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TESI DI LAUREA

The cardiovascular response to exercise in children with congenital heart diseases

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ABSTRACT

Background: Patients with congenital heart disease (CHD), although most of heart defects can be successfully corrected, have reduced cardiovascular fitness and low quality of life. Thus, regular follow-up evaluations are needed, including cardiopulmonary exercise testing (CPET) and echocardiography. While the behaviour of cardiorespiratory and gas exchange indices is well studied during maximal exercise testing, much less is known regarding the recovery. We analysed the recovery phase after CPET, particularly regarding the respiratory exchange ratio (RER) overshoot phenomenon, in a population of patients with 4 different kinds of CHD.

Material and methods: 103 patients with CHD and 28 healthy controls were enrolled in this cross-sectional retrospective trial. Patients were evaluated with CPET by assessing cardiorespiratory fitness and efficiency as well as the RER overshoot during recovery after an incremental maximal exercise test.

Results: When compared to healthy subjects, patients with CHD showed a reduced cardiorespiratory fitness and efficiency. RER overshoot was also significantly attenuated in the CHD group, even though RER at peak exercise was comparable between the two groups. Correlations between the recovery parameters and other common CPET measures were performed. RER max and RER mag showed significant correlations with most of the indices of cardiorespiratory efficiency. In fact, both RER max and RER mag were correlated to VO_2 peak pro kg and OUES. A negative correlation between RER mag and HR/VO_2 slope, a parameter of cardiovascular efficiency, was also displayed. No correlations were found between the RER overshoot phenomenon and left ventricular function.

Conclusion: This is the first study evaluating the RER overshoot in the recovery phase in a population of young patients with CHD. The attenuation of this phenomenon in this population, as well as its relationship with cardiorespiratory fitness, may open new approaches in the functional evaluation of patients with CHD. Future studies assessing prospectively the recovery phase from maximal exercise testing may further improve the diagnostic value of CPET in subjects with CHD.

1. INTRODUCTION

Congenital heart disease

Definition and epidemiology

Congenital heart disease (CHD) is a term referred to a large heterogeneous group of diseases consisting of cardiac or great vessel abnormalities present from birth.

They represent the most frequent congenital malformations, with an incidence at birth of around 1% [1] and a prevalence in Europe of about 8.2/1000 live births [2]. With the improvement of surgical techniques for the treatment of CHD, the number of children affected by these diseases reaching adulthood is continuously increasing, with a mortality rate before the age of 20 which today is less than 10%. This is also a considerable fact from the health economy's point of view, given that this population of heart patients is constantly growing and requires frequent follow-up visits [3].

Etiopathogenesis

The etiopathogenesis of these diseases remains a very broad field of study whose understanding is not fully clear yet [4]–[8].

In the 1960s it was believed that the vast majority of CHD (70-75%) could be explained by a multifactorial model, that is, by the combination of polygenic and environmental risk factors [9]. Although this model is still valid, the role of genetic anomalies in the etiology of CHD has become increasingly important. Numerous genes (mainly encoding transcription factors or proteins involved in signalling) have been found which, if mutated, can cause CHD; some mutated genes are also associated with autosomal monogenic diseases, such as DiGeorge, Holt-Horam, Noonan, Marfan, and Alagille syndromes [8].

Among the genetic causes are also found chromosomal abnormalities such as trisomy 21 or Down syndrome (mainly associated with the presence of a complete atrioventricular canal or, less frequently, of defects of the interventricular

septum), trisomy 13, trisomy 18 and Turner syndrome (mainly related to the presence of coarctation of the aorta). They account for approximately 5-6% of all congenital heart disease.

In the literature it has also been highlighted that the risk of developing CHD is higher among relatives of ill subjects; in particular, a 3 times greater risk of disease recurrence was found in first degree relatives than in the general population [10]. This means that there is a sort of genetic predisposition in these families to develop such pathologies.

Finally, a very important role, especially in the multifactorial etiopathogenetic model, is that of environmental risk factors. Numerous studies have been conducted that have highlighted the presence of maternal risk factors during pregnancy. Among these, those with the most evidence in the literature are diabetes mellitus and gestational diabetes, obesity, smoking and alcohol consumption, low folic acid intake, rubella virus infection, and use of teratogenic agents such as thalidomide or drugs like lithium, some anticonvulsants and antiarrhythmics [4].

Cardiac embryogenesis

The development of the heart in the embryo takes place between the third and eighth week of gestation. The heart derives from cells of the splanchnic lateral mesoderm specialized in vasculogenesis from the so-called cardiogenic area. Starting from the third week of gestation, these cells progressively begin to organize themselves forming the right and left endocardial tubes; the primitive dorsal aortas are placed medially to these. On the 22nd day the two endocardial tubes undergo fusion, and the heart starts beating; together with the fusion there is also the displacement of this structure from the cervical to the thoracic area. Also during the 22nd day the splanchnic mesoderm thickens, forming myocardium and epicardium. The heart tube has grooves that make it possible to distinguish dilations which in the caudo-cranial sense are the sinus venosus, the primitive atrium, the primitive ventricle and the bulbus cordis (Figure 1) [11], [12].

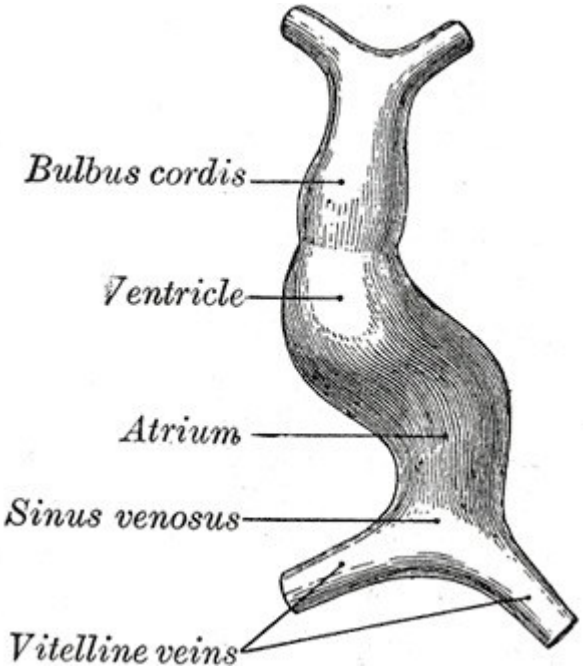

Figure 1: Representation of the heart tube [11].

The embryonic heart in this stage is connected to a symmetrical vascular system: the aortic arches, formed by the fusion of the ventral aortas with the dorsal ones, constitute the outflow tract that departs from the bulb, while the common cardinal, vitelline and umbilical veins constitute the inflow routes, connected to the right and left horns of the venous sinus.

The endocardial tube then undergoes folding, with the bulb moving forward and to the right, the ventricle down and to the left, the atrium back and up.

From the fourth week, the process of sepimentation begins, by which the heart tube is converted into the four-chamber heart. Around the 28th day, endocardial cushions form anteriorly and posteriorly, protrude at the level of the atrioventricular canal and, continuing to proliferate, towards the fifth week undergo fusion creating the right and left atrioventricular canals. With the formation of the septum intermedium, atrioventricular orifices are also created, from which the atrioventricular valves will develop [12].

The venous sinus is initially a paired structure made up of right and left horns, both of which receiving blood from three veins: cardinal, vitelline and umbilical veins. Progressively the venous sinus begins to move to the right until it communicates with the right atrium only. This occurs initially as a result of the transformation of

the vitelline and umbilical veins, with the right vitelline vein becoming the last part of the inferior vena cava and the umbilical vein obliterating; the right cardinal vein, on the other hand, will constitute the superior vena cava. The process of deviating blood flow to the right is completed with the connection between the two cardinal veins through which the blood of the left cardinal vein passes to the right one. The left veins are obliterated and the left horn, smaller than the contralateral, will become the coronary sinus [11].

Towards the end of the fourth week, a membranous fold originates from the roof of the primitive atrium, the so-called septum primum, which growing towards the endocardial cushions divides the primitive atrium into a right and a left part. The blood will be able to pass from the right atrium to the left through an opening called ostium primum. This will then undergo obliteration when the septum primum unites with the endocardial cushions. After this process, the ostium secundum is formed, which also allows the flow of blood from right to left, following the apoptosis of some cells in the upper part of the septum primum. The septum secundum forms to the right of the septum primum and is muscular in nature. At the level of the septum secundum, an opening will remain, called foramen ovale, which ensures communication between the two atria. The regression of the septum primum, in addition to forming the ostium secundum, will also create the membrane which, with the activation of lung function after birth, will adhere to the septum secundum obliterating the foramen ovale and forming the definitive interatrial septum [11], [12].

Simultaneously with the division of the primitive atrium, the formation of the two ventricles also takes place. From the lower part of the primary ventricle, a median muscular crest begins to grow, the interventricular septum. Above, an opening remains, the interventricular foramen, which allows communication between the right and left ventricle and closes around the seventh week.

The outflow component is the so-called conotruncal region, in communication with the distal part of the primitive right ventricle. From the opposite walls of the cone and trunk originate the so-called bulbar crests which, increasing in size and merging with each other, form the aortic-pulmonary spiral septum around the

eighth week, from which the aorta and pulmonary trunk will originate. After the closure of the interventricular foramen, the pulmonary trunk will be in continuity with the right ventricle, while the aorta will communicate with the left ventricle [11], [12].

Classification

CHD can be classified in various ways. One of the most used classifications is the one that subdivides this type of disease based on the presence or absence of cyanosis in the patient, which means a bluish coloration of skin and mucous membranes that occurs when the concentration of deoxygenated haemoglobin in arterial blood is higher at 5 g/dL. In particular, the following are distinguished:

- non-cyanotic CHD: these are heart diseases in which cyanosis is not present. In turn this group can be divided into:
    - heart disease with increased pulmonary blood flow. This group includes all diseases which, through a shunt of blood from the left heart portions (where pressure is normally higher) to the right ones, cause an increase in the blood volume that reaches the pulmonary arteries. The pulmonary arterioles are not used to supporting this blood flow, therefore they adapt to this condition by facing a process of irreversible non-physiological plexiform hyperplasia. If the underlying disease is not resolved, this process leads to an increase in pulmonary resistances that exceeds those of systemic vessels, with consequent inversion of the shunt, which then becomes a right-to-left shunt that leads to the appearance of cyanosis (Eisenmenger syndrome). The best-known congenital heart diseases that are part of this group are the atrial septal defect and interventricular septal defect, the patent ductus arteriosus and the atrioventricular canal;
    - heart disease with obstruction of blood flow from the ventricles. This group includes diseases in which there is an obstructive lesion in the outflow ducts. This determines an increase in the pressure

levels that the ventricles cope with, resulting in the development of eccentric ventricular hypertrophy. The best-known congenital heart diseases that are part of this group are aortic stenosis, coarctation of the aorta and pulmonary stenosis;

- cyanotic CHD: these are heart diseases that cause cyanosis. In turn this group can be divided into:
    - heart disease with decreased pulmonary blood flow. They are characterized by reduced blood flow in the pulmonary artery. This group includes pathologies such as tetralogy of Fallot, tricuspid atresia and pulmonary atresia with intact ventricular septum;
    - heart disease with mixed blood flow. They are characterized by the presence of mixing between oxygenated and deoxygenated blood. Diseases such as common arterial trunk, abnormal pulmonary venous drainage and hypoplastic left heart syndrome are included in this group;
    - heart disease with parallel circuits. The transposition of the great arteries is classified within this group: it is a pathology in which the aorta originates from the right ventricle, while the pulmonary artery arises from the left ventricle, thus there is ventriculo-arterial discordance. Because of this, the non-oxygenated venous blood that reaches the right atrium is introduced into the aorta and then to the rest of the body, while the oxygenated blood coming from the pulmonary veins that reaches the left atrium is then introduced into the pulmonary artery: this means that in the transposition of the great arteries there are two parallel circulations incompatible with postnatal life.

Symptoms, diagnosis and treatment of the congenital heart disease analysed in this study

The CHD studied in this work are the coarctation of the aorta, the tetralogy of Fallot, the univentricular heart and the transposition of the great arteries, so they will be those treated in this paragraph.

Coarctation of the aorta

Coarctation of the aorta (CoA) is a narrowing of the lumen of the aorta located at the level of the aortic isthmus, in a distal position at the origin of the left subclavian artery and near the arterial duct (Figure 2). It constitutes 6-8% of all CHD; about 10-20% of patients with Turner syndrome suffer from this disease.

CoA is classified into three subtypes depending on the location of the narrowing: it is defined as preductal if the narrowing is proximal to the ductus arteriosus, ductal if it is at the level of the duct insertion, and postductal if it is distal to the ductus arteriosus. This classification is important not only from an anatomical point of view, but also from a clinical and diagnostic point of view.

Physiologically, CoA has two important consequences: a pressure overload upstream of the narrowing and hypoperfusion downstream. Objectively, in fact, in patients with CoA it is characteristic to find increased pressure levels with pulsating pulses in the upper part of the body, as opposed to the lower limbs in which the pressure levels are reduced with hyposphygmic or even absent pulses. It is also common to find a systolic ejective murmur at the level of the left superior sternal margin and at the interscapular level [13], [14].

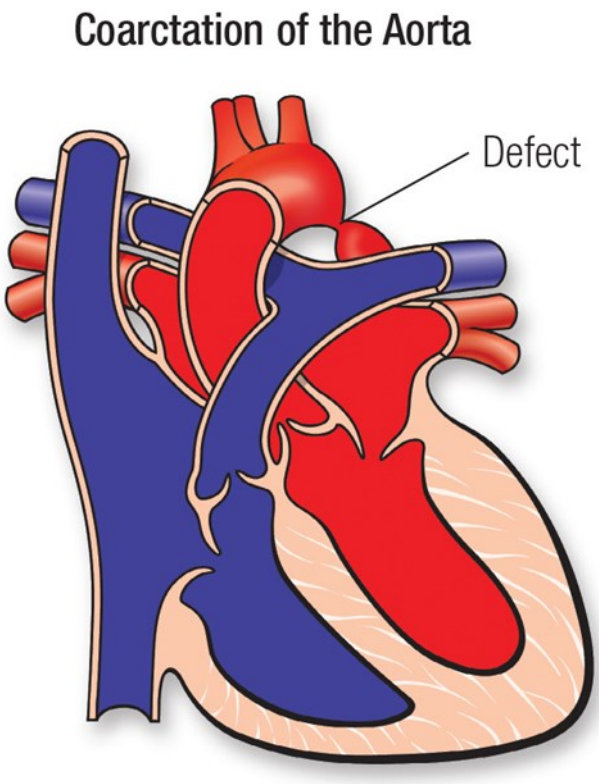

Figure 2: Representation of CoA [14].

From a clinical point of view, symptoms are very variable depending on the location and the severity of the narrowing of the aortic lumen. Severe and/or preductal and ductal coarctations typically appear when the ductus arteriosus closes: newborns with these conditions usually show signs of cardiovascular shock within the first hours after birth. On the other hand, patients with mild-moderate and/or postductal coarctations are usually asymptomatic during childhood or have mild symptoms such as hypertension in the upper limbs, headache, dyspnoea, chest pain, and cold skin, asthenia and claudication of the lower limbs, especially under exertion. However, if left untreated, this disease in the long run leads to left ventricular hypertrophy, heart failure and hypertensive heart disease, as well as an increased risk of intracranial haemorrhage and infective endocarditis [13], [15].

The diagnosis, in addition to clinical findings, is based on instrumental examinations. The diagnosis of certainty is usually done with echocardiography, whereas prenatal diagnosis is difficult because the presence of the arterial duct makes it difficult to visualize the narrowing at the isthmus level; ECG can detect signs of left ventricular hypertrophy or be normal. In subjects over 5 years of age

with mild-moderate postductal CoA chest X-ray usually shows costal erosions, given the development of collateral circulation at the level of the intercostal arteries; it is also possible to find an increased heart size.

As regards medical therapy, in case of severe and symptomatic CoA, it is recommended to administer prostaglandins in the first hours after birth to keep the arterial duct patent; for the treatment of hypertension, on the other hand, the use of β-blockers is preferred.

The definitive treatment in newborns mainly consists of classical surgery. The most used option involves the resection of the coarctated tract and end-to-end anastomosis of the adjacent aortic segments; the other most common surgical technique, on the other hand, is aortoplasty with a patch or with a portion of the subclavian artery [13]. The post-correction prognosis is usually very good, however an increased risk of arterial hypertension, premature atherosclerosis, left ventricular insufficiency, aneurysms and relapse of coarctation persists. For newly found aortic coarctations in youth or adulthood or for relapses, percutaneous treatment via balloon angioplasty and subsequent stent placement is usually preferred: hypertensive subjects with a pressure difference between upper and lower limbs of at least 20 mmHg, with significant left ventricular hypertrophy or with a coarctation greater than 50% of the aortic diameter are directed to this type of intervention [13].

Tetralogy of Fallot

The tetralogy of Fallot (ToF) is defined by four fundamental anatomical components:

- large interventricular septal defect;
- overriding aorta;
- pulmonary valve stenosis;
- right ventricular hypertrophy.

These components are actually the result of a single defect, that is the antero-cephalic deviation of the infundibular septum (Figure 3).

ToF constitutes about 7-10% of all congenital heart diseases and it is common to find it in the context of some genetically determined diseases such as Down (8% of ToF), DiGeorge (11%) and Alagille syndromes; patients with ToF often have other heart defects as well [16], [17].

From the pathophysiological point of view, ToF is a congenital heart disease that causes cyanosis; this is due to the presence of pulmonary outflow obstruction with consequent pressure increase in the right ventricle and right-to-left shunt through the ventricular septal defect which carries non-oxygenated blood to the left ventricle and therefore to the systemic circulation (Fallot blue). The extent of cyanosis depends on the degree of pulmonary valve stenosis: in the case of mild obstruction, cyanosis is absent and we speak of pink Fallot.

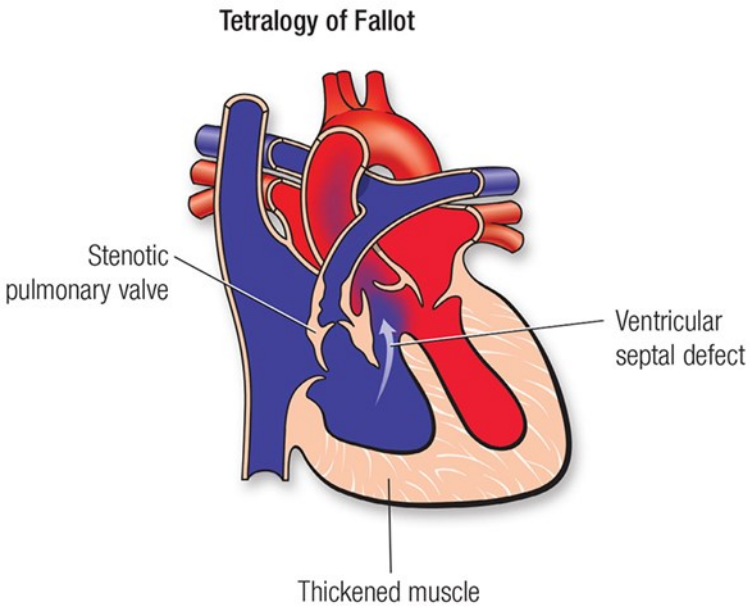

Figure 3: Representation of ToF [14].

From the clinical point of view, the so-called cyanotic spells are characteristic, with a marked bluish colour especially of the lips, hands and feet. These crises usually occur when the baby cries, fidgets or eats and are caused by an acute and complete (or almost complete) obstruction of the outflow tract of the right ventricle, resulting in a sudden reduction in arterial oxygen saturation. The findings of a systolic murmur at the focus of pulmonary auscultation (due to

pulmonary stenosis) and digital hippocratism (due to hypoxemia) are also common [16].

The diagnosis is based not only on clinical findings, but also on instrumental examinations:

- the chest X-ray shows the characteristic boot-shaped heart;
- on the ECG, signs of right ventricular hypertrophy are seen;
- the diagnosis of certainty is based on echocardiography that allows to view the heart anatomy and therefore to visualize ToF's characteristic lesions.

Antenatal diagnosis is possible after 12 weeks of gestation. Usually, foetuses with ToF for which specific foetal echocardiography is indicated due to the high risk of CHD have more severe disease phenotypes [16], [18].

The clinical management of patients with ToF depends above all on the degree of pulmonary stenosis: in the most serious cases it is necessary to proceed with the infusion of prostaglandins from the first hours after birth to preserve the patency of the ductus arteriosus in order to guarantee an adequate blood flow to the lungs. The definitive treatment is surgical and currently involves the closure of the interventricular septal defect and the removal of the pulmonary outflow obstruction: the first is obtained by placing a patch, the latter by a cut at the level of the ventricular infundibulum and consequent pulmonary valvuloplasty. The operation is usually carried out around 4-6 months of life. In children with complex anatomy and in serious clinical conditions, palliative interventions are preferred: in the past, a Blalock-Taussig shunt was made, connecting the right subclavian artery to the right branch of the pulmonary artery, today it is preferred to use a goretex tube that connects the two arteries (modified Blalock-Taussig shunt). The goal in both cases is to increase the blood flow that reaches the lungs. Palliative intervention is also possible percutaneously by placing a stent to keep the Botallo duct open or to unblock the pulmonary outflow tract [16].

As for prognosis, patients with corrected ToF in the first years of life have an 85% long-term rate of survival, but have a life expectancy still lower than that in the healthy population [19], [20]. Thanks to the improvement in medical and surgical management, life expectancy of these patients is expected to improve in the

future. However, patients with ToF still require long-term follow-up after corrective surgery, as they commonly develop haemodynamic complications in the long run such as pulmonary insufficiency or stenosis, right or left ventricular dysfunction and atrio-ventricular arrhythmias [16], [20], which forces them to undergo further surgical and percutaneous corrective interventions.

Univentricular heart

This concept refers to some CHD in which the normal biventricular circulation is not possible due to the conformation of one or more valves or to the incomplete development of a ventricle. These pathologies include hypoplastic left heart syndrome, tricuspid atresia and pulmonary atresia with intact septum (Figures 4-5). They make up about 5-8% of all CHD [21].

In hypoplastic left heart syndrome, the left ventricle does not form properly due to genetic-environmental factors or due to abnormalities in the development of the mitral and/or aortic valve. The ascending aorta is also often hypoplastic and an atrial septal defect and/or the patent ductus arteriosus are usually present. The oxygenated blood that arrives in the left atrium passes through the interatrial communication to the right atrium and here it mixes with the systemic venous blood, then gets to the right ventricle and finally reaches the systemic circulation through the arterial duct, essential for the survival of the newborn. This explains cyanosis in patients with hypoplastic left heart syndrome.

In tricuspid atresia and in pulmonary atresia with intact septum, instead, it is the right ventricle that does not fully form and is hypoplastic due to the abnormal valvular development. In both diseases, the presence of an atrial septal defect is frequent, while the patency of the ductus arteriosus (or a ventricular septal defect in tricuspid atresia) is essential for survival, because it allows blood to flow also in the lungs. Cyanosis is in fact due to the reduced pulmonary blood flow.

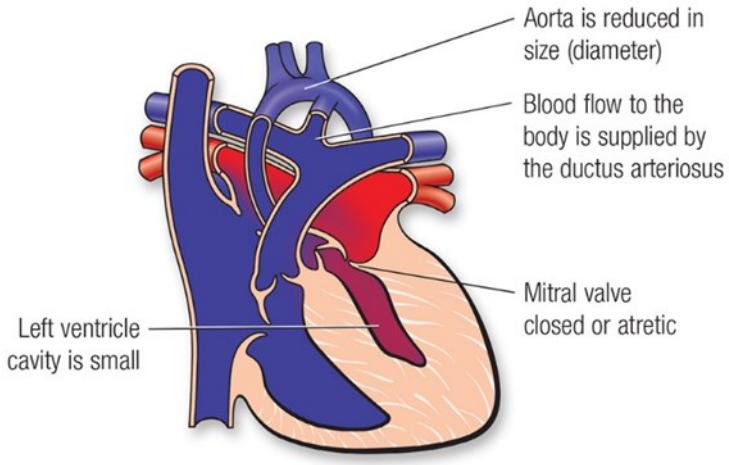

Figure 4: Representation of hypoplastic left heart syndrome [14].

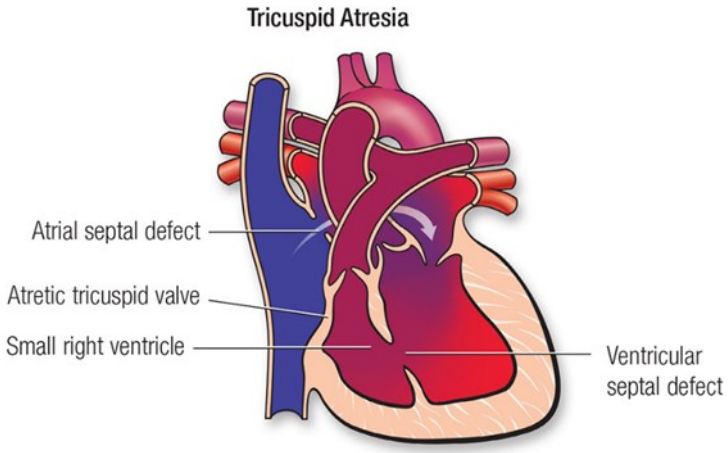

Figure 5: Representation of tricuspid atresia [14].

In patients with univentricular heart, symptoms appear abruptly after the first 24-48 hours after birth when the Botallo duct begins to close: cyanosis and signs of cardiogenic shock appear such as dyspnoea, tachypnoea, weak pulse, lethargy, metabolic acidosis, pallor, oligo-anuria [21].

Diagnosis is often made during pregnancy by targeted foetal echocardiography. At birth, however, the findings of the instrumental tests are very indicative:

- chest X-ray shows an enlarged heart and pulmonary venous congestion in patients with hypoplastic left heart syndrome. Cardiomegaly is also present in patients in whom the only functioning ventricle is the right, with

the addition of pulmonary hypodiafania due to the poor blood supply that reaches the lungs;

- on the ECG signs attributable to hypertrophy of the non-hypoplastic ventricle and possible right or left axial deviation can be seen;
- the lesions that characterize these pathologies are clearly visible even on postnatal echocardiography [21].

Treatment is primarily medical in the first days of life and involves the infusion of prostaglandins to keep the Botallo duct open. Surgical treatment consists of several interventions that ultimately culminate in the Fontan procedure (Figure 5):

- in patients with hypoplastic left heart syndrome the right ventricle will have to function, contrary to normal physiology, as a systemic ventricle. The first surgical stage is the Norwood surgery, performed during the first week of life: a modified Blalock-Taussig shunt or a right ventriculo-pulmonary arterial duct is inserted to ensure constant blood flow to the lungs, while the pulmonary artery is closed distally and remodelled proximally, and joined with the hypoplastic aorta in order to create a functioning neo-aorta. The second surgery, performed at about 3-6 months of life, consists of the Glenn procedure or of a hemi-Fontan, with which the superior vena cava is connected to the right pulmonary artery (in the hemi-Fontan a connection between superior vena cava and right atrium remains). Finally, the third stage involves performing the Fontan procedure at 18-36 months of life, with which the blood flow from the inferior vena cava is also connected to the convergence between the superior vena cava and the right pulmonary artery through a duct positioned internally or externally to the right atrium;
- in patients with tricuspid or pulmonary atresia the systemic ventricle will be the left. The first surgical stage consists only of the creation of a systemic-pulmonary shunt in the first days of life, the other two stages are the same as those presented above [21].

Prognosis has improved in the last decades, with a survival rate of around 90% 10 years after surgery [21], [22], however the complex anatomy of patients with Fontan circulation favours the development of late complications with negative

consequences on quality of life and on life expectancy. Arrhythmias (especially supraventricular), thromboembolic events, ventricular dysfunction with heart failure, protein-dispersing enteropathy, plastic bronchitis, fibrosis and liver cirrhosis are common findings in these subjects [23], [24].

When the long-term complications of the Fontan procedure become clinically relevant, cardiac transplantation is the main option for treatment left; on the other hand, in newborns it is done very rarely due to the few organs available and also because of the high mortality of the surgery [24]. In this sense, in adolescents and adults with Fontan circulation the evaluation of functional capacity through cardiopulmonary exercise testing is one of the main diagnostic tools to put these patients on the waiting list for transplantation [25].

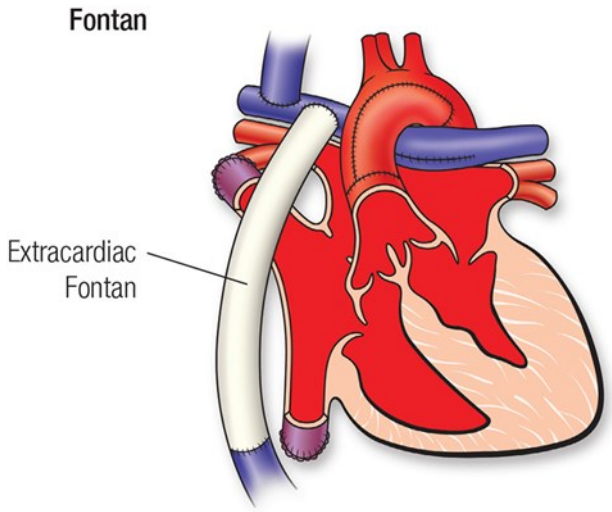

Figure 6: Representation of the final result of Fontan procedure [14].

Transposition of the great arteries

The transposition of the great arteries (TGA) is a congenital cardiac malformation in which the aorta arises from the right ventricle, while the pulmonary artery from the left ventricle (the simultaneous presence of an atrial or ventricular septal defect is also frequent): there are therefore two parallel circulations that, in the absence of any sort of communication, are completely incompatible with extra-uterine life (Figure 7). The one just described is the most common variant, the so-

called dextro-transposition of the great arteries (D-TGA). There is also a much rarer type called levo-transposition of the great arteries (L-TGA) or congenitally corrected transposition of the great arteries in which there is atrio-ventricular and ventricular-arterial discordance, that means the aorta originates from what morphologically is the right ventricle which however is placed on the left in continuity with the left atrium, vice versa the pulmonary artery arises from what morphologically is the left ventricle which however is placed on the right in continuity with the right atrium [26]. TGA is usually referred to D-TGA, being by far the most common variant.

This disease, in general, accounts for about 5-7% of all congenital heart disease.

From a pathophysiological point of view, since there are two parallel circulations, the non-oxygenated blood that reaches the right portions of the heart is then introduced into the aorta returning to the systemic circulation without having first passed through the lungs, while the oxygenated blood, after reaching the left heart sections, is introduced into the pulmonary artery and therefore will continue to oxygenate itself indefinitely. This explains the severe cyanosis at birth and the incompatibility with postnatal life.

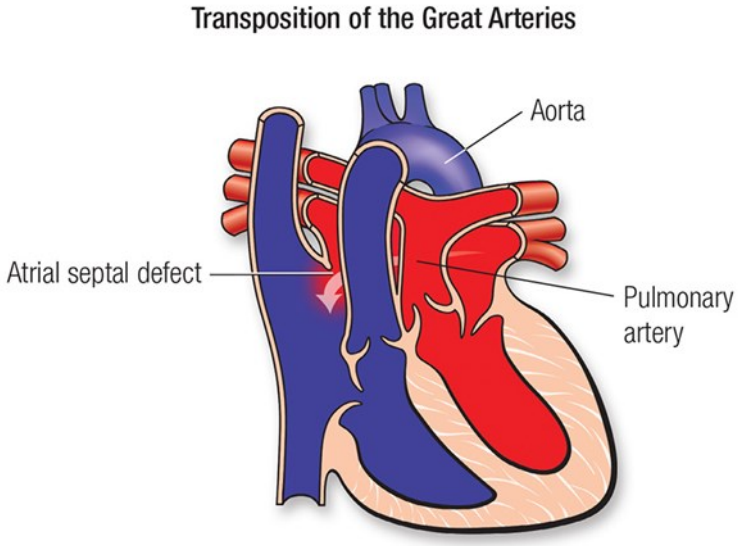

Figure 7: Representation of D-TGA [14].

The clinical picture at birth represents a neonatal emergency: cyanosis, tachypnoea and metabolic acidosis are present. If in addition to the TGA there is

also a large defect of the interventricular septum, cyanosis may not be immediately visible. In this case, symptoms of congestive heart failure due to increased ventricular work prevail during early childhood, such as tachycardia, tachypnoea, gallop rhythm, failure to thrive and even hepatomegaly [26].

Prenatal diagnosis through foetal echocardiography with visualization of the two parallel circulations is very important; this allows, among other things, to organize the birth in a third-level equipped centre. Even with echocardiography after birth, the two parallel circulations are visible; other useful instrumental tests are the chest X-ray, which shows an egg-like appearance of the heart with thinning of the mediastinal profile, and ECG, in which signs of hypertrophy of the right sections appear since the right ventricle has to pump blood in the aorta and therefore overcome resistances higher than the physiological pulmonary ones.

The treatment must be early: it is essential to maintain a mixing between the two circulations, so in addition to the administration of prostaglandins to keep the arterial ductus open, the Rashkind procedure is performed, through which a stable communication is created at the level of the atrial septum with the use of a catheter (atrioseptostomy).

The definitive surgical treatment currently involves the so-called arterial switch or Rastelli surgery, in which the aorta is reimplanted on the left ventricle and the pulmonary artery on the right ventricle; it is performed within the first two weeks of life. The results are excellent, and patient's quality of life after surgery is good, even though they still appear to have a reduced functional capacity [27]: the most frequent complication, since in any case with the arterial switch the aorta will be located between the two pulmonary arteries, is the compression of the pulmonary branches. Until the 1980s, on the other hand, atrial switch surgery was performed (Mustard and Senning procedures), with which venous returns were redirected through patches: the right ventricle was therefore destined to pump blood to the systemic circulation (where resistances are much higher than those of the pulmonary circulation), with the inevitable development over the years of ventricular dysfunction and heart failure, as well as the possible appearance of arrhythmias and obstructions of systemic or pulmonary venous returns. Given the

higher and more frequent number of complications, atrial switch surgery was in fact abandoned in favour of arterial switch [26].

Role of cardiopulmonary exercise testing in congenital heart disease

The epidemiology of congenital heart disease has significantly changed in recent years and now the number of adult patients is about double that of children, reflecting how, thanks to the improvement in medical and surgical management, more and more patients can safely reach adulthood [3].

These people, given their pathology and given the surgical sequelae of the corrective or palliative interventions they undergo, need to be followed for their whole life. Cardiopulmonary exercise test (CPET) is, in this sense, a valid tool to use in the follow-up of these patients from the paediatric age following guidelines [28]–[31].

CPET allows in these subjects to determine the functional capacity, to assess the status of the cardiopulmonary system, to verify the presence of abnormal events or arrhythmias during exercise, to ascertain the effectiveness of medical and surgical therapies, to make decisions on further possible therapies, and to follow the progress of these treatments over time [28]. In addition to this, it also allows each patient to be advised individually on the type of sport and exercises that they can undertake [32], [33], an aspect currently relevant given the protective attitude used in the past.

Also given the inability of these subjects to quantify their ability to exercise (often reported by themselves or by their family members as normal or only slightly lower than their healthy peers [34], [35]) CPET assessment is essential and cannot be replaced by anamnesis alone or by simple questionnaires on the quality of life and on aspects related to physical exercise.

CPET involves the use of the following equipment [28], [29], [36] (Figure 8):

- an ergometer (4 in Figure 8), which can be a cycle ergometer or a treadmill. It is the fundamental tool for carrying out the test since it is used to set the physical exercise load to be administered to the patient according to certain protocols. The choice of the ergometer depends on many variants:

although the treadmill tends to be more familiar to most patients than the cycle ergometer and detects higher VO_2 max values, it is more expensive, more cumbersome, makes ECG and blood pressure monitoring more difficult and it does not allow to measure power. Furthermore, in younger children, the size of the treadmill and the not yet fully developed ability to exercise through running or walking make the choice of the cycle ergometer mandatory in some cases;

- an ECG recording system (3 in Figure 8). It allows to monitor the electrocardiographic trace during the test and to highlight any alterations at rest, during exercise or during recovery. The electrocardiographic assessment, associated with the evaluation of CPET parameters, allows a more specific diagnostic evaluation;
- a blood pressure measurement system (1 in Figure 8). Blood pressure monitoring is performed at rest before the test, repeatedly during the test, and also during the recovery phase. The evaluation of this parameter allows to highlight any abnormal pressure responses, for example an excessive or lack of pressure increase, or a sudden drop in blood pressure levels during exercise;
- a pulse oximeter (5 in Figure 8). It is used to measure arterial oxygen saturation before, during and after the test;
- a ventilation and exhaled gas analysis system (2, 6 in Figure 8). It consists of a face mask connected to a sensor that allows to evaluate the ventilation and concentration of exhaled gases "breath by breath" (with each breath) and a central computer that allows the calculation of the oxygen consumed and the CO_2 produced;
- some monitors for the continuous evaluation of the ECG trace and of the specific parameters of CPET (7 in Figure 8).

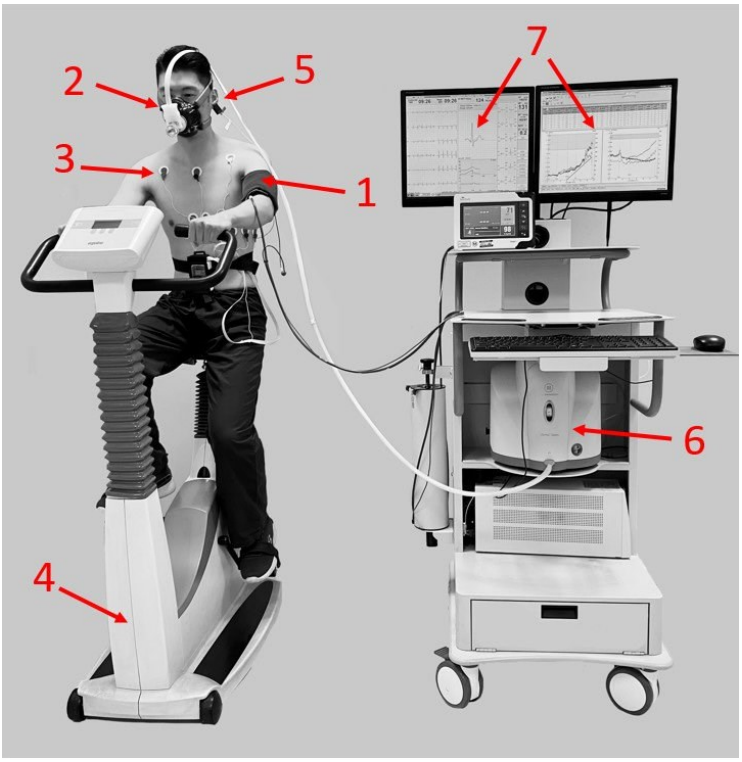

Figure 8: CPET equipment [36].

Cardiopulmonary exercise testing requires that medical history and physical examination are performed before the actual test begins. These preliminary assessments are used to determine the level of physical activity of the patient and the presence of a previous history of symptoms at rest or under exertion such as dyspnoea, heart rate and chest pain, and of contraindications to carrying out the test (Table 1).

In addition to medical history and physical examination, it is also recommended to perform a spirometry before performing the test, in order to highlight any restrictive or obstructive pulmonary pathologies, that allows the correct interpretation of the parameters obtained with CPET.

Absolute contraindications to carrying out CPET	**Relative contraindications to carrying out CPET**
Acute myocardial infarction (3-5 days)	Left coronary stenosis
Unstable angina	Moderate stenotic valve disease
Symptomatic uncontrolled arrhythmias	Severe hypertension not adequately treated at rest (systolic BP>200 mmHg and/or diastolic BP>120 mmHg)
Syncope	Tachi/bradyarrhythmia
Endocarditis, myocarditis or acute pericarditis	High-grade atrioventricular block
Symptomatic severe aortic stenosis	Hypertrophic cardiomyopathy
Uncontrolled heart failure	Severe pulmonary hypertension
Acute pulmonary embolism or deep vein thrombosis	Advanced or complicated pregnancy
Suspected dissecting aneurysm	Electrolyte disorders
Uncontrolled asthma	Orthopaedic problems that prevent to carry out the test
Acute pulmonary oedema	
Respiratory failure	
Any acute condition that may affect the exercise performance (fever, infections, kidney failure, thyrotoxicosis ...)	
Mental impairment leading to inability to cooperate	

Table I: Absolute and relative contraindications to CPET [37].

Once it is ascertained that the patient does not present any kind of contraindication to the test, the ECG electrodes are positioned, preliminary measurements of blood pressure and arterial oxygen saturation are taken, and the mask is connected to the sensor that analyses the exhaled gas.

Subsequently, the patient positions himself on the ergometer and the actual test begins: the load, if an incremental protocol is used, becomes progressively more and more important as the speed and slope (if the treadmill is used) or resistance (if the cycle ergometer is used) increase.

The duration of exercise phase depends on the protocol chosen for the test and on the functional capacity of the patient. The purpose of the test is to ensure that the patient reaches the maximum of his capabilities. There are various criteria that allow the clinician to establish that the exercise test was actually maximal and therefore allow him to stop the test:

- there are clinical criteria such as the patient reaching a score of 18/20 on the Borg's fatigue scale, the onset of dyspnoea and the achievement of a plateau in the number of revolutions per minute;
- there are criteria based on the cardiovascular parameters of CPET such as reaching 85-90% of the theoretical maximum heart rate and reaching a VO_2 plateau;
- there are ventilatory criteria such as the increase in VE/VCO_2 and the achievement of a respiratory reserve value (that is the difference between maximum voluntary ventilation and maximum ventilation during exercise) of less than 15%. These criteria are less used in clinical practice;
- finally, there are metabolic criteria such as the achievement of a respiratory exchange ratio of 1.10-1.15 or a lactate serum concentration over 5-8 mmol/l.

The test is not always stopped when it meets the criteria to be considered maximal, because even in the case of the appearance of considerable arrhythmias or ST segment depression on the ECG, symptoms such as heart-pounding, dyspnoea, chest pain, dizziness and syncope, abnormal blood pressure or oxygen saturation, the test must be stopped immediately, otherwise it could be dangerous for the patient's life [37].

Cardiopulmonary exercise test parameters

What makes cardiopulmonary exercise testing unique is the analysis of ventilation and exhaled gases: this allows the physician to evaluate parameters that, on the other hand, cannot be monitored in a common exercise test.

Normally, what is observed during the CPET is the Wasserman 9-panel plot (Figure 9), which allows the evaluation during the entire duration of the test of the specific parameters of the cardiopulmonary exercise test [38]–[40]:

- the first panel describes the relationship between ventilation and test time. At rest a normal subject ventilates about 7-9 l/min, however, as the load increases, the ventilation increases progressively as well (in athletes it can reach up to 150-200 l/min), and especially after the second ventilatory threshold (respiratory compensation point or RCP) to support the expulsion of CO_2 produced by the body during exertion in the form of lactic acid. The increase in ventilation under exercise, in fact, is due to a greater extent to the need to eliminate the CO_2 produced by anaerobic metabolism rather than to the body's need for oxygen;
- the fourth panel describes the relationship between ventilation and the volume of CO_2 expelled. This graphic gives indications on the degree of respiratory efficiency: a greater slope of the curve indicates that for the same ventilated litres the subject under examination is able to expel a lower quantity of carbon dioxide;
- the seventh panel shows the tidal volume in relation to ventilation. In normal subjects the tidal volume reaches a plateau at about 60% of the vital capacity, which corresponds to about 40% of VO_2 peak. In this graphic, patients with obstructive pulmonary diseases will show a higher tidal volume than normal with the same ventilated volume, while patients with restrictive pulmonary diseases will show a lower-than-normal tidal volume, which they compensate with an increased respiratory rate;
- the second panel shows the relationship between heart rate (HR) and the time of the test or the workload on one side (red line), and the relationship between VO_2 and HR on the other (blue line), the so-called oxygen pulse.

The heart rate progressively increases as the workload increases in order to support the demands of the body under stress; it is essential to remember that the cardiac output, that is the blood expelled from the left ventricle in one minute, is given by the product of the heart rate and the systolic output. At peak effort, if the test was maximal, a HR of at least 85-90% of the theoretical maximum HR should be expected (calculated as: 220 - patient's age).

By subtracting the HR at rest from the maximum HR obtained during the test, we obtain the so-called Heart Rate Reserve (HRRes), which is a parameter that expresses the ability of the heart to adequately increase the HR in order to meet the metabolic demands of the body during physical exercise. This parameter has been studied in patients who have undergone Fontan surgery and a reduced HRRes was found, probably due to a reduced ventricular filling and a reduced systolic output [41].

The HR trend in recovery is also normally evaluated, that is the progressive reduction in the number of beats per minute with the cessation of exercise (Heart Rate Recovery, HRRec).

The oxygen pulse (VO_2/HR), on the other hand, represents a valid estimate of the other determinant of cardiac output, that is, systolic output: the contribution of the latter in determining cardiac output is 30-35% and is exhausted at approximately 50% of VO_2 peak. In this graphic it is important to observe the trend of the oxygen pulse curve during the test: normally this reaches a plateau at 40-50% of the VO_2 peak, while in subjects with heart failure or pulmonary hypertension the oxygen pulse increases less, or in the case of myocardial ischemia, the so-called “double-slope” occurs, with flattening of the curve due to the contractile deficit induced by the appearance of ischemia;

- the fifth panel shows the change in heart rate (red line) and carbon dioxide production (blue line) in relation to oxygen consumption.

  HR/VO_2 slope represents the slope of the curve that describes the relationship between heart rate and the amount of oxygen consumed. It is a parameter that assesses the efficiency of the chronotropic response in

meeting the increased metabolic needs during exercise. The slope of the curve is considered normal if it is lower than 3.5/5 beats per ml/min/kg of VO_2: if the slope is higher than these values it means that the subject must increase his heart rate to maintain a certain value of oxygen consumed. This parameter is still little studied [42], however it is known that an HR/VO_2 slope above reference values is frequently associated with paraphysiological conditions such as poor training, anxiety and hyperthermia, but also with diseases such as heart failure, hypertrophic cardiomyopathy, restrictive and obstructive pulmonary diseases and pulmonary hypertension; drugs such as β-blockers, on the other hand, reduce the slope since they tend to reduce heart rate.

As for the ratio between VCO_2 and VO_2, the first increases in parallel with the second up to the first ventilatory threshold (anaerobic threshold or AT), then the production of carbon dioxide increases more than the consumption of oxygen because the body must also eliminate the extra quote of CO_2 deriving from the production of lactic acid in the skeletal muscles;

- the third panel shows the variation of VO_2 (red line) and VCO_2 (blue line) with respect to time. As previously underlined, up to the first ventilatory threshold the two curves go hand in hand, then the slope of the VCO_2 curve increases more in relation to the production of lactic acid. This change in slope is one of the methods used to identify that the anaerobic threshold has been reached. One of oxygen consumption curve's most important features is VO_2 max, defined as the maximum amount of oxygen that the body is able to consume during exercise. VO_2 max actually represents the highest point where the curve describing the trend of oxygen consumption forms a plateau, while the maximum value of O_2 consumed near peak effort is called VO_2 peak. It is universally recognized as an estimate of functional capacity as well as a universally used prognostic marker. Indeed, it reflects the severity of many conditions, including pulmonary hypertension, COPD, interstitial lung diseases and especially heart failure (it is no coincidence that Weber's classification of heart failure based on

VO_2 peak exists) [43]. VO_2 max is a parameter that has also been studied in the evaluation of congenital heart disease: in particular, several studies in literature have shown that VO_2 max in these patients is significantly reduced compared to healthy peers, especially for the more complex CHD [44], [45];

- the eighth panel shows the trend of the respiratory exchange ratio (RER) during the test. RER is defined as the ratio between the carbon dioxide produced and the oxygen consumed ($RER=VCO_2/VO_2$). This parameter is influenced by various factors and especially by the type of energy substrate that is used by skeletal muscles: for carbohydrates the RER is 1 (because the oxidation of a glucose molecule requires the consumption of 6 molecules of O_2 with the production of 6 molecules of CO_2), while for lipids it is approximately 0.7. By evaluating the RER value, it is therefore possible to understand what type of substrates the subject under examination is using: for example, for a RER of 0.85 the substrates used are roughly 50% lipids and 50% carbohydrates. During exercise the RER increases progressively, because the quantity of carbohydrates used rises when the workload increases: when it reaches values higher than 1, it is possible to say with certainty, based on the reasoning set out above regarding the trend of the VO_2 and VCO_2 curves, that the first ventilatory threshold has been surpassed, while at the peak of exercise in normal subjects it reaches values around 1.10-1.15. However, the maximum RER values are reached during the recovery phase, in which the so-called RER overshoot occurs;
- the sixth panel shows the trend of the so-called breathing equivalents (oxygen in red, carbon dioxide in blue) during the test. With this term we mean the relationship between ventilation and consumption of O_2 or production of CO_2 (therefore VE/VO_2 and VE/VCO_2), and these respectively represent the ventilation necessary to consume a certain volume of oxygen and the ventilation necessary to expel a certain volume of carbon dioxide, constituting parameters of ventilatory efficiency. In healthy subjects, in the first part of the test both VE/VO_2 and VE/VCO_2 progressively reduce and both touch their nadir below the value of 30. The ventilatory equivalent of

oxygen reaches its minimum value at the first ventilatory threshold, then with the increase in ventilation in response to increased lactic acid production it begins to grow. The breathing equivalent of carbon dioxide, on the other hand, reaches the nadir at the second ventilatory threshold, that is when the production of CO_2 is maximum due to the exhaustion of the lactic acid buffer consisting of bicarbonates, then it grows due to the further increase in ventilation to expel CO_2 in response to the depletion of bicarbonates.

High values of breathing equivalents can be a sign of the presence of ventilation-perfusion mismatch. The VE/VCO_2 curve, in particular, has been the subject of several studies in literature that have shown that in patients with heart failure the values of the ventilatory equivalent of CO_2 tend to be higher than normal [46]; there are also some ventilatory classes that allow to stratify these patients from a prognostic point of view according to their VE/VCO_2 slope [38]. This parameter was also assessed in congenital heart disease: despite the lack of real reference values for the paediatric population, it was found that in CHD children the VE/VCO_2 values are higher than in healthy children, especially in patients with univentricular heart and in those with residual lesions in the right ventricle [47];

- the ninth panel shows the "end tidal" pressures (at the end of expiration) of oxygen ($PETO_2$, red line) and carbon dioxide ($PETCO_2$, blue line). They represent estimates of the partial pressures of O_2 and CO_2 at the alveolar level. The $PETO_2$ at rest is equal to about 90 mmHg, decreases up to the first ventilatory threshold due to the consumption of oxygen by the skeletal muscles and then increases due to the increase in ventilation; $PETCO_2$, on the other hand, at rest is about 36-42 mmHg, increases by about 3-8 mmHg up to the first ventilatory threshold and then describes a plateau between the first and second threshold due to the action of the bicarbonate buffer; after the RCP, however, the $PETCO_2$ value decreases due to the increase in ventilation and therefore to the increased expulsion of carbon dioxide. In the case of respiratory disease, both end tidal

pressures remain lower than normal during the entire duration of the test; a lower $PETCO_2$ is also associated with the presence of heart failure [38];

- an index that does not appear in Wasserman 9-panel plot but which is still routinely analysed is the OUES, an acronym that stands for Oxygen Uptake Efficiency Slope (see Figure 9). This parameter is obtained from the logarithmic relationship between VO_2 and ventilation and is an index describing the ventilatory response during exercise [48]. OUES has the advantage that, unlike other parameters, it does not require a maximal test in order to accurately assess the functional cardiorespiratory capacity and has therefore carved out an important role from the diagnostic and prognostic point of view in many pathologies, especially in heart failure, a pathology in which patients, due to their cardiogenic limitation to exercise and to their poor physical fitness, struggle to obtain a true maximal test at CPET [49]. This parameter, therefore, is correlated to VO_2 peak and can accurately estimate the functional capacity even in patients who fail to reach exhaustion;
- another index that does not appear in Wasserman 9-panel plot but which is normally analysed in clinical practice is that of METs (Metabolic Equivalent of Task). One MET represents the amount of oxygen consumed while sitting at rest and by definition is equal to 3.5 ml/min/kg of O_2. It is a very practical and easy to understand parameter that allows to express the energy cost of an activity as a multiple of the resting metabolic rate. In addition to this, METs are also useful to quantify the exercise tolerance of the subject under examination, to identify which activities he can participate in depending on his pathology and/or his training program and also to define his functional capacity, similarly to what can be done with VO_2 max [50], [51].

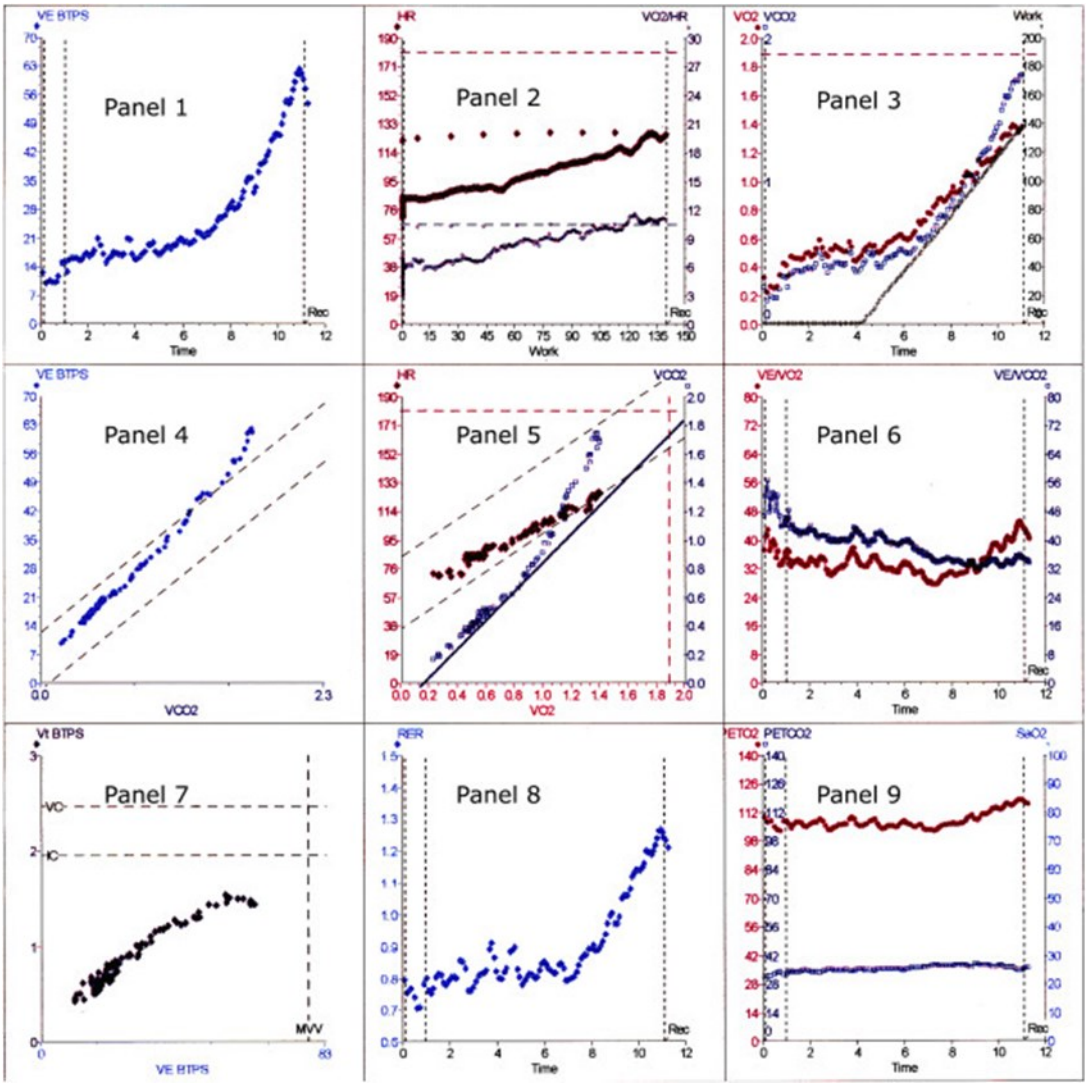

Figure 9: Wasserman 9-panel plot [40].

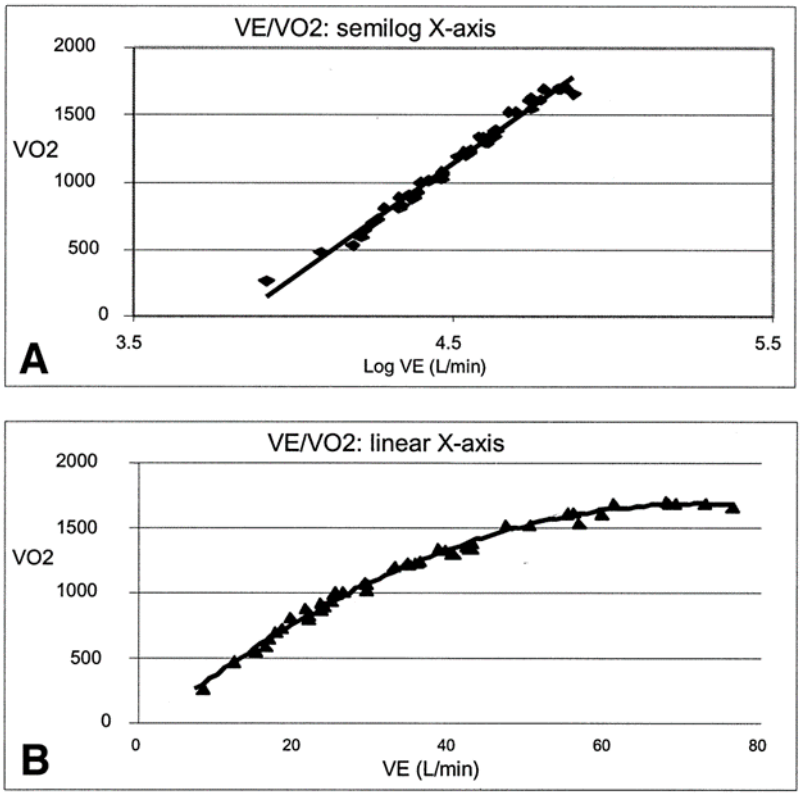

Figure 10: The semilogarithmic relationship between VE and VO_2 (above), and their linear relationship (below) [49].

Behaviour of cardiopulmonary exercise test parameters during the recovery phase

This work is mainly focused on the evaluation of the behaviour of CPET parameters during the recovery phase, thus after the end of the actual test. The main parameters analysed in clinical routine during the recovery phase are the heart rate and blood pressure trends, the behaviour of the RER, of the breathing equivalents and of end tidal pressures of oxygen and carbon dioxide.

As previously discussed, the HR trend is extensively analysed during the stress test (Figure 9, panel 2), however the recovery phase can also be included in this evaluation. In particular, after the end of exercise phase, it is possible to study the body's efficiency in returning to normal HR values. The parameter that considers this relationship is called Heart Rate Recovery (HRRec) and represents an estimate of the efficiency of the parasympathetic system: in normal subjects, the HR is reduced by at least 6 beats per minute after one minute from the end of the test. This parameter has already been studied in the literature and a slow HRRec

kinetics (and therefore an abnormal HRRec) has been identified as an accurate predictor of mortality in patients with no history of heart failure [52], [53].

The trend of blood pressure (BP) is also evaluated during the execution of the cardiopulmonary exercise test. International guidelines, in fact, recommend measuring the patient's blood pressure during the exercise phase several times, but also before the start of the test (supine or sitting) and during the recovery phase.

At rest, a blood pressure below 140/90 mmHg is considered normal and optimal if below 120/80 mmHg. During exercise the systolic BP of a healthy subject increases by about 3.6 mmHg per ml/min/kg of VO_2 consumed, while during the recovery phase the pressure decreases until it returns to values close to those present at rest before the test. An increased BP response to physical exercise may indicate the presence of a greater risk of the onset of hypertension in subjects previously considered normotensive [54]; slow BP recovery after exercise, on the other hand, was associated with a higher risk of myocardial infarction [55], [56] in subjects with no previous history of cardiovascular disease.

The behaviour of the RER in recovery is one of the topics that has attracted the most attention in recent times. In healthy subjects, what typically occurs is the so-called phenomenon of RER overshoot, that is the increase of the values of the respiratory exchange ratio during recovery compared to those registered at peak exercise. Given that the RER represents the ratio between the carbon dioxide produced and the oxygen consumed, it can be considered an extremely representative parameter for the evaluation of respiratory indices.

The most significant works in the literature have shown that RER overshoot is reduced in patients with left heart failure and therefore with cardiogenic limitation to physical exercise [57]; the same thing cannot be said, however, for patients with peripheral limitations, for example kidney transplant recipients (KTR) [58]. Reduced RER overshoot in patients with left heart failure was mainly interpreted as the result of delayed recovery of normal VO_2 and cardiac output; the slow recovery kinetics of these parameters is testified by numerous publications in the literature [59], [60].

The breathing equivalents (VE/VO_2 and VE/VCO_2) can be evaluated in the sixth Wasserman panel (Figure 9). As previously mentioned, during the test the values of the breathing equivalents progressively decrease up to AT for VE/VO_2 and up to RCP for VE/VCO_2; the study of the latter curve proved to be particularly important in the prognostic stratification of patients with heart failure [38]. After reaching their nadirs, the two curves of the breathing equivalents grow progressively due to the increase in ventilation; in the recovery phase, an initial growth of VE/VO_2 is observed, due to the fact that the restoration of normal values of VE and VCO_2 in a normal subject is slower than those of VO_2 [61]. In cardiac patients, on the other hand, in which the recovery of VO_2 is also delayed after the phase of maximal physical exercise [60], it can be expected that the phenomenon of VE/VO_2 overshoot is reduced compared to a normal subject [61].

The end tidal pressures of oxygen and carbon dioxide are evaluated in the ninth Wasserman panel (Figure 9): as already explained above, $PETO_2$ initially decreases and then progressively increases after the first ventilatory threshold, while $PETCO_2$ grows up to AT, describes a plateau between the two thresholds and then decreases after RCP.

To understand the trend of $PETO_2$ in the recovery phase, the reasoning is the same regarding VE/VO_2: in normal subjects, since ventilation and VCO_2 return to pre-exercise values more slowly than VO_2, $PETO_2$ will also describe an overshoot, which seem to be reduced in heart failure patients [57].

The echocardiography: how it works and its role in congenital heart disease

Echography's general principles

Echography is an imaging examination that is based on the use of ultrasound. It is a generally non-invasive examination, easy to perform and which does not emit ionizing radiation, but has the disadvantage of being very operator-dependent [62], [63].

Ultrasounds are elastic mechanical waves with a frequency greater than 20 kHz; in diagnostics a range of waves between 1 and 20 MHz is used. The ultrasound speed is 1540 m/s, while the wavelength is inversely proportional to the frequency [63].

In echography, the ability of ultrasounds to propagate inside the body through compressions and rarefactions is exploited. When they pass through tissues with different acoustic impedance, thus with a different resistance to being deformed by ultrasounds (for example, the bone has the highest impedance, while the lung has the lowest impedance), these mechanical waves are reflected in the exact direction opposite due to the phenomenon of reflection. Not all waves are reflected: the greater the difference in acoustic impedance between the two tissues, the more the waves come back, while the smaller this difference the more the transmission phenomenon is favoured, so the ultrasounds will continue to propagate to a greater extent trough the examined tissues. The angle at which they will propagate, however, will not be the same as the incidence one due to the phenomenon of refraction. In addition to reflection and refraction, the phenomenon of scattering must also be considered, that is, the multidirectional reflection created by jumps in point-like acoustic impedance. Eventually, the reflected waves returning will form the ultrasound image [63].

The instrument with which ultrasounds are performed is the echograph: the most important component is certainly the transducer, thanks to which the ultrasounds are produced and received due to the piezoelectric effect.

Another component of the ultrasound is the so-called acoustic coupler, which allows to equalize the acoustic impedance of the instrument and of the skin so that the ultrasounds produced by the transducer are not immediately reflected; the gel applied to the patient's skin also has the same aim.
When analysed, the reflected ultrasounds are then shown as an echographic image on a monitor [63].

As previously mentioned, due to the presence of a piezoelectric element, the transducer is able both to produce ultrasounds and to receive reflected waves. These are analysed and create an analogue trace that is immediately converted into a digital signal on a matrix that allows to represent the analysed tissue according to the return time of the reflected waves (directly proportional to the depth in which the jump in acoustic impedance occurs) and based on the intensity of these waves (directly proportional to the difference in acoustic impedance). The transducers currently used, analysing multiple 2D images at the same time, are even capable of producing 3D ultrasound reproductions of the tissues examined [63].

For the study of the flow and movement of tissues, in ultrasound imaging the Doppler effect is frequently used, such that the frequency of a sound wave increases or decreases depending on whether it moves away from or towards the listener. In the specific case of echography, the dynamic reflectors that make it possible to exploit the Doppler effect are the red blood cells: as it is possible to estimate their speed, dynamic images of the tissue examined can be obtained in real time. Through the Doppler signal it is therefore possible to assess the speed of the flow, its direction, its intensity and its properties (whether it is laminar or turbulent) [64, Ch. 1].

Echocardiography

Echocardiography is an ultrasound imaging method used to study the anatomy and function of the heart, valve structures and large vessels.

Transthoracic echocardiography: functioning, main parameters and clinical indications

There are several types of echocardiography, and certainly the most used is transthoracic echocardiography (TTE), in which, as can be easily understood, the ultrasound probe is placed on the patient's chest. Normally the patient is positioned in left lateral decubitus with the left hand behind the head, in order to bring the heart closer to the chest wall and widen the intercostal spaces to allow a better visualization of the cardiac structures.

Not all points of the chest are suitable for accurately studying cardiac anatomy: the probe is in fact usually placed in the suprasternal (1 in Figure 11), parasternal (2), apical (3) and subcostal (4) positions. These four positions allow to view the heart from different angles and to analyse the different structures from several points of view [64, Ch. 2]. Usually, the parasternal and apical windows are the ones that provide the most useful images in the adult, while in the child the subcostal window is also very important [65].

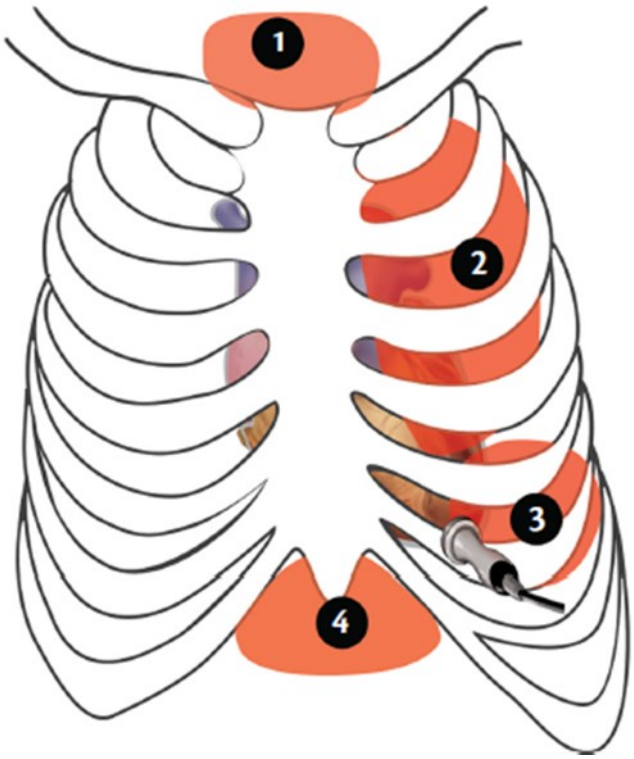

Figure 11: Probe positioning for TTE [64, Ch. 2].

The main guidelines recommend performing the echocardiographic study with 2D (and 3D), M-mode and Doppler techniques [66]:

- 2D echocardiography is a two-dimensional tomographic image of the heart tissue. It is the main echocardiographic technique both because it is the initial investigation with which cardiac structures are studied, and because the images acquired with this modality then serve as a reference for the M-mode and Doppler methods. To date, 3D echocardiography is also increasingly used in order to obtain a real time three-dimensional image of cardiac structures;
- M-mode is a method in which along a fixed scanning line there are continuous refreshments of the position of the various echoes that do not overlap the previous ones, but are placed side by side in succession to each other thus giving information on the motility of the part investigated along that single scan line over time. M-mode allows a much higher scanning speed than 2D ultrasound (2000 frames per second against 40-80 frames per second), with a high spatial and temporal resolution. Thanks to this, although 2D echocardiography has mostly replaced the M-mode technique, the latter is still used today above all in the evaluation of moving structures such as the aortic, pulmonary, mitral and tricuspid valves, but also the aortic root, the left atrium and the two ventricles;
- the main Doppler techniques used in echocardiography are spectral echo Doppler, echo color doppler and tissue doppler imaging. The first allows to analyse the speed and direction of the blood flow without giving spatial information; the second also studies the speed and direction of blood flow, but also the size and anatomy of the heart; the third measures the speed of myocardial contraction allowing to evaluate the systolic and diastolic function and to identify ischemia during stress tests. In echocardiography, the Doppler effect is widely used to assess valve stenosis and insufficiency, shunts and abnormal cardiac connections, and ventricular function [67]–[69].

Among the many parameters analysed in a routine echocardiographic investigation, biventricular function indices are certainly the best known and most used in the clinical setting. The ejection fraction (LVEF) is the best-known parameter that assesses the systolic function of the left ventricle: LVEF is the ratio (expressed as a percentage) between the volume of blood expelled during systole from the left ventricle and the end-diastolic ventricular volume; this parameter is so important both prognostically, diagnostically and even therapeutically, that heart failure is classified according to the ejection fraction of the left ventricle [70]. In echocardiography, LVEF can be calculated using M-mode, 2D and even 3D techniques:

- M-mode measurements are no longer recommended in clinical practice because, although they offer better spatial resolution than two-dimensional echocardiography, they are difficult to reproduce and have other important limitations [71];
- two-dimensional echocardiography is the method suggested by international guidelines for the measurement of LVEF [71]. The main technique with which it is evaluated is the modified Simpson method, which is based on the calculation of the ventricular volume (and consequently of the LVEF) by adding a series of elliptical discs of equal height [72];
- three-dimensional echocardiography measurements are becoming increasingly popular.

LVEF is considered normal if it is higher than 55%, while it is considered reduced for lower values: if its value is between 45 and 54% it is considered slightly reduced, for values between 30 and 44% it is moderately reduced, finally a severely reduced LVEF is for values below 30%.

As regards to the right ventricle, tricuspid annular plane systolic excursion (TAPSE) and fractional area change (FAC) are the main parameters that evaluate its systolic function.

TAPSE represents the displacement of the tricuspid valve plane towards the cardiac apex during ventricular systole. As well as FAC, this parameter, measured in M-mode, is related to the systolic function of the right ventricle and is

considered normal for values greater than 16 mm, while lower values indicate right ventricular systolic dysfunction [71], [73].
On the other hand, FAC represents the percentage of shortening of the right ventricle between systole and diastole:

FAC = (RV end-diastolic area - RV end-systolic area) / RV end-diastolic area.

This index, measured in 2D mode, provides an overall estimate of the systolic function of the right ventricle and is considered normal for values greater than 35% [71], [73].

TTE currently plays a crucial role in the diagnostic-therapeutic pathway for a great variety of pathological conditions, including myocardial infarction, heart failure, valve diseases, endocarditis, evaluation of organ damage in arterial hypertension, pericarditis, cardiac tamponade, pulmonary hypertension, emboli, cardiac masses, cardiomyopathies and congenital heart disease [62], [74].

Transesophageal echocardiography

Transesophageal echocardiography is another type of echocardiography: this examination is considered invasive because it requires the probe to be introduced into the patient's esophagus, with consequent ultrasound observation of the cardiac structures from the esophagus and stomach, avoiding the interposition of the thoracic cage and lungs that occurs in classical transthoracic echocardiography. Transesophageal echocardiography allows to visualize in greater detail the posterior structures of the heart (left atrium, left auricle and interatrial septum for example), the valve structures and the ascending aorta. The imaging modalities that are acquired with transesophageal echocardiography are the same that were previously discussed for transthoracic echocardiography [75].

Transesophageal echocardiography is frequently used for intraoperative evaluation during interventions (both percutaneous and surgical) such as left auricle closure, aortic and mitral valve repair, treatment of obstructive hypertrophic cardiomyopathy and congenital heart disease. The guidelines also indicate its role in the evaluation of endocarditis, in the diagnosis of aortic

dissection and aneurysm, in the search for possible sites of embolism, in the evaluation of intracardiac masses and in the diagnosis of prosthetic valvular disorders [75], [76].

Role of echocardiography in congenital heart disease

As explained extensively above, the number of patients with CHD reaching adulthood is constantly increasing; for this reason, it is essential that these subjects are followed throughout their entire life. In this sense, transthoracic echocardiography represents a first-line imaging investigation for the diagnosis and follow-up of patients with CHD, allowing the evaluation of the complex anatomy and pathophysiology of the heart of these patients. An appropriate use of echocardiography, among other things, reduces the number of invasive diagnostic investigations that these patients have to undergo over the course of their life, such as cardiac catheterization (once almost mandatory to make an accurate diagnosis) and magnetic resonance [31], [77].

Very often the diagnosis of these diseases is made by echocardiography. If a high risk of CHD is already identified during pregnancy, for example due to the presence of a positive family history for this type of disorder or for genetic diseases, doubtful or pathological findings on obstetric ultrasound, and altered screening examinations during pregnancy, a second level foetal echocardiography is performed to look for this type of lesion. Often this early investigation is diagnostic, especially for more complex congenital heart diseases such as ToF, hypoplastic left heart syndrome or TGA; an early diagnosis often improves the post-natal outcome of these pathologies [78]–[80]. If the disease is not diagnosed during pregnancy with foetal echocardiography, it is still possible that the disease is found at birth at the onset of the first symptoms (cyanosis, dyspnoea, signs of heart failure), and even in this case echocardiography is the first-line examination required for the definitive diagnosis. If the disease is less severe, such as in patients with atrial or ventricular septal defects or with mild aortic coarctation, the diagnosis can be reached, again by echocardiography, several years after birth when the first symptoms of the underlying disease appear.

As mentioned above, TTE is performed, together with other imaging methods such as CT and magnetic resonance, also in the follow-up of these patients because it allows to evaluate the state of the lesions of these subjects after surgical correction. With echocardiography, in fact, it is possible to study the morphology of the heart chambers, the ventricular function, the presence of shunts and the state of the heart valves; among other things, this imaging method is constantly evolving and allows more and more accurate measurements of the cardiac anatomy and of its function.

As previously discussed, the parameters describing ventricular function are the best known and most used in the clinical setting. This is also true in patients with CHD [77]: in addition to the undisputed importance in all CHD of LVEF from a diagnostic and prognostic point of view, in these patients the evaluation of the function of the right ventricle plays an important role as well. This is particularly true in diseases like ToF, given the presence of an interventricular septal defect, of right ventricular hypertrophy and pulmonary outflow stenosis. In patients with Fontan circulation, ventricular function is not always quantitatively assessed with the parameters mentioned above, but more often qualitatively, by evaluating its contractility and the presence of dilatation.
Among other noteworthy aspects, in patients with TGA and CoA echocardiography routinely evaluates the presence of stenosis (especially near surgical sites) and its gradient; this is true also for ToF patients. Another parameter often evaluated in all CHD is the mean pulmonary artery pressure [81]: this index, alongside the evaluation of CPET gas exchange indices such as VE/VCO_2, then allows the diagnosis of pulmonary hypertension, a very common complication in these patients.

Echocardiography also allows the physician to decide which type of treatment is most suitable for each patient. For example, guidelines show that [31]:

- in patients with atrial or interventricular septal defects echocardiography allows to establish the precise location of the defect, quantify the extent of the shunt and verify the presence of right and left ventricular dilatation,

in order to possibly refer the patient to surgery or percutaneous treatment;

- in patients with corrected tetralogy of Fallot, echocardiography allows to evaluate and quantify the presence of residual shunts at the level of the interventricular septum or residual pulmonary stenosis (which can arise even years after surgery), in order to be able to treat these lesions.

Transesophageal echocardiography, on the other hand, is widely used immediately before or during interventions such as the positioning of devices for occlusion of a shunt, atrioseptostomy (Rashkind procedure), the repairing of dysfunctional valves and stenting. The main guidelines recommend using transesophageal echocardiography even if the transthoracic approach did not provide ultrasound images of adequate quality [82].

2. INTRODUCTION AND GOALS OF THE STUDY

Congenital heart disease (CHD) is a structural abnormality of the heart or of intrathoracic vessels that is potentially of functional significance [83]. CHD accounts for nearly one-third of all major congenital anomalies and its birth prevalence worldwide and over time is suggested to vary [2]. Recent data extracted from European Surveillance of Congenital Anomalies show an average total prevalence of CHD in Europe around 8.0 per 1000 births [84]. In this patient population, long-term survival is decreased [85], with lesion severity and repair status as risk factors for increased mortality [86]. However, due to improvements in medical, surgical, and intensive care interventions, the life expectancy of patients born with CHD has been rising over time [85].

As patients with CHD have to live their whole life with the pathophysiological consequences of their malformations, they require a long term cardiological follow-up. Among all diagnostic investigations, echocardiography is one of the most important to evaluate the anatomical and functional complexity of these patients [31]. It is an easy to perform, reproducible test which does not emit ionizing radiation, and its appropriate use in CHD patients avoids the need for invasive investigations such as CT, magnetic resonance and cardiac catheterization [31], [77]. Among the numerous echocardiographic parameters, the evaluation of the systolic function of the left ventricle (such as LVEF: left ventricular ejection fraction) and of the right ventricle (like TAPSE: tricuspid annular plane systolic excursion, and FAC: fractional area change) are of main importance [77].

Cardiorespiratory fitness is highly heterogeneous both within and between individuals with CHD, with the more severe conditions presenting with lower levels of fitness and efficiency [87]. In this context, cardiopulmonary exercise testing (CPET) has emerged as an important tool for risk stratification and may guide clinicians in assessing prognosis and planning interventions in CHD patients [88], [89]. Indeed, many cardiopulmonary parameters have been recognized as important prognostic markers in patients with cardiac limitation to exercise: primarily peak oxygen uptake (VO_2 peak) and the ventilation to carbon dioxide production ratio (VE/VCO_2) [25]. VO_2 peak is an index of cardiorespiratory fitness

and a strong predictor of cardiovascular disease and all-causes mortality [90]. VE/VCO_2, instead, is a parameter that measures the cardiorespiratory efficiency of the patient [91]. Among the less studied CPET parameters, instead, HR/VO_2 slope is a parameter that assesses the efficiency of the chronotropic response in meeting the increased metabolic needs during exercise, thus it is an index of cardiovascular function [42].

Most of the studies about CPET are focused on the cardiopulmonary response during exercise [25], [92]; on the contrary, there is very little evidence about the behaviour of respiratory gas indices during recovery from maximal exercise testing. In patients with heart failure the recovery from maximal exercise testing has been studied with the overshoot phenomenon of the VO_2, that is a transient increase of VO_2 in the first post-exercise period [93]. This phenomenon has been linked to the brief rise in cardiac output due to an imbalance between afterload reduction and cardiac contractility, possible reasons that have been proposed to explain this phenomenon are either a gradual reduction in adrenergic tone or the repayment of the accumulated O_2 deficit [60], [94].

In the past years Takayanagi et al. [57] have investigated the overshoot phenomena of other cardiopulmonary parameters, like respiratory exchange ratio (RER: VCO_2/VO_2), end-tidal partial pressure of O_2 ($PETO_2$) and the ventilation to oxygen production ratio (VE/VO_2). In this article the overshoot magnitudes of this parameters between heart failure patients and healthy subjects have been compared, demonstrating that overshoots tended to be larger in subjects with better cardio-pulmonary function during exercise. Additionally, the authors discovered no correlation between the overshoot magnitude of the investigated parameters and the degree of left ventricle ejection dysfunction, indicating that the resting cardiac function is not directly related to this phenomenon [57].

To consider also the possible impact of peripheral (e.g., muscular and vascular) factors in the genesis and modulation of this phenomenon, Patti et al. have investigated the recovery of the RER in a population of patients with peripheral limitations (kidney transplant recipients) and absence of significant heart disease. The results were concordant with previous studies: patients with diminished cardiorespiratory fitness and efficiency (higher VE/VCO_2 slope, lower oxygen

uptake efficiency slope (OUES)) had smaller RER overshoot magnitudes [58]. There is currently no evidence in literature about the characterization of the respiratory gas indices after maximal exercise testing in CHD patients.

The aim of the present study is thus to evaluate the behaviour of the RER overshoot during recovery in a population of patients with 4 different kinds of CHD and compare the results with an age-matched healthy control group.

3. MATERIALS AND METHODS

The proposed study is a cross-sectional retrospective case-control study that included 103 patients with CHD undergoing functional evaluation and exercise prescription at the Division of Sports and Exercise Medicine of the Department of Medicine – University of Padova between 2018 and 2021. Patients with Transposition of the Great Arteries (TGA), Coarctation of the Aorta (CoA), Tetralogy of Fallot (ToF) and with Fontan circulation were included in the study. Furthermore, 28 healthy subjects undergoing medical examination for preparticipation screening for competitive sports were included. The age of the study participants (both patients with CHD and healthy controls) ranged from 7 to 20 years.

The exclusion criteria for the study were:

- cardiovascular and orthopaedic problems that contraindicated the execution of the test;
- patients taking β-blocker therapy;
- patients with pacemaker;
- patients whose gas exchange monitoring in the recovery phase after the test lasted less than two minutes;
- patients in whom RER max was not clearly identifiable (Figure 12);
- patients who have not reached a maximal test for RER (<1.10) or maximum HR (<85% of predicted HR max).

Cardiopulmonary exercise test protocol

For each patient, medical and drug history was collected, and a thorough physical examination was performed before cardiopulmonary exercise testing (CPET). All subjects underwent functional assessment after signing their informed consent. The stress test was performed on a treadmill (COSMOS model T170 DE-med).

An incremental ramp protocol was used for the exercise test, which was adapted to the characteristics of each patient and to their level of physical activity with the

aim of reaching exhaustion within 8-15 minutes. The test was performed until patients achieved a Borg rating of perceived exertion greater than or equal to 18/20. In addition, cardiac activity was continuously monitored through a 12-lead electrocardiogram and blood pressure through auscultatory evaluation before the test, during exercise and also during the recovery phase.

The respiratory gas exchange (VO_2, VCO_2) and ventilation (VE) were monitored "breath by breath" throughout the duration of the test and in the first 4 minutes of recovery (Jaeger Masterscreen CPX system, Carefusion, Hoechberg, GE).

VO_2 peak was defined as the highest value reached in a 30 second interval at the peak of exertion. Age-predicted maximum heart rate (HR) was calculated using the formula 220 - age, and expressed in bpm. The first ventilatory threshold was identified using the simplified V-slope method; if the AT was not clearly detectable with this method, it was evaluated by two experienced doctors considering the behaviour of the ventilatory equivalents. In addition to the first ventilatory threshold, the respiratory compensation point, or the second ventilatory threshold, was also assessed by two experienced doctors considering the behaviour of the ventilator equivalents and the $PETCO_2$.

The slope of the VE/VCO_2 curve was calculated as a linear regression coefficient obtained by plotting the VE and VCO_2 data from the beginning of the exercise to the RCP.

The slope of the HR/VO_2 curve was obtained from a linear regression coefficient evaluated by plotting heart rate and VO_2 data after initial HR stabilization up to the RCP.

The slope of the OUES was calculated as the coefficient of the linear relationship between oxygen consumption and the logarithm of total ventilation.

All the analysed data are the result of weighted averages over 5 seconds of the individual "breath by breath" measured values to avoid possible confounding values due to inconstant ventilation or sampling errors.

The behaviour of RER during recovery was analysed and evaluated based on five parameters (Figure 12):

- RER peak: it was defined as the highest RER value reached during exercise;
- RER max: it was defined as the highest RER value reached during the recovery phase;
- RER mag: it was calculated as the relative increase (%) of RER during recovery comparing RER max to RER peak;
- RER slope: it was calculated by linearly regressing RER values compared to time from RER peak to RER max;
- time to RER max: it was defined as the time in seconds to reach the maximum RER value starting from RER peak.

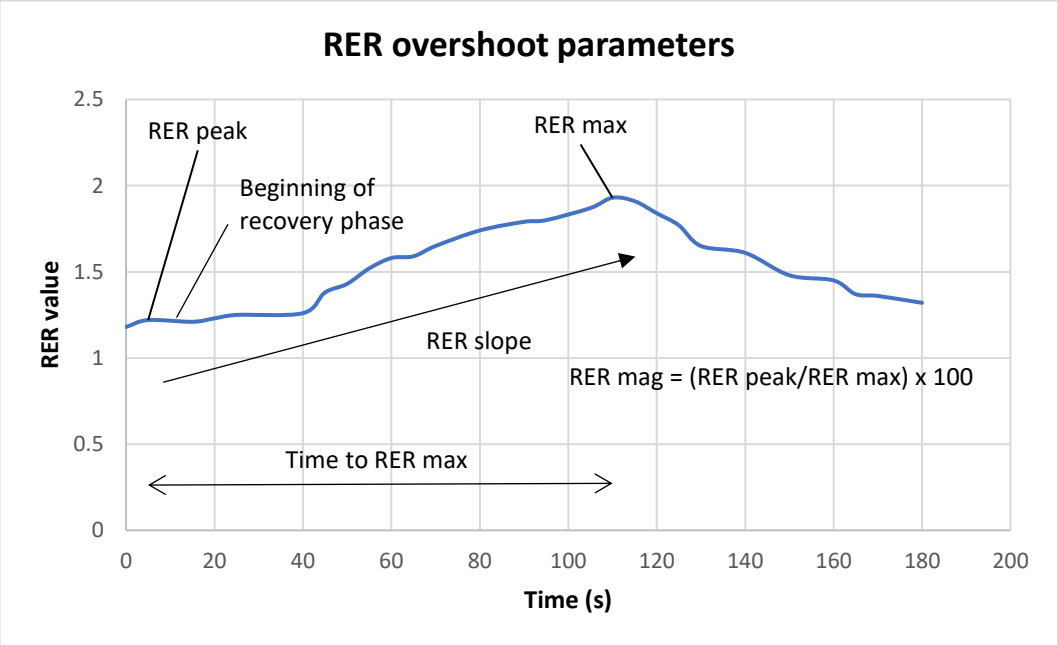

Figure 12: Visual representation of the RER overshoot parameters described above (obtained from a patient included in the study).

Ventricular function assessment

Data regarding ventricular systolic function were obtained by echocardiographic evaluation. All the echocardiography assessment from which these data were obtained have been performed in the context of the follow-up of these patients at the Department of Women's and Children's Health – University of Padova.

The parameter chosen to quantify the systolic function of the left ventricle is the ejection fraction (LVEF), which indicates the ratio (expressed as a percentage)

between the volume of blood expelled during systole from the left ventricle and the end-diastolic volume. For the systolic function of the right ventricle, on the other hand, tricuspid annular plane systolic excursion (TAPSE), which is the displacement of the tricuspid valve plane towards the cardiac apex during ventricular systole, and fractional area change (FAC), as shortening percentage of the right ventricle between systole and diastole, were evaluated. LVEF and FAC were measured with 2D-mode echocardiography (except for 6 cases in which EF was quantified in M-mode), while TAPSE with M-mode echocardiography.

Subgroups analysis

Four subpopulations of patients were identified from the cohort of the initial general sample of CHD to specifically study the behaviour of CPET parameters during the recovery phase in different pathologies, in order to highlight any functional and prognostic differences. The four groups of CHD patients refer to different pathologies: Transposition of the Great Arteries (TGA), s/p Fontan procedure, Coarctation of the Aorta (CoA) and Tetralogy of Fallot (ToF).

Statistical analysis

The normality was assessed using the Shapiro-Wilk test. To describe the quantitative variables that were found to be normally distributed, the data were expressed as mean ± standard deviation; otherwise, the median and variance were provided. For data relating to the qualitative variables, the absolute value and the percentage of the total were used. The difference between subgroups was assessed with a t-test for the normally distributed variables and a Mann–Whitney U test for the non-normally distributed variables. The various classes of CHD were compared with each other with an ANOVA test for normally distributed variables and with a non-parametric test for non-normally distributed variables. The correlations were evaluated with Pearson's correlation index if they were normally distributed and Spearman's correlation index if they were non-normally

distributed. Linear correlations between the main determinants of RER overshoot and the main cardiopulmonary parameters were evaluated. Statistical analysis was performed using IBM SPSS Statics software version 25. A statistical significance level of $p \leq 0.05$ was used for all analyses.

4. RESULTS

131 young subjects were initially recruited into the study, including 103 patients with CHD and 28 healthy subjects, aged between 7 and 20 years.

In the CHD group, 7 patients were excluded from the study because it was not possible to clearly identify an overshoot during the time interval recorded during the recovery phase, one patient was excluded due to a sampling error during the test, and 2 patients were excluded because they did not reach a maximal test (failure to reach a RER>1.10 or because of premature termination of the test for reasons other than exhaustion). At the end of the inclusion process, the CHD group was made up of 93 elements.

In the healthy group, 3 patients were excluded because it was not possible to clearly identify a RER peak during the recovery phase, and one patient because he was unable to reach the needed criteria for exhaustion. The healthy group, therefore, was made up of 24 subjects.

Baseline characteristics

The general anthropometric and clinical characteristics of the study participants are represented in Table II.

Variables	Healthy	CHD	TGA	Fontan	CoA	ToF
Females, n (%)	11 (46%)	34 (37%)	4 (17%)	9 (41%)	9 (38%)	12 (50%)
Age (years)	14.00 (12.73 – 14.95)	14.00 (13.75 – 15.06)	14.00 (13.18 – 15.60)	16.00 (13.57 – 16.16)	14.00 (12.46 – 15.29)	14.00 (13.00 – 16.09)
Height (cm)	156.00 ± 14.60	161.50 ± 13.51	164.80 ± 10.53	161.82 ± 14.90	159.30 ± 13.80	160.25 ± 14.65
BMI (Kg/m^2)	19.70 (18.47 – 20.65)	20.10 (19.79 – 21.60)	21.40 (20.26 – 24.79)	19,70 (17.98 – 20.13)	20.39 (18.59 – 22.31)	19.80 (18.80 – 22.57)
SBP rest, (mmHg) [a]* [b]***	106.20 ± 15.10	114.25 ± 14.38	118.22 ± 11.92	104.64 ± 15.05	119.92 ± 14.65	113.60 ± 11.50
DBP rest, (mmHg) [a]*	53.80 ± 9.50	64.92 ± 9.80	63.35 ± 10.30	63.60 ± 8.61	66.12 ± 9.64	66.50 ± 10.65
Desaturation at rest, n (%) [b]*	0 (0%)	5 (5%)	0 (0%)	5 (23%)	0 (0%)	0 (0%)
Competitive sports, n (%)	23 (96%)	2 (2%)	0 (0%)	0 (0%)	2 (8%)	0 (0%)
Cardio-Aspirine, n (%)	0 (0%)	72 (77%)	1 (4%)	18 (82%)	0 (0%)	2 (8%)
Anti-hypertensive drugs, n (%)	0 (0%)	9 (96%)	1 (4%)	7 (32%)	1 (4%)	0 (0%)

*Table II: Clinical characteristics of the study subjects. Normally distributed variables are expressed with mean and standard deviation, non-normally distributed variables are expressed with median and confidence intervals; qualitative variables are expressed with percentage of the total. BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; [a] = statistically significant difference between the healthy and the CHD group; * = p<0.001; [b] = statistically significant difference between the 4 subgroups; ** = p<0.05.*

Among the clinical characteristics at baseline of the subjects included in the study, resting systolic and diastolic blood pressures were higher in CHD patients than in healthy controls: SBP was 114.25 ± 14.38 mmHg in the CHD group (p=0.022) and 106.20 ± 15.10 mmHg in the healthy group, while DBP was 64.92 ± 9.80 mmHg in the CHD group and 53.80 ± 9.50 mmHg in the healthy group (p<0.001). Statistically

significant differences were found between the 4 subgroups of CHD in SBP (p=0.001), with patients with CoA having the highest mean resting SBP (119.92 ± 14.65 mmHg).

None of the subjects included in the control group had a lower-than-normal oxygen saturation at rest, while 5 patients (all belonging to the Fontan group) also desaturated at rest before the start of the exercise phase.

Cardiopulmonary exercise testing and echocardiography assessments

All patients performed their respective treadmill stress tests with the same protocol (Bruce Ramp) until perceived exhaustion (rate of perceived exertion ≥ 18/20 of the Borg scale) with no reported symptoms. The results of the CPET are described in Tables III and IV. The echocardiographic indices of left and right ventricle systolic function are shown in Table IV.

Variables	Healthy	CHD	p Value
HR peak (bpm)	190.00 (185.35 – 192.89)	184.00 (178.21 – 185.41)	0.013
HR peak % predicted (%)	91.00 (89.82 – 93.70)	90.00 (86.41 – 89.97)	0.042
HRRes (bmp)	116.00 (111.59 – 120.17)	111.00 (103.6– 111.78)	0.087
HRRec 1 (-bpm)	-33.00 (-44.12 – (-30.84))	-26.00 (-31.03 - (-25.71))	0.007
HR/VO_2 slope	7.03 ± 3.12	8.34 ± 3.34	0.140
O_2 pulse (mL)	11.10 (10.45 – 13.55)	10.20 (10.25 – 11.69)	0.174
O_2 pulse % predicted (%)	104.00 (100.93 – 118.19)	93.00 (91.02 – 99.63)	0.005

Oxygen Pulse Behaviour	Normal: 24 (100%)	Normal: 65 (70%) Early Plateau: 25 (27%) Deflection: 3 (3%)	0.007
SBP peak (mmHg)	150.00 (140.60– 157.00)	150.00 (143.9– 153.40)	0.947
DBP peak (mmHg)	50.00 (45.48 – 56.12)	60.00 (58.29 – 64.40)	< 0.001
SpO_2 peak (%)	99.00 (98.86 – 99.53)	98.00 (95.11 - 96.84)	< 0.001
Desaturation at peak, n (%)	0 (0%)	19 (21%)	0.012
VE/VCO_2 slope	27.93 (26.36 – 29.35)	29.14 (28.73 – 30.61)	0.102
OUES (mL/logL)	1849.19 (1739.05- 2281.50)	1784.00 (1739.96- 1994.13)	0.365
VO_2 peak pro kg (mL/min/kg)	43.72 ± 6.13	36.27 ± 8.33	< 0.001
VO_2 % predicted (%)	108.84 ± 15.82	86.70 ± 17.90	< 0.001
VO_2 at AT (mL/Kg/min)	23.90 (22.34 – 26.22)	22.80 (21.81 – 24.50)	0.229
VO_2 at RCP (mL/Kg/min)	34.50 (32.28 – 38.89)	28.200 (27.69 – 30.57)	< 0.001
METs	16.76 ± 2.09	15.03 ± 2.48	0.001

Table III: CPET parameters of the healthy and the CHD group. Normally distributed variables are expressed with mean and standard deviation, non-normally distributed variables are expressed with median and confidence intervals; and qualitative variables are expressed with percentage of the total. HR = Heart Rate; HRRes = Heart Rate Reserve (maximal HR – resting HR); HRRec 1 = Heart Rate Recovery after one minute; VO_2 = oxygen uptake; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; SpO_2 = oxygen saturation; VE/VCO_2 slope = minute ventilation/carbon dioxide production slope; VCO_2 = carbon dioxide production; AT = Anaerobic Threshold; RCP = Respiratory Compensation Point; OUES = Oxygen Uptake Efficiency Slope; METs = Metabolic Equivalents of Task.

Variables	TGA	Fontan	CoA	ToF	p Value
HR peak (bpm)	187.00 (173.36 – 193.25)	176.00 (166.44 – 180.10)	190.00 (184.74 – 194.51)	182.50 (174.01 – 186.74)	< 0.001
HR peak % predicted (%)	92.00 (84.13 – 94.05)	85.50 (80.80 – 87.65)	92.00 (89.37 – 94.22)	89.00 (84.22 – 90.53)	0.001
HRRes (bmp)	122.00 (99.22 – 120.70)	103.50 (90.68 – 108.23)	117.00 (107.70 – 121.83)	104.50 (100.11 – 112.14)	0.036
HRRec 1 (-bpm)	-28.00 (-35.61 – (-24.13))	-18.50 (-25.79 – (-16.39))	-30.00 (-37.50 – (-27,34))	-26.00 (-35.20 – (-23.88))	0.006
HR/VO_2 slope	7.30 ± 2.65	9.27 ± 3.72	7.28 ± 2.42	9.55 ± 3.87	0.350
O_2 pulse (mL)	11.10 (11.27 – 13.77)	8.85 (8.44 – 10.76)	10.85 (9.61 – 13.07)	9.05 (8.83 – 11.92)	0.006
O_2 pulse % predicted (%)	100.00 (90.19 – 109.38)	86.00 (76.20 – 96.98)	97.50 (92.38 – 108.70)	92.00 (86.76 – 100.91)	0.057
Oxygen Pulse Behaviour	Normal: 15 (65%) Early Plateau: 6 (26%) Deflection:2 (9%)	Normal: 16 (73%) Early Plateau: 6 (27%) Deflection: 0	Normal: 21 (87%) Early Plateau: 3 (12%) Deflection: 0	Normal: 13 (54%) Early Plateau: 10 (42%) Deflection: 1 (4%)	0.147
SBP peak (mmHg)	150.00 (142.77 – 157.66)	137.50 (130.25 – 147.02)	150.00 (146.54 – 168.88)	147.50 (136.69 – 157.89)	0.088
DBP peak (mmHg)	60.00 (55.90 – 69.75)	60.00 (54.24 – 65.77)	50.00 (52.37 – 65.55)	60.00 (57.27 – 69.81)	0.562
SpO_2 peak (%)	98.00 (97.37 – 98.36)	92.00 (89.46 – 94.14)	98.00 (97.03 – 98.88)	97.50 (93.85 – 97.42)	< 0.001
Desaturation at peak, n (%)	0 (0%)	12 (60%)	1 (4%)	6 (27%)	< 0.001

VE/VCO_2 slope	28.25 (27.14 – 30.72)	31.06 (29.10 – 33.20)	28.17 (26.47 – 30.47)	28.68 (28.28 – 32.17)	0.204
OUES (mL/logL)	1990.00 (1804.69 – 2220.96)	1613.50 (1460.38 – 1949.52)	1887.50 (1695.67 - 2342.09)	1565.50 (1475.68 - 1972.49)	0.066
VO_2 peak pro kg (mL/min/kg)	36.83 ± 8.70	32.05 ± 5.90	40.98 ± 8.40	34.90 ± 7.85	< 0.001
VO_2 % predicted (%)	83.30 ± 15.80	76.64 ± 14.40	99.00 ± 17.10	86.92 ± 17.10	< 0.001
VO_2 at AT (mL/Kg/min)	22.80 (21.11 – 24.22)	21.40 (19.47 – 22.89)	25.60 (22.82 – 26.26)	21.60 (19.19 – 29.06)	0.082
VO_2 at RCP (mL/Kg/min)	28.80 (25.93 – 31.63)	25.10 (23.52 – 28.75)	31.45 (29.83 – 36.15)	28.00 (25.50 – 30.76)	0.005
METs	15.00 ± 2.61	14.72 ± 1.95	15.65 ± 2.80	14.75 ± 2.52	0.560
LVEF* (%)	63.00 (61.25 – 69.00)	58.00 (50.47 - 63.24)	68.00 (64.51 – 70.93)	66.00 (61.08 – 68.52)	0.004
TAPSE (mm)**	17.00 (15.21 – 18.10)	12.60 (9.15 – 18.59)	25.10 (22.24 – 27.10)	19.00 (16.67 – 20.59)	< 0.001
FAC* (%)**	40.50 (34.15 - 46.85)	48.00 (33.63 – 55.17)	42.50 (37.60 – 47.40)	44.00 (38.89 – 46.66)	0.895

*Table IV: CPET and echocardiographic parameters of the CHD subgroups. Normally distributed variables are expressed with mean and standard deviation, non-normally distributed variables are expressed with median and confidence intervals; qualitative variables are expressed with percentage of the total. HR = Heart Rate; HRRes = Heart Rate Reserve (maximal HR – resting HR); HRRec 1 = Heart Rate Recovery after one minute; VO_2 = oxygen uptake; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; SpO_2 = oxygen saturation; VE/VCO_2 slope = minute ventilation/carbon dioxide production slope; VCO_2 = carbon dioxide production; AT = Anaerobic Threshold; RCP = Respiratory Compensation Point; OUES = Oxygen Uptake Efficiency Slope; METs = Metabolic Equivalents of Task; LVEF = Left Ventricular Ejection Fraction; TAPSE = Tricuspid Annular Plane Systolic Excursion; FAC = Fractional Area Change; * = LVEF was reported in the echocardiographic reports of 86 patients: 21 from the TGA group, 18 from the Fontan group, 25 from the CoA group, 22 from the ToF group; ** = TAPSE was reported in the echocardiographic reports of 64 patients: 22 from the TGA group; 4 from the Fontan group; 18 from the CoA group, 20 from the ToF group; *** = FAC was*

reported in the echocardiographic reports of 22 patients: 2 from the TGA group, 5 from the Fontan group, 2 from the CoA group, 13 from the ToF group.

Considering the study population, the cardiovascular indices analysis reported numerous relevant data. Peak HR was lower in the CHD group than in the control group (p=0.013). The comparison of peak HR between the subgroups was statistically significant (p=0.001), with patients with Fontan having the lowest median (176 bpm). Even the HRRec after 1 minute showed statistically significant differences both between healthy subjects and CHD patients (p=0.007), as well as between subgroups (p=0.006), where patients with Fontan showed the slowest recovery.

As for the oxygen pulse, an anomalous behaviour was recorded in 28 patients with CHD, whereas all healthy control had a normal oxygen pulse behaviour during the test. Regarding the oxygen pulse as a percentage of predicted, patients with CHD showed lower values compared to healthy controls (p=0.005); statistically significant differences between the 4 classes of CHD were displayed as well (p=0.057).

The analysis of peripheral saturation at peak exercise (SpO_2 peak) showed that 19 patients with CHD desaturated at peak exercise (12 from the Fontan group), while none of the healthy controls had a lower-than-normal peripheral saturation.

Furthermore, aerobic capacity was significantly lower in patients with CHD compared to healthy subjects; statistically significant differences were also displayed between the 4 subgroups (in both cases p<0.001). Patients with Fontan recorded the lowest VO_2 peak pro kg values (32.05 ± 5.90 ml/min/kg), while those with CoA had the highest aerobic capacity (40.98 ± 8.40 ml/min/kg).

Respiratory exchange ratio overshoot analysis

Table V shows the comparison between the parameters concerning the phenomenon of RER overshoot during recovery phase between the groups.

Variables	Healthy	CHD	p Value	TGA	Fontan	CoA	ToF	p Value
RER peak	1.22 ± 0.11	1.23 ± 0.12	0.819	1.24 ± 0.14	1.22 ± 0.11	1.20 ± 0.12	1.24 ± 0.10	0.714
RER max	1.94 ± 0.28	1.77 ± 0.23	0.010	1.80 ± 0.25	1.74 ± 0.24	1.80 ± 0.21	1.75 ± 0.24	0.851
RER mag (%)	58.54 ± 14.72	44.41 ± 14.75	0.010	43.74 ± 13.81	42.31 ± 13.10	49.95 ± 15.23	41.42 ± 15.94	0.182
Time to RER max (s)	146.00 (126.31 - 164.17)	139.00 (129.47 - 151.50)	0.403	130.00 (107.60 - 151.87)	151.50 (137.58 - 186.60)	145.00 (119.90 - 170.51)	119.00 (108.58 - 143.92)	0.116
RER slope*100	34.40 ± 16.50	27.63 ± 13.52	0.037	29.81 ± 15.40	23.12 ± 10.84	28.80 ± 13.70	28.50 ± 13.60	0.349

Table V: RER overshoot parameters in the healthy group, in the CHD group and in the subgroups. Normally distributed variables are expressed with mean and standard deviation, non-normally distributed variables are expressed with median and confidence intervals. RER = Respiratory Exchange Ratio.

All included patients showed an overshoot of the RER after exercise. Although during exercise patients and controls showed similar RER peak, the behaviour of the RER during recovery was significantly different. Moreover, RER max, RER mag and RER slope revealed a lower RER overshoot for patients with CHD when compared to the healthy controls. However, no statistically significant difference was found for the RER overshoot parameters when CHD subgroups are compared.

Correlations

The correlations between RER overshoot parameters during the recovery phase and some of the main cardiopulmonary indices were assessed (Table VI).

Variables	RER peak	RER max	RER mag	RER slope	Time to RER max
Age (years)	0.428 (p=0.001)	0.277 (p=0.007)	-0.034 (p=0.744)	-0.085 (p=0.418)	0.174 (p=0.095)
Peak HR (bpm)	0.227 (p=0.021)	0.323 (p=0.001)	0.366 (p=0.001)	0.297 (p=0.004)	-0.042 (p=0.692)
HR/VO_2 slope	0.059 (p=0.581)	-0.135 (p=0.103)	-0.232 (p=0.004)	-0.154 (p=0.418)	-0.095 (p=0.089)
HRRec 1 (-bpm)	0.412 (p<0.001)	0.253 (p=0.014)	-0.042 (p=0.687)	0.122 (p=0.242)	0.006 (p=0.950)
VE/VCO_2 slope	-0.429 (p=0.001)	-0.343 (p=0.001)	-0.100 (p=0.334)	-0.201 (p=0.054)	-0.021 (p=0.840)
VO_2 at AT (mL/kg)	-0.265 (p=0.008)	-0.115 (p=0.274)	0.100 (p=0.343)	0.123 (p=0.245)	-0.060 (p=0.573)
VO_2 peak pro kg	-0.100 (p=0.314)	0.212 (p=0.040)	0.393 (p=0.001)	0.297 (p=0.004)	-0.048 (p=0.650)
OUES (ml/logL)	0.213 (p=0.031)	0.370 (p=0.001)	0.311 (p=0.002)	0.137 (p=0.191)	0.143 (p=0.170)

Table VI: Correlations between the RER recovery and CPET parameters expressed as Pearson's r for the normally distributed data and Spearman's ρ for the non-normally distributed data. HR = Heart Rate; VO_2 = oxygen consumption; HRRec 1 = Heart Rate Recovery after one minute; VE/VCO_2 slope = minute ventilation/carbon dioxide production slope; VCO_2 = carbon dioxide production; AT = Anaerobic Threshold; OUES= Oxygen Uptake Efficiency Slope; RER = Respiratory Exchange Ratio.

Peak HR showed significant correlations with both RER max (ρ=0.323; p<0.001) and RER mag (r=0.366; p<0.001). A significant negative correlation between RER mag and HR/VO_2 slope was displayed (Figure 13), as well as a positive correlation between RER max and HRRec after one minute.

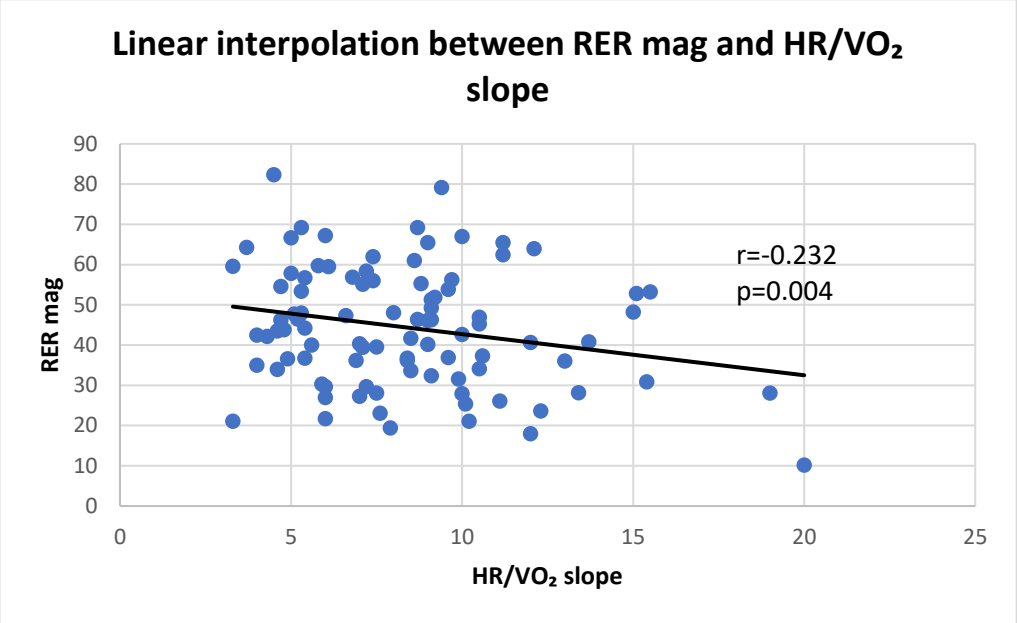

Figure 13: Graphic representation of the linear correlation between RER mag and HR/VO_2 slope. The line shows the linear interpolation between the single values obtained from the scatter plot.

Although the time to reach RER max in the recovery phase (time to RER max) and the linear slope of the RER during recovery (RER slope) showed few and weak correlations with the main CPET parameters, RER max and RER mag were significantly correlated with important cardiorespiratory fitness and efficiency indices, such as VO_2 peak pro kg and OUES. Correlation between RER mag and these two parameters are also visually displayed in Figures 14-15. Figures 16-17 show visual examples of different RER and VO_2 peak pro kg behaviours from patients included in the study.

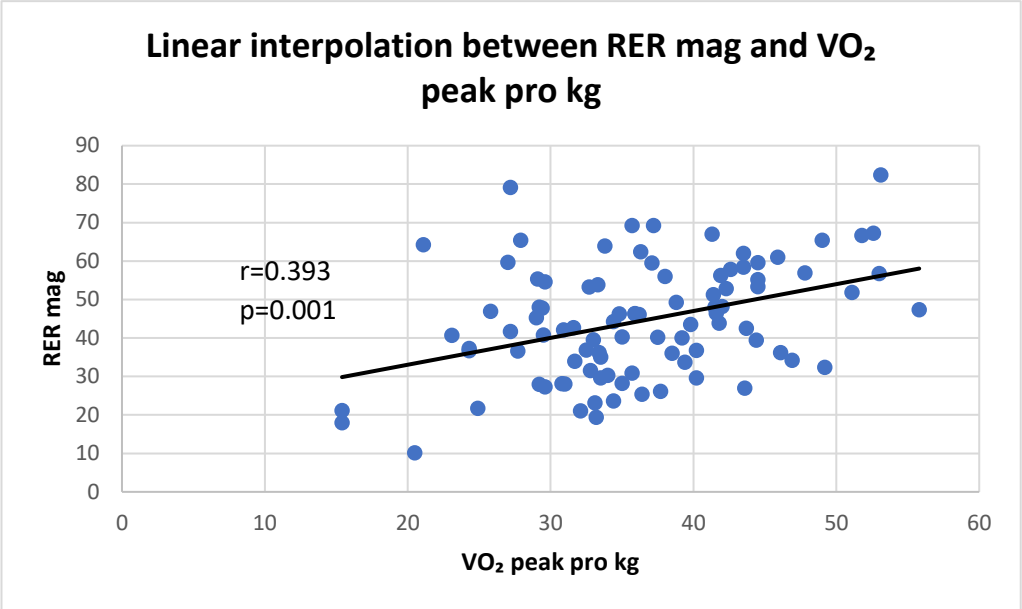

Figure 14: Graphic representation of the linear correlation between RER mag and VO_2 peak pro kg. The line shows the linear interpolation between the single values obtained from the scatter plot.

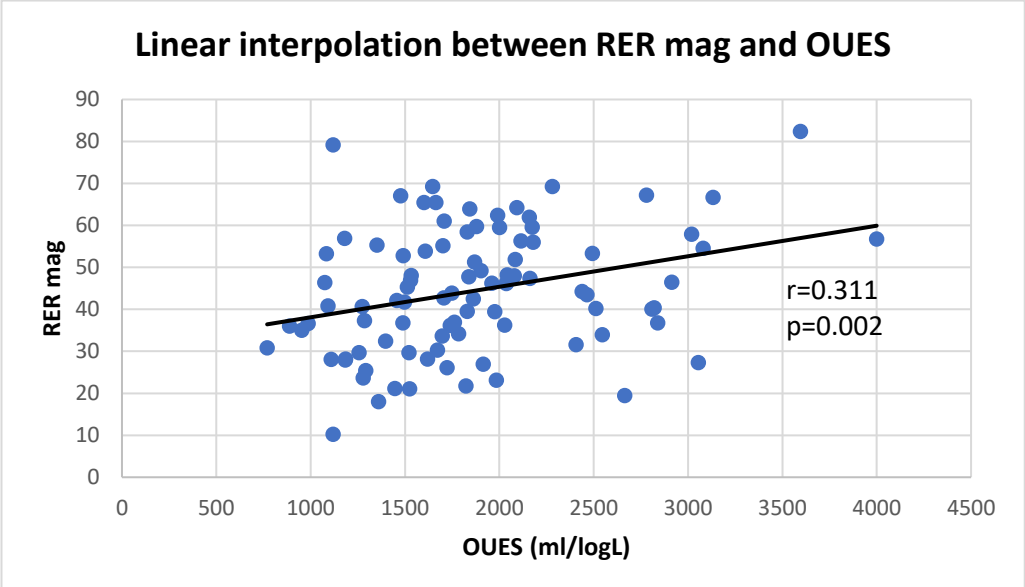

Figure 15: Graphic representation of the linear correlation between RER mag and OUES. The line shows the linear interpolation between the single values obtained from the scatter plot.

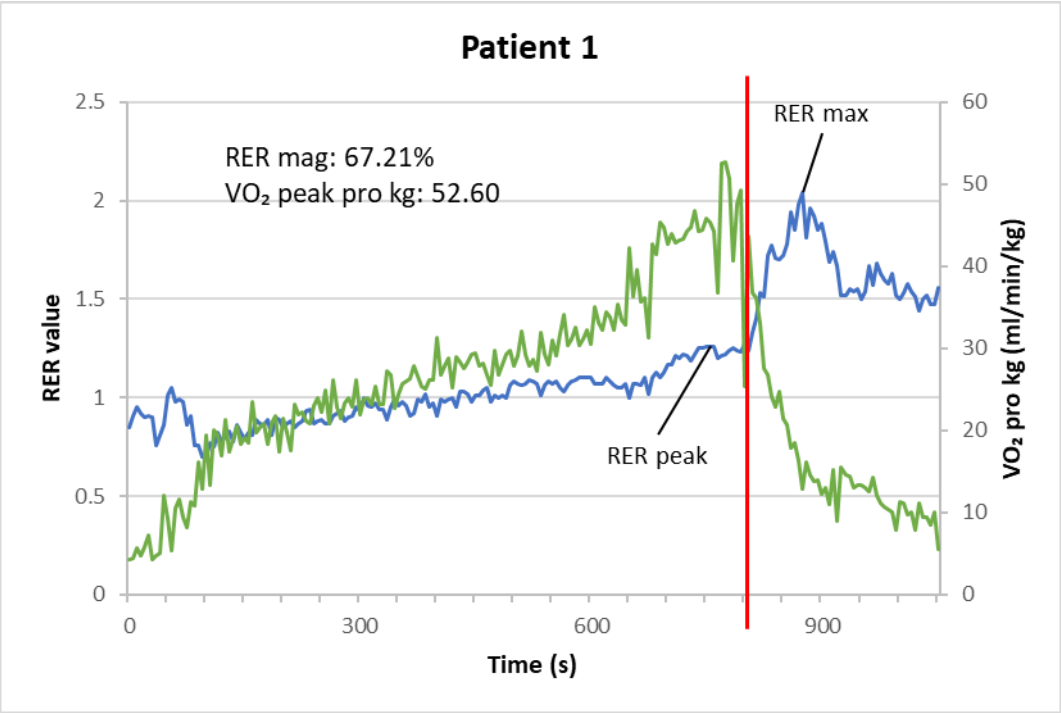

Figure 146: RER (blue line) and VO_2 pro kg (green line) during CPET and recovery (starting from red line) of a patient with TGA included in the study. This is an example of a patient with high RER overshoot and aerobic capacity.

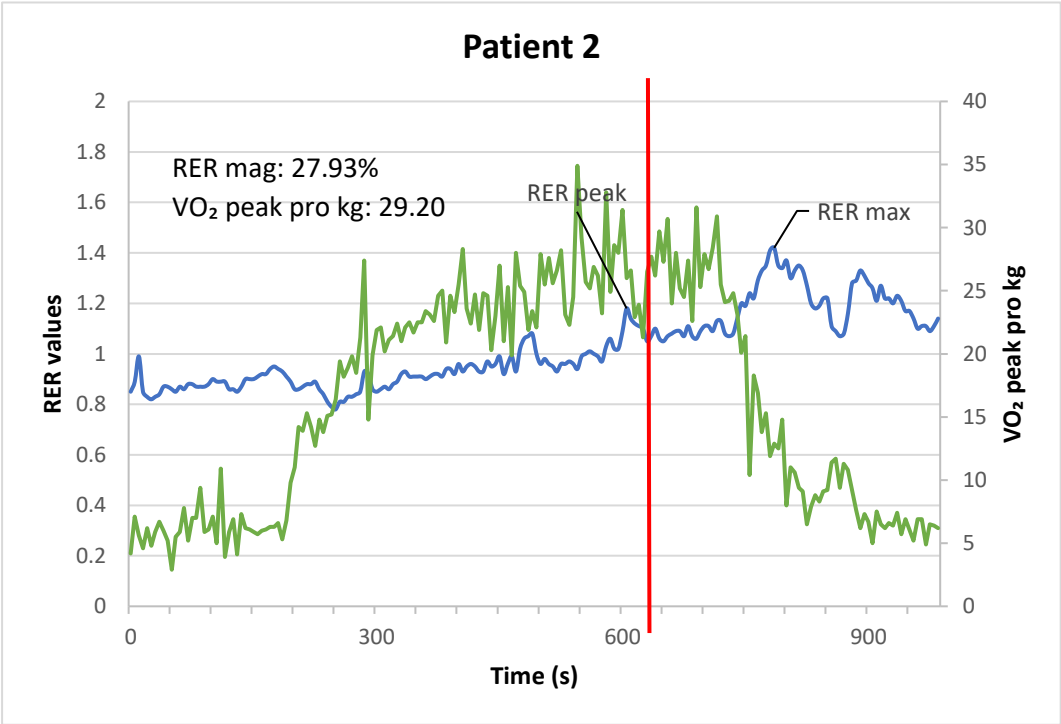

Figure 157: RER (blue line) and VO_2 pro kg (green line) during CPET and recovery (starting from red line) of a patient with Fontan circulation included in the study. This is an example of a patient with high RER overshoot and aerobic capacity.

Table VII does not show statistically significant correlations between the parameters that characterize the RER overshoot and LVEF, index of systolic function of the left ventricle. On the other hand, a significant correlation between TAPSE and RER max (ρ=0.312; p=0.012) emerged, without any other significant associated correlations.

Echocardiographic variables	RER peak	RER max	RER mag (%)	RER slope	Time to RER max
LVEF (%)	0.056 (p=0.608)	-0.003 (p=0.975)	0.002 (p=0.989)	0.083 (p=0.449)	-0.072 (p=0.510)
TAPSE (mm)	0.241 (p=0.057)	0.312 (p=0.012)	0.151 (p=0.234)	-0.083 (p=0.516)	0.192 (p=0.132)
FAC (%)	0.199 (p=0.365)	-0.068 (p=0.764)	-0.065 (p=0.772)	0.035 (p=0.877)	-0.090 (p=0.692)

Table VII: Correlations between the RER recovery and echocardiographic variables expressed as Pearson's r for the normally distributed data and Spearman's ρ for the non-normally distributed data. LVEF = Left Ventricular Ejection Fraction; TAPSE = Tricuspid Annular Plane Systolic Excursion; FAC = Fractional Area Change; RER = Respiratory Exchange Ratio.

5. DISCUSSION

To the best of authors' knowledge, this is the first study that has evaluated the overshoot parameters of the respiratory gas exchange and in particular the behaviour of the RER during recovery from maximal exercise testing in young patients with CHD.

Patients with CHD are subjects who, despite the improvement in medical and surgical therapies occurred over the last few years, are still forced to live their whole life with the pathophysiological alterations due to their disease and to the sequelae of surgical interventions. These alterations mainly involve the cardiovascular system (with consequent cardiogenic limitation to physical exercise), but, in complex CHD, also the whole organism [23], [24]. Therefore, a comprehensive functional evaluation with maximal CPET is strongly recommended in current guidelines [31]. Since most of the literature concerning the evaluation of CHD by CPET focuses on the exercise phase, the aim of this study is to analyse the behaviour of the main cardiopulmonary indices during recovery in a population of young CHD patients and to compare it with an age-matched healthy population. In this context, the RER was chosen as the most representative parameter to be evaluated as it reflects the behaviour of both VO_2 and VCO_2. The main outcomes of the present study led to the following:

- it was the first study to provide values of the RER max, RER mag, time to RER max and RER slope in a population of young patients with CHD, and the presence in all patients of an overshoot of the RER during recovery after maximal exercise testing was confirmed;
- RER overshoot and cardiovascular efficiency parameters showed a strong relationship;
- RER max and RER mag seemed to be the most relevant variables as they were significantly correlated with the most important indices of cardiorespiratory fitness and efficiency, independently from the RER peak reached during exercise;
- no correlations were found between RER overshoot and resting left ventricular function.

Background

Currently, the literature includes a large number of studies dedicated to the cardiopulmonary response during exercise in different clinical populations, yet there is still little evidence on the behaviour of CPET parameters during recovery. Some authors have analysed how the kinetics of the recovery of VO_2 are delayed in patients with heart failure after maximal and submaximal incremental exercise testing compared to healthy subjects [59], [61], [95]; moreover, these findings were also associated with a worse prognosis in these patients [61], [96]. In most of these trials, a slow recovery of energy stores in skeletal muscles was believed to be responsible of the delayed recovery of VO_2 [97]. In addition, in patients with heart failure a delayed recovery of VE and VCO_2 was also found. This phenomenon has been attributed to the retention of CO_2 in the muscles after exercise, justifying the consequent increase in ventilation to maintain a state of eucapnia [61]. In this regard, it is noteworthy to underline that parameters describing the recovery phase seemed to have a more significant correlation than peak parameters with muscle strength in both healthy controls and cardiac patients [98].

In patients with heart failure the phenomenon of VO_2 overshoot during recovery has also been described: it represents the increase in VO_2 compared to the values at peak exercise [60]. This overshoot has been found in a significant number of cardiac patients and seems to be associated with a worse prognosis [99]. Other authors also found a paradoxical increase in cardiac output in the recovery phase after cardiopulmonary exercise testing [100], which may explain VO_2 overshoot. This increase in cardiac output would be attributable to the collapse of peripheral vascular resistances at the end of the exercise, but also to the contribution of skeletal muscles to repay the oxygen deficit or to a relatively slower decline in the blood concentration of catecholamines during recovery [94], [100].

More recently, the attention has been focused on the overshoot phenomenon of gas exchange indices like RER, $PETO_2$ and VE/VO_2 during the recovery phase after maximal exercise testing [57]. Takayanagi et al. identified an attenuation of this phenomenon in heart failure patients with LVEF<40% when compared to healthy subjects [57]; in the latter, the overshoot of gas exchange indices seems to be a

direct consequence of VE and VCO_2 returning to normal more slowly than VO_2, due to the carbon dioxide deposits produced by the anaerobic metabolism during exercise that the body has to eliminate. On the other hand, in cardiac patients the reduced overshoots of RER, $PETO_2$ and VE/VO_2 were attributed to the slow recovery kinetics of VO_2 described above, including the VO_2 overshoot and paradoxical increase of cardiac output [57]. An important correlation between the magnitude of these overshoots and parameters of cardiorespiratory efficiency was also found; however, no correlation with the LVEF was identified, highlighting how these metrics accurately characterize cardiopulmonary fitness during exercise, but not at rest [57].

Similarly, Patti et al. analysed the phenomenon of RER overshoot during recovery after maximal exercise testing in a population of kidney transplant recipients (KTRs) with normal cardiac function; RER peak, RER max, RER mag, time to RER max and RER slope were the metrics assessed in the trial [58]. Although there was no group of healthy controls, it was found that in KTRs the phenomenon of RER overshoot is not reduced compared to the reference values used for the healthy population. Specifically, the RER mag of KTR population (28.4 ± 12.7%) appeared to be comparable to that of healthy subjects (29.3 ± 10%) [57], [58]. These findings suggest that cardiogenic limitations have a greater impact than peripheral alterations in the attenuation of the RER overshoot phenomenon. The study also revealed significant correlations between RER overshoot (especially RER mag) and the most important cardiorespiratory fitness and efficiency indices, such as VO_2 peak, VO_2 at AT, OUES and VE/VCO_2; these results were fully comparable to those obtained from previous studies on a population of patients with cardiogenic limitations [57]. In this study it was also hypothesized that not only VO_2, but even VCO_2 may be partly responsible for the reduction of RER overshoot, probably through the retention of CO_2 in skeletal muscles during exercise, with a consequent increase in VE/VCO_2 slope [58].

Cardiopulmonary exercise testing parameters comparison

Given the nature of the study population, cardiovascular parameters were initially analysed, both at rest and during exercise. Statistically significant differences were found between patients and healthy subjects regarding cardiocirculatory efficiency during exercise and recovery. These findings, associated with the fact that aerobic and functional capacity were significantly reduced in patients with CHD compared to healthy controls (43.72 ± 6.13 ml/min/kg in the former and 36.27 ± 8.33 ml/min/kg in the latter) may suggest the presence of cardiogenic limitations to exercise in patients with CHD.

The assessment of RER overshoot showed that patients have significantly reduced RER max and RER mag values compared to healthy controls, despite the RER peak value being comparable between the two groups (1.22 ± 0.11 and 1.23 ± 0.12, respectively). In particular, a RER max value of 1.77 ± 0.23 was recorded in the CHD group, and of 1.94 ± 0.28 in the healthy group; RER mag, on the other hand, was 44.41 ± 14.75% in the first, and 58.54 ± 14.72% in the latter. These findings seem to confirm that, in subjects with cardiogenic limitations to physical exercise like patients with CHD, the phenomenon of RER overshoot is reduced [57].

Correlations

The correlation between RER overshoot and parameters that reflect cardiovascular function during the test was also assessed. HR/VO_2 slope describes the body's ability to adequately increase heart rate to meet the increased metabolic demands during the exercise, and it is a cardio-circulatory efficiency index that has been poorly studied in the literature so far, particularly in patients with CHD [42]. A significant negative correlation was found between RER mag and HR/VO_2 slope ($r=-0.232$, $p=0.004$). Although there are no other studies that analyse this correlation, it could be hypothesized that patients with a hyperkinetic response during exercise and thus lower cardiocirculatory efficiency have also a reduced RER overshoot in the recovery phase, probably due to cardiac limitations. Furthermore, also the maximal HR at peak exercise seems to determine the RER

overshoot. Indeed, patients with better exercise tolerance and thus higher peak HR have shown a more significant RER overshoot. It needs to be investigated whether this observation is due to cardiac limitations regarding the chronotropic response or simply due to a lower exercise tolerance.

To further address this issue, the correlations between RER overshoot and HRRec after one minute of recovery were also evaluated. This is a parameter that evaluates the efficiency of the parasympathetic system in reducing heart rate after the end of exercise [52]: HRRec was positively correlated to RER peak and RER max, but not to RER mag. The interpretation of this finding is made difficult by the lack of literature regarding this index, and it may also depend on the lower exercise tolerance of these patients, i.e., RER peak. However, all these data could suggest that the attenuation of this phenomenon in the recovery is predominantly due to a cardiogenic limitation, also considering the study population and previous reports [57], [58].

A relevant finding that emerged from the analysis of the RER overshoot during recovery is the presence of significant correlations between this phenomenon and the main parameters of cardiorespiratory fitness and efficiency. In particular, RER max and RER mag are the metrics that showed the strongest correlations with cardiopulmonary indices. RER max and RER mag both had significant correlations with VO_2 peak pro kg and OUES; a significant correlation between RER max and VE/VCO_2 slope was also displayed. Differently from the data in the literature, in the present study no correlations appeared between RER mag and VE/VCO_2 slope [57], [58]: this could be explained by the fact that the population included in the study was young and might not have a relevant degree of ventilatory-perfusion mismatch yet. Alternatively, since RER peak, and thus also RER max, seem to correlate with VE/VCO_2 slope, data may suggest the ventilatory-perfusion mismatch has a huger impact on exercise tolerance and affects less the recovery phase [101]. In any case, these findings confirm the presence of statistically significant associations between the RER overshoot and the main parameters of cardiorespiratory fitness and efficiency [57], [58]. This supports the assumption that the analysis of CPET metrics during recovery can add valid information for the interpretation of the test.

The cardiogenic limitations of CHD patients require numerous follow-up examinations: among these, one of the most important is echocardiography, which is used to evaluate the anatomy and pathophysiological adaptations in time [77]. Similarly to what has been discussed in other studies, correlations between RER overshoot and resting biventricular function were investigated [57]: in the present study no correlation with LVEF was found, once again suggesting the absence of relationships between RER overshoot and left ventricular function at rest [57]. Correlations with TAPSE and FAC, parameters describing right ventricular function, were also evaluated, and a single positive correlation was found between TAPSE and RER max, without any other significant associations. It might be tempting to think of a possible link between right ventricular dysfunction and attenuation of RER overshoot, however the actual significance of this correlation is conditioned by the low sample size (this index was present only in the echocardiographic reports of 64 patients). The reduced numbers of reports in which FAC was assessed (only 22) prevents further validation of this hypothesis. No other studies assessing correlations between RER overshoot and right ventricular systolic function are yet available. However, this observation could be used as study hypothesis for future studies, investigating whether right ventricular dysfunction may affect the recovery and RER overshoot of patients with CHD.

So far, the recovery phase after exercise has been studied in relatively few clinical populations and often by applying different methods and metrics. The present study seems promising in the perspective of integrating variables of the recovery phase in CPET interpretation, which might help to improve the diagnostic and prognostic stratification of these patients. RER max and RER mag appeared to be the most useful and feasible metrics that could also be evaluated in the clinical setting.

Limitations and perspectives

This was a retrospective trial assessing the recovery phase after maximal exercise testing using CPET evaluations performed for clinical purposes. The retrospective

nature of the study prevented a standardization of the protocol used and of the time to of analysis during recovery. Furthermore, having a higher sample size could provide more evidence and higher statistical power regarding the parameters evaluated. In particular, a larger sample and specific trials are needed in order to investigate the impact of right ventricular systolic function on the RER overshoot during recovery, as echocardiographic data have been assessed for clinical purpose and were thus not available for all patients. Further studies may also investigate how left and right ventricular function during exercise will influence the RER overshoot during recovery; cardiac output could be directly measured during exercise testing. Future trials should analyse the behaviour of gas exchange indices after maximal exercise testing in populations with different functional limitations, in order to improve the understanding of the pathophysiological mechanisms that determine its behaviour and the clinical interpretation of this phenomenon. Finally, future studies are needed, aiming to prospectively investigate the prognostic value of the RER overshoot parameters on hard clinical endpoints.

6. CONCLUSIONS

The present study adds new evidence to functional assessment in patients with CHD. Respiratory gas exchange parameters were studied by evaluating the RER behaviour during recovery from maximal cardiopulmonary exercise testing. Our data showed the occurrence of a RER overshoot during recovery in all evaluated patients. Significant correlations were confirmed between the determinants of RER overshoot (in particular RER max and RER mag) and CPET indices of cardiorespiratory fitness and efficiency. Patients with complex CHD had the lowest values of both RER overshoot and cardiorespiratory fitness and efficiency. Significant correlations were also found between RER overshoot parameters and indices of cardiovascular function, suggesting that cardiogenic limitations may play a role in reducing the RER overshoot phenomenon. Resting left ventricular function seems not to play a role, while the evidence of a possible relationship with right ventricular function has to be further studied. RER mag and RER max proved to be the most significant variables to assess the recovery of the patients. Thus, the evaluation of the RER during recovery could be included in clinical CPET interpretations to provide more data on the function status of patients with CHD.

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