inhibit angiogenesis and thus vasculature remodeling.[230] In experimental animal studies on splenectomized mice, micro platelet-derived particles are significantly increased and act as procoagulants for thrombus formation

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including in situ.[230] [19] Post-splenectomy megakaryocyte migration and release of platelet precursors into the pulmonary capillary bed have been described to lead to in situ thrombus formation.[20] [21] Also, after splenectomy, there is evidence of increased endothelin-1 which is a potent pulmonary vascular constrictor.[22]

The mechanism behind splenectomy and pulmonary hypertension development is complex and multifactorial and should always be taken into account where there is history and no other explained causes for increased pulmonary arterial pressures. Because it takes a long time for pulmonary hypertension to develop in these patients, yearly echocardiographic screening for pulmonary hypertension should be done and thus pharmacological intervention should be done from the early stages of the disease.

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CHAPTER 8

CLINICAL PROTOCOL FOR ACUTE RIGHT HEART FAILURE

IOAN RADU LALA

Regardless of the cause of acute right heart failure, the initial phase is to ameliorate symptoms of dyspnoea and anxiety, to support the RV output and manage the consequences of RV failure.

The second phase would be to determine the etiology of ARHF and administer specific treatment. A useful management algorithm is to determine the presence of pulmonary hypertension, primary myocardial disease or pericardial disease as soon as possible. A close history taking and ECG can quickly guide you to an acute condition of RHF such as PE or RV myocardial infarction. The next step is to perform transthoracic bedside echocardiography which can rapidly assess the LV structure and function, the pericardial sack and also the integrity of the valves. At this level, if there is a high suspicion of PE immediate CT angiography should be performed. After eliminating LV failure, acute valvulopathy, and pericardial effusion, the next step would be to focus on the lungs, the second most common cause of RHF after left heart disease. This implies functional lung tests, high-resolution CT, overnight oximetry. Finally, liver disease, kidney disease, thyroid disease and rare connective tissue diseases should all be ruled out. Careful vital signs, ECG and hemodynamic parameters including central venous pressure monitoring should be done on a routine basis. If by now, despite adequate therapy (including supportive and specific therapy), the patient is still hemodynamically unstable, advanced life support therapy such as ECMO or RVAD should be sought for temporary use until the patient is stabilized or as bridging to emergency transplantation.

In the following, we propose a rapid clinical approach and step by step management of acute right heart failure syndrome according to aetiologies.

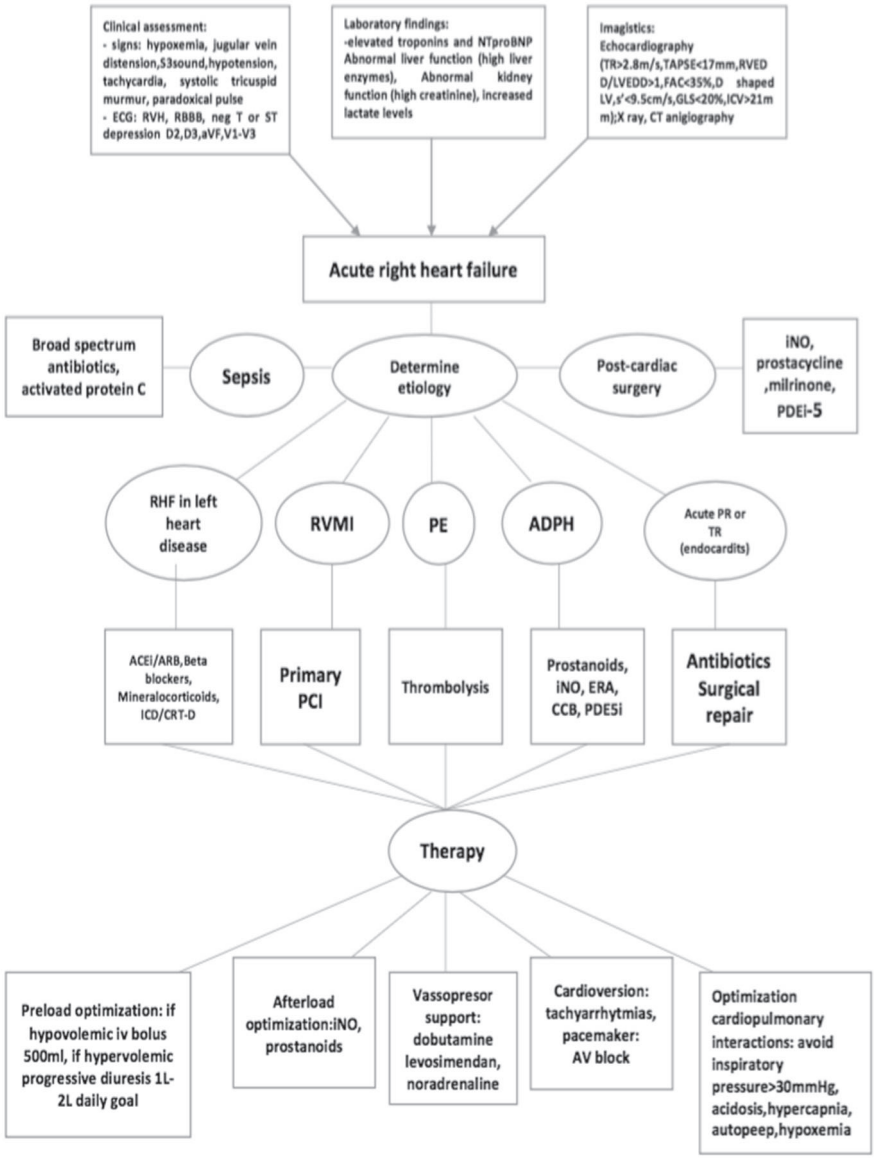

Figure 8. ARHF clinical protocol; RVMI- right ventricular myocardial infarction, ADPH – acute decompensated pulmonary hypertension, PE- pulmonary embolism, PR – pulmonary regurgitation, TR – tricuspid regurgitation, iNO- inhaled nitric oxide, CCB-calcium channel blockers, ERA- endothelin receptor antagonists, PDE5i- phosphodiesterase inhibitors

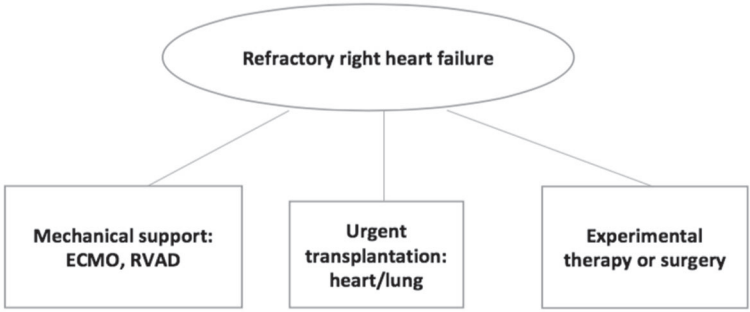

Figure 8 – ARHF clinical protocole cont.

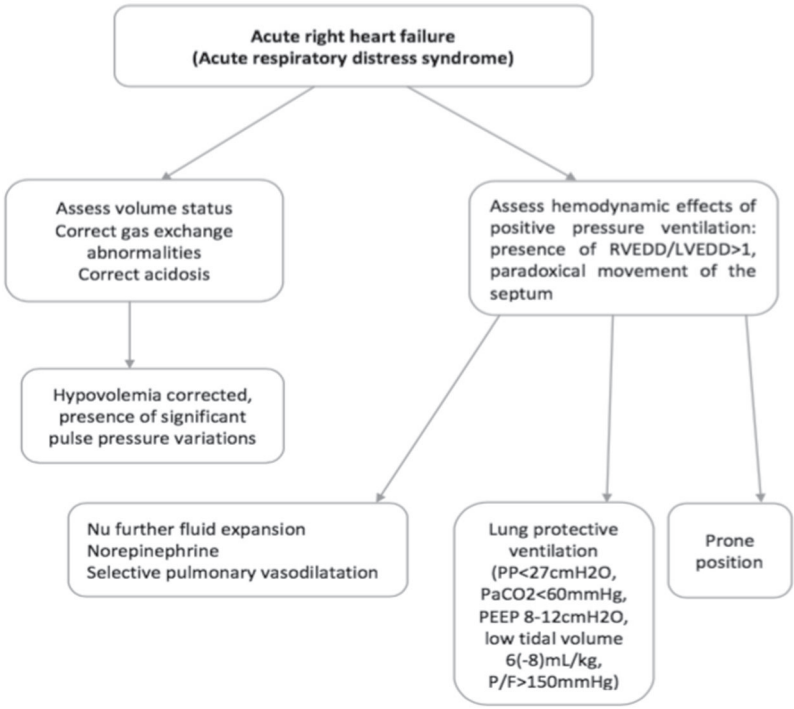

Figure 9. ARHF clinical protocol in ARDS; RVEDD – right ventricular end-diastolic diameter, LVEDD – left ventricular end-diastolic diameter, PP – pulse pressure, PEEP- positive end-expiratory pressure

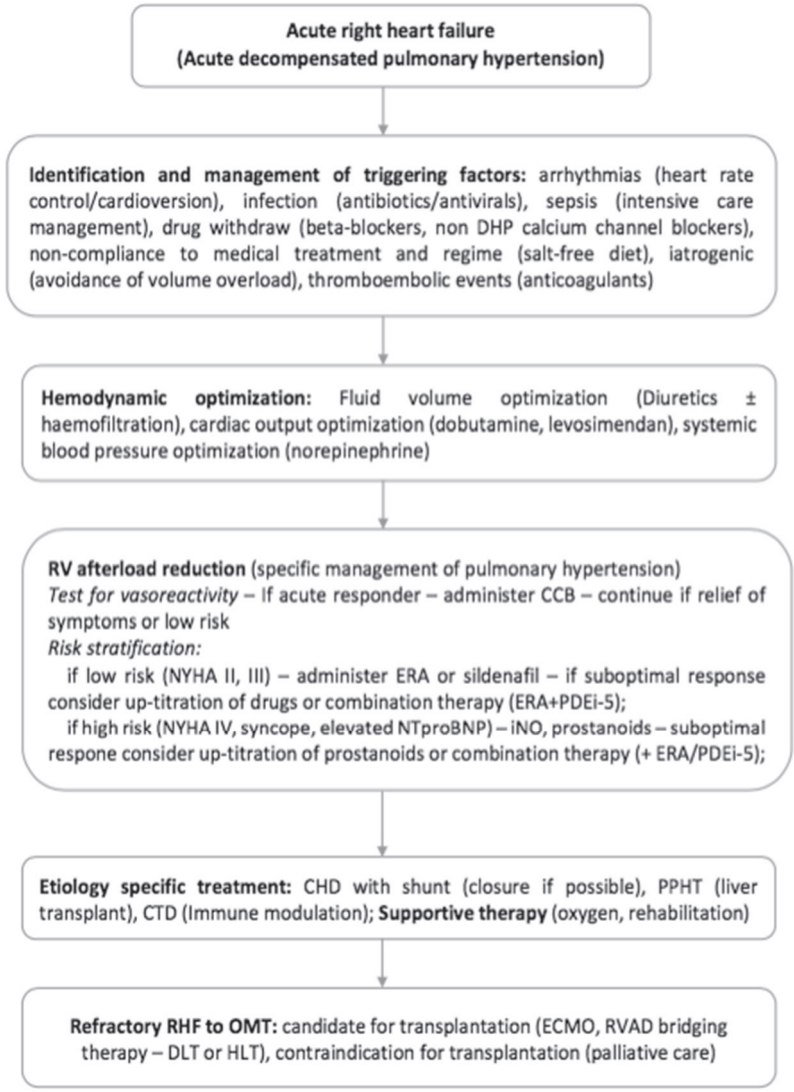

Figure 10. Step by step clinical protocol in ARHF; CTD- connective tissue disease, CHD- congenital heart disease, OMT- optimal medical treatment, ERA- endothelin receptor antagonists, PDEi5- phosphodiesterase inhibitors, DLT- double lung transplant, HLT- heart-lung transplant, PPHT- porto pulmonary hypertension

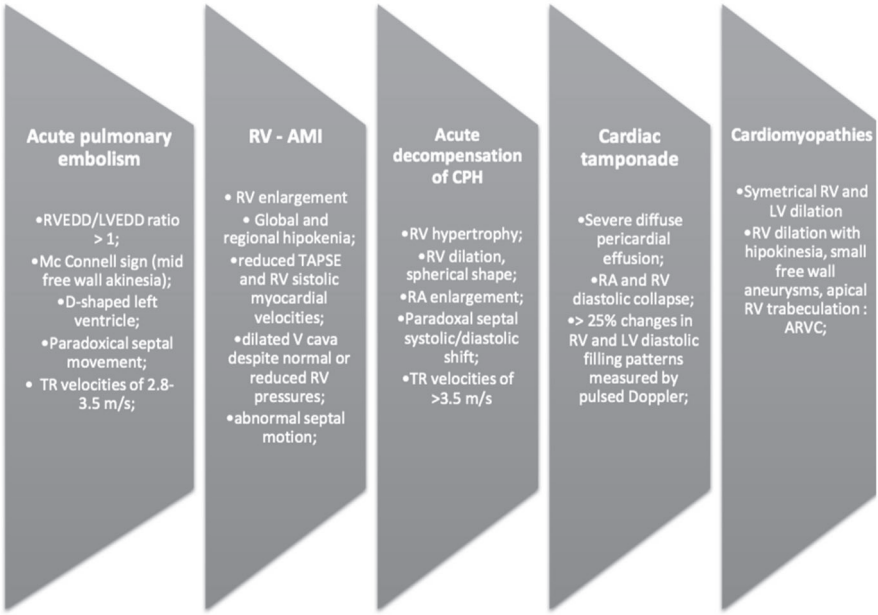

Figure 11. ARHF echocardiographic assessment according to etiology

CHAPTER 9

RIGHT HEART FAILURE AND TRANSPLANTATION

IOAN RADU LALA

Heart transplant is the recommended treatment for patients with end-stage heart failure. To improve survival rates and quality of life after transplant, a careful selection should be made on those patients with end-stage heart failure. Exclusion criteria are as following: active infection, cerebrovascular disease, irreversible pulmonary hypertension, cancer, irreversible chronic kidney disease, systemic disease, obesity, alcohol or drug consumption.[1]

According to the ACC/AHA guidelines, patients who should undergo cardiac transplantation are in: refractory cardiogenic shock that requires mechanical support device, cardiogenic shock requiring continuous intravenous inotropic therapy, a peak VO2(VO2max) less than 10 ml/kg per min, NYHA class III and IV with maximal medical therapy and resynchronization therapy, recurrent life-threatening ventricular arrhythmias despite the presence of an implantable intracardiac defibrillator (ICD) and antiarrhythmic therapy or ablation therapy, congenital hear failure without pulmonary hypertension.[2]

When it comes to right heart failure, patients with irreversible cardiogenic shock secondary to right ventricular infarction despite revascularization treatment, fulminant myocarditis with acute right heart failure and refractory cardiogenic shock or advanced arrhythmogenic right ventricular cardiomyopathy despite ICD therapy are suitable candidates for heart transplant.

Patients with advanced right heart failure secondary to left heart disease should be carefully evaluated for heart transplant. The reason for this is that frequently due to prolonged increased right atrial pressures and

[1] Mancini D, Lietz K. *Circulation.* 2010;122:173-83.
[2] Jessup M, Abraham WT, Casey DE et al. *Circulation.* 2009;119:1977-2016.

systemic venous hypertension these patients present cardiac cirrhosis which is a predictive factor for early mortality after cardiac surgery and major complications such as infection, bleeding and hepatic failure.[3] The hallmark of cardiac cirrhosis is the presence of ascites. Besides cardiac cirrhosis, there are two other forms of clinical presentation of patients with right heart failure: those with alterations of functional liver tests and those with ischemic hepatitis.[4] [5] Also, variants of cardiac cirrhosis are described: from focal, incomplete to complete cirrhosis with broad fibrous transformation of the liver. Patients with mild cardiac cirrhosis can tolerate cardiac surgery although studies have shown that patients with advanced liver cirrhosis are prone to major postoperative complications and an in-hospital mortality rate of 50% up to 100%.[6] [7] A study performed by Hsu et al. on a population undergoing heart transplantation, showed that the operative mortality rate was 50% in those with extreme right ventricular failure and refractory ascites or advanced liver failure.[385] The rates were similar to patients with non-cardiac liver cirrhosis undergoing surgery.

Heart transplantation for patients with advanced irreversible liver disease is an absolute contraindication, as recommended by the ACC/AHA guidelines.[384] This is why a liver biopsy should be done to assess the severity of cardiac cirrhosis in patients with right heart failure and ascites, in need of heart transplant.

For patients with right heart failure in the context of irreversible pulmonary artery hypertension, congenital heart disease with Eisenmenger syndrome or parenchymal pulmonary affection, things are more complicated as they usually require heart-lung transplantation.[8] Survival after heart-lung transplant has improved over time from 3 to a median of 10 years and this is due to improved patient selection criteria, the advances in surgical techniques, improvement of immunosuppressive regimens and better management of factors associated with increased morbidity and mortality.[9]

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[9] Yusen RD, Edwards LB, Dipchand AI et al. *J Heart Lung Transplant* 2016;35:1170-84.

Nevertheless mortality rates still remain high and are mostly associated in the first month with graft failure, technical complications, and infection; one year after the transplant, bronchiolitis obliterative syndrome and chronic allograft dysfunction are predominant.[390]

According to the International Society of Heart and Lung Transplantation Registry (ISHLT), on a population of 959 patients, the most common indication for heart and lung transplantation was idiopathic pulmonary artery hypertension, congenital heart disease and cystic fibrosis.[10] However, more recent data showed changes in the last decade and the most common indication for heart and lung transplantation remained congenital heart disease.[390] This is likely because since certain studies showed no statistical difference in post-transplant survival between heart-lung transplantation and double lung transplantation for patients with idiopathic pulmonary artery hypertension and right ventricular failure.[11] Moreover, Gorter et al. showed the recovery of right ventricular function after double lung transplant with an improvement of right ventricular ejection fraction, the decrease of right ventricular volumes, area of the tricuspid valve annulus and left ventricular eccentricity index all confirmed by cardiac MRI.[12] Currently, there is no threshold for determining unrecoverable right ventricular function before transplant to consider heart-lung transplantation. The ESC on pulmonary artery hypertension guidelines recommends that all patients with inadequate clinical response to initial monotherapy or combination therapy, class WHO-FC III and IV, should be considered for lung transplantation.[132] It is reasonable to consider the etiology of pulmonary hypertension, as patients with connective tissue disease or pulmonary veno-occlusive disease have the worst prognosis and are frequently unresponsive to medical treatment than those with idiopathic PAH or congenital heart disease and should be listed early for lung transplantation management before irreversible right ventricular function.[13] Overall, survival rates after lung transplantation remain up to 75% in patients with pulmonary artery hypertension.[14]

The RV function is the main determinant of outcome in patients with heart failure and whenever reversibility of function is futile, heart, heart-lung or lung transplantation should be taken into account.

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Conclusions

Ioan Radu Lala

Acute RV failure is a complex life-threatening syndrome with different clinical scenarios for which appropriate and prompt management requires a good knowledge of RV structure and function. It is important to rapidly identify possible triggering factors for known RHF and diagnose etiologies behind the acute episode so that specific treatment be administered.

The most common cause of RV failure is left heart disease followed by interstitial and parenchymal lung disease. For many years, the RV was disregarded in the management of left heart failure when its failure is the final pathway of left-sided heart disease. RV failure in patients with left-sided heart failure carries the worst prognosis. Furthermore, the presence of RV dysfunction from the early stages of the disease influences the outcome. Pulmonary hypertension is the most common cause of RHF and it is the link between LHF and the RV. Any acute increase of RV afterload will determine the disproportionate rise of RV filling pressures which will counteract the physiological adaptation mechanisms leading to RV failure and thus lead to a series of effects that will eventually compromise LV function. The most feared scenario of acute RV failure is a shock caused not only by reduced RV contractility or output but also by decreased LV filling and output. Anterograde systemic hypoperfusion together with retrograde systemic congestion will lead to multi-organ failure and thus worsening prognosis and survival.

It is essential to master RV supportive therapy, by reduction of afterload, reversal or avoidance of hypoperfusion, improvement of contractility and last but not least treatment of underlying pathology.

Contrary to old beliefs, fluid management of acute RV failure has changed in recent years and volume loading by intravenous fluid administration should be avoided because of the potential increase of filling pressures with consequent RV overdistension, increased wall stress, decreased contractility, altered diastolic ventricular interdependence, LV impairment and finally reduced cardiac output. Other specific RV management failures include: thrombolysis in case of PE, primary PCI in case of RVMI, diuretics rather than fluids, oxygen therapy in case of SO2 < 90% to avoid pulmonary

vasoconstriction, selective pulmonary vasodilators to reduce RV afterload, noradrenaline if in shock, inotropic agents to improve RV contractility and lung-protective mechanical ventilation in case of ARDS.

Despite the improvement in management and the existence of guidelines, acute RV failure remains a serious medical emergency with many uncertainties that carries a poor outcome without proper intervention. That is why clinical trials are needed to test the efficacy and safety of pharmacological, surgical and mechanical interventions for the treatment of this highly burdening disease.

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