INTRODUCTION

Pulmonary hypertension PH is a haemodynamic and pathophysiological disorder associated with a variety of cardiovascular and respiratory conditions, including congenital heart disease (CHD) but are all defined by a mean pulmonary arterial pressure of 25 mm Hg or greater at rest as assessed by right heart catheterization ***(Galiè et al., 2016).***

The classification scheme was updated to recognize five groups of pulmonary hypertension ***(Simonneau et al., 2013)***:

- Pulmonary arterial hypertension
- Pulmonary hypertension due to left heart disease
- Pulmonary hypertension due to lung diseases and/or hypoxia, chronic thromboembolic pulmonary hypertension (CTEPH), and Multifactorial pulmonary hypertension.

Pulmonary arterial hypertension (PAH) is a complication of congenital heart disease, in turn, impacts on quality of life and survival of these patients ***(Chessa et al., 2017)***.

However, the importance of different hemodynamic parameters and their correlation with exercise capacity is unclear. We investigated several hemodynamic parameters measured by right and left echocardiographic assessment and evaluate which parameter is the most independent predictor of functional capacity determined by 6-minute walk test.

AIM OF THE WORK

Study the correlation between echocardiographic hemodynamic parameters and functional capacity in patients with pulmonary hypertension due to congenital heart disease and detection which parameter is the most independent predictor of functional capacity in patients with PAH-CHD.

Chapter (1):

PULMONARY HYPERTENSION

Definition: Pulmonary hypertension is a common, complex group of disorders that result from different pathophysiologic mechanisms but are all defined by a mean pulmonary arterial pressure of 25 mm Hg or greater measured by RHC ***(Galiè et al., 2016).***

PAH–CHD represents a preventable form of PAH in the recent decades, advances in diagnostic procedures and cardiac surgery have resulted in the prevention of PAH in most children with CHD and systemic-pulmonary shunts in Western countries; this is, unfortunately, not yet the case in developing countries ***(Chessa et al., 2017).***

The clinical classification of pulmonary hypertension according to international pulmonary hypertension guidelines *(Simonneau et al., 2013):*

1- Pulmonary arterial hypertension.

2- Pulmonary hypertension due to left heart disease.

3- Pulmonary hypertension due to lung diseases and/or hypoxia.

4- Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions.

5- Pulmonary hypertension due to unclear and/or multifactorial mechanism.

Pathophysiology:

All congenital heart defects, in which a large intra or extra cardiac communication allows unrestricted pressure and volume overload of the pulmonary circulation, can lead to the development of pulmonary arterial hypertension (PAH), unless repair takes place in early childhood ***(Dimopoulos et al., 2014).***

Pulmonary arterial hypertension (PAH, group 1) is a clinical condition characterized by the presence of pre-capillary PH and pulmonary vascular resistance >3 Wood units, in the absence of other causes of pre-capillary PH ***(Galiè et al., 2016).***

Clinical classification of pulmonary arterial hypertension associated with congenital heart disease (Galie et al., 2016):

1. Eisenmenger's syndrome (ES):

Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of PVR and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present.

2. PAH associated with prevalent systemic-to-pulmonary shunts:

- Correctable.
- Non-correctable.

Includes moderate to large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunting is still prevalent, whereas cyanosis at rest is not a feature.

3. PAH with small/coincidental defects:

Marked elevation in PVR in the presence of small cardiac defects (usually ventricular septal defects <1 cm and atrial septal defects < 2 cm of effective diameter assessed by echo), which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. Closing the defects is contra-indicated.

4. PAH after defect correction:

Congenital heart disease is repaired, but PAH either persists immediately after correction or recurs/develops months or years after correction in the absence of significant postoperative haemodynamic lesions.

Additional types of pulmonary vascular disease related to CHD (Dimopoulos et al., 2014)

1. Segmental pulmonary hypertension:

In these cases, part of the lung vasculature develops pulmonary vascular disease, while other areas may be normally perfused or hypoperfused.

2. Raised PVR in Fontan patients, patients with a previous Fontan-type operation can develop a rise in PVR, despite low pulmonary arterial pressure.

Anatomical-pathophysiological classification of congenital systemic-to-pulmonary shunts associated with pulmonary arterial hypertension (Simonneau et al., 2004):

1. Type:

1. Simple pre-tricuspid shunts:

Atrial septal defect (ASD)

1. Ostium secundum.
2. Sinus venosus.
3. Ostium primum.
4. Total or partial unobstructed anomalous pulmonary venous return.

2. Simple post-tricuspid shunts:

1. Ventricular septal defect (VSD).
2. Patent ductus arteriosus (PDA).
3. Combined shunts: describe combination and define predominant defect.

4. Complex congenital heart disease:
   - Complete atrioventricular septal defect.
   - Truncus arteriosus.
   - Single ventricle physiology with unobstructed pulmonary blood flow.
   - Transposition of the great arteries with VSD (without pulmonary stenosis) and/or patent ductus arteriosus.
   - Other.

2. Dimension (specify for each defect if more than one congenital heart defect exists):

1. Haemodynamic (specify Qp/Qs)
   - Restrictive (pressure gradient across the defect)
   - Non-restrictive

2. Anatomical
   - Small to moderate (ASD ≤2.0 cm and VSD ≤1.0 cm)
   - Large (ASD >2.0 cm and VSD >1.0 cm)

3. ***Direction of shunt:***

1. Predominantly systemic-to-pulmonary.
2. Predominantly pulmonary-to-systemic.
3. Bidirectional.

4. ***Associated cardiac and extracardiac abnormalities.***

5. ***Repair status***

1. Unoperated.

2. Palliated (specify type of operation/s, age at surgery)

3. Repaired (specify type of operation/s, age at surgery)

Epidemiology:

PAH accounts for only 3% to 4% of all causes of PH, the vast majority being due to left heart (78–80%) and/or lung (10–12%) diseases ***(D'Alto et al., 2015).***

Congenital heart disease accounts for nearly one-third of all major congenital anomalies, nearly 1 in 100 children are born with congenital heart disease (6–10/1000 live births), making it one of the most common inborn birth defects worldwide ***(Van der Linde et al., 2011).***

4–28% of those patients are expected to develop PAH ***(D'Alto and Mahadevan, 2012).***

Approximately 3% to 10% of adults with congenital heart disease (ACHD) will develop pulmonary hypertension (PH) ***(Van Riel et al., 2014).***

The heterogeneity of the lesions included in CHD run the gamut from simple septal wall defects to complex cardiac lesions associated with single ventricle disease.

Improvements in surgical correction or palliation concomitant with advancements in the ability to detect CHD lesions have allowed improved survival into adulthood ***(Van der Bom et al., 2012).***

Increasing survival may be beneficial. However, survival also carries the burden of associated complications, such as the development of pulmonary arterial hypertension (PAH), bringing new obstacles in the management of CHD.

Epidemiological data on APAH-CHD and ES has been gleaned from natural history studies and recent studies utilizing PAH registries ***(Frank et al., 2015).***

The true number of both pediatric and adult APAH-CHD patient is not known as many patients are likely lost to follow up, especially upon completion of the repair ***(Mackie et al., 2009).***

Nonetheless, APAH-CHD prevalence differs between the adult and pediatric population ***(Frank et al., 2015).***

Data from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL), the PAH registry from France, the PAH registry from the Netherlands (CONCOR), the Scottish Morbidity record, and a group of tertiary European PH centers (Euro Heart Survey) reveal a prevalence of APAH-CHD in 10%, 11%, 4%, 23%, and 28% of all PAH cases, respectively ***(Frank et al., 2015).***

This slight variability likely reflects inclusion criteria differences and ability to recruit patients.

Eisenmenger's syndrome has a prevalence of 1.1%, 12.3%, and 7.6% of all APAH-CHD according to the CONCOR registry, Euro Heart Survey, and REVEAL registry, respectively ***(Duffels et al., 2007), (Engelfriet et al., 2007).***

Patients with PAH and coincidental CHD represent the smallest subgroup of the overall PAH–CHD population: they only account for 5% in a recent analysis of a large cohort of PAH–CHD patients ***(Manes et al., 2014).***

In the Euro Heart Survey, the prevalence of postoperative PAH in adults with previously corrected atrial septal defect (ASD) or ventricular septal defect (VSD) was 12% and 13%, respectively ***(Engelfriet et al., 2007).***

Pathophysiology:

Pulmonary arterial hypertension is a serious complication of congenital heart disease, particularly in patients with left-to-right (systemic-to-pulmonary) shunts. Persistent exposure of the pulmonary vasculature to increased blood flow and pressure may result in vascular remodelling and dysfunction. This leads to increased pulmonary vascular resistance (PVR) and, ultimately, to reversal of the shunt and development of Eisenmenger's syndrome ***(D'Alto et al., 2012).***

Pulmonary hypertension can develop at any stage of a CHD patient's life and, when it does, impacts on quality of life, exercise capacity, and morbidity and mortality ***(Dimopoulos et al., 2014).***

The pathophysiology involved in aberrant pulmonary vascular remodeling in PAH associated with CHD arises early in disease. Protection of the pulmonary vascular bed is an innate function of the cardiopulmonary system initiated in fetal life. The low resistance of the placental circulation and high resistance of the pulmonary circulation, due in some part to hypoxia, ensures that a very low percentage of the cardiac output reaches the pulmonary vascular bed. Much of this is accomplished through shunting of blood through the foramen ovale and ductus arteriosus. Postnatal changes in the pulmonary vasculature occur immediately with the first breath. Theory suggests that an increase in alveolar distension providing

mechanical forces and exposure to oxygen both play some part in the drop in PVR and, thus, increase in pulmonary blood flow. An increase in pulmonary blood flow leads to an increase in left atrial filling and pressure, closing the foramen ovale. Over the next few days, exposure to oxygen and other vasoconstrictor factors closes the ductus arteriosus, further increasing pulmonary blood flow ***(Rudolph et al., 2009).***

The equalization of ventricular pressures seen in fetal life continues postnatally in the setting of a large communication between the aorta and pulmonary artery or right and left ventricles. Thus, pulmonary arterial (PA) pressures will remain high with a significant delay in in the normal decrease in PVR. Normally, the pulmonary arteries remodel and thin postnatally, but in the presence of high PVR, there can be persistence in the thickness of the medial layer of pulmonary arteries. Eventually, the PA pressures fall and right ventricular (RV) compliance decreases. The resultant increased pulmonary blood flow can elicit shear stress and mechanical stretching of the pulmonary vessels. These events may lead to abnormal endothelial cell activation and set off a cascade of growth factors, vasoconstrictors, and extracellular matrix degradation. In addition, over time the medial layer can extend peripherally to the normally non-muscularized pulmonary arterioles, reducing the compliance of the vessel wall and thus further increasing PVR. Over time, these changes lead to significant PAH. Eventually, the right ventricular pressure becomes

suprasystemic, and the shunting of blood through the defect reverses or becomes bidirectional ***(Frank et al., 2015).***

While all defects associated Eisenminger share some common pathophysiological mechanisms, there are clearly differences as patients present with ES at various stages of life. Pre-tricuspid shunts such as atrial defects tend to present later in life while post-tricuspid shunts present as early as infancy in the case of some patients with AVSDs ***(Moceri et al., 2015).***

PAH predominantly affects the small resistance pulmonary arteries, characterized by intimal hyperplasia, medial hypertrophy, adventitial proliferation, in situ thrombosis, and inflammation ***(Rich et al., 2010).***

Plexiform arteriopathy, which refers to capillary-like, angioproliferative vascular channels within the lumina of small muscular arteries, is the pathognomonic lesion of PAH ***(Tuder et al., 2013).***

Plexiform lesions often appear at branch points, frequently have fibrin thrombi within the lumen, and have varying channel diameter, giving them a disordered appearance ***(Rich et al., 2010).***

The endothelium is a source of both vasoconstrictor and vasodilator agents that are maintained in a delicate balance. Upon abnormal activation by insults such as shear stress, mechanical stretch, or hypoxia, the balance of vasoactive mediators can be

disrupted. A decrease in the production of vasodilators such as nitric oxide-cyclic guanosine monophosphate (NO-cGMP) and prostacyclin (PGI_2) concomitant with an increase in the release of vasoconstrictors such as endothelin (ET-1), Rho GTPases, and thromboxane can lead to abnormal activation of cell signaling pathways causing aberrant vascular remodeling ***(Morrell et al., 2009).***

In the neonatal lamb systemic-to-pulmonary shunt model, there is not only increased ET-1 production but also diminished NO-cGMP signaling ***(Fratz et al., 2011).***

Similarly, phophodiesterase-5 (PDE5), an enzyme involved in the degradation cGMP, is upregulated in another animal model of flow-induced PH ***(Rondelet et al., 2004).***

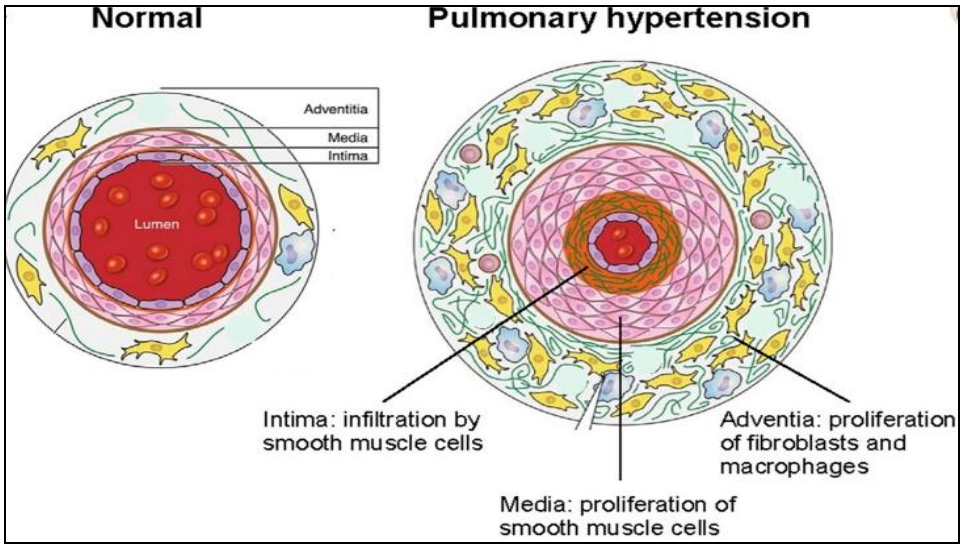

Figure (1): Schematic cross-sectional representation of a normal pulmonary arteriole and a pulmonary arteriole affected by pulmonary hypertension ***(Pugliese et al., 2015).***

The Right ventricle pathophysiology:

A recent study points out the physiological differences between pre-tricuspid and post-tricuspid shunts. Pre-tricuspid shunts such as an atrial septal defect have impaired RV function compared to post-tricuspid shunts ***(Moceri et al., 2015).***

Systemic PA pressures occur early in life in post-tricuspid shunts and expose a RV that still contains some characteristics of a more adaptive fetal-like RV ***(Hopkins and Waggoner, 2002).***

Because pre-tricuspid shunt patients develop pulmonary vascular disease later in life, they may have lost any remnant of RV plasticity to develop adaptability to high PA pressures ***(Frank et al., 2015).***

The chronic elevation in RV afterload due to increased PVR induces right ventricular hypertrophy (RVH), which can be either adaptive or maladaptive. Adaptive RVH, characterized by concentric hypertrophy with minimal eccentric dilatation and fibrosis, maintains normal ejection fraction, cardiac output, and filling pressures ***(Rich et al., 2010).***

However, maladaptive RVH shows eccentric dilatation, increased fibrosis, and capillary rarefaction with reduction in ejection fraction and cardiac output and elevation in filling pressures ***(Ryan et al., 2014).***