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Importance of Hemodynamic Right and Left Ventricular Parameters and CPET-Data in Fallot-Patients and Patients with Fallot-like Pathologies

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DEDICATION

To my parents.

CONTENT

ABBREVIATIONS

AG	Allograft
Ao	Aorta
BSA	Body Surface Area
CCVD	Congenital CardioVascular Defects
CMR	Cardiac Magnetic Resonance
CO	Cardiac Output
CoA	Coarctatio Aortae
CPET	CardioPulmonary Exercise Test(ing)
DE	Doppler Echocardiography
HG	Homograft
IVS	Intact Ventricular Septum
LA	Left Atrium
LPA	Left Pulmonary Artery
LV	Left Ventricle
LVCO	Left Ventricular Cardiac Output

LVH	Left Ventricular Hypertrophy
LVSV	Left Ventricular Stroke Volume
MPA	Main Pulmonary Artery
MRI	Magnetic Resonance Imaging
PA	Pulmonary Atresia
PBF	Pulmonary Blood Flow
PPVI	Percutaneous Pulmonary Valve Implantation
PS	Pulmonary Stenosis
PV	Phase Velocity
QoL	Quality of Life
RA	Right Atrium
rf	radio frequency
RPA	Right Pulmonary Artery
RV	Right Ventricle
RVCO	Right Ventricular Cardiac Output

RVH	Right Ventricular Hypertrophy
RVOT	Right Ventricular Outflow Tract
RVOTO	Right Ventricular Outflow Tract Obstruction
RVSV	Right Ventricular Stroke Volume
TA-GVHD	Transfusion Associated Graft Versus Host Disease
TAP	TransAnnular Patch
ToF	Tetralogy of Fallot
VSD	Ventricular Septal Defect
VO_2max	Maximum O_2-uptake per minute
$VO_2max\%$	Maximum O_2-uptake in percent of a reference value
Wmax	Maximum Power on the Ergometer per bodyweight in kg
XG	Xenograft

Table 1 – Abbreviations

1 INTRODUCTION

It is known that patients with Tetralogy of Fallot (ToF) are likely to develop pulmonary regurgitation after surgical correction in childhood. However, there are also many ToF-patients with persistence or recurrence of stenosis of the right ventricular outflow tract (RVOT). One of these two states, namely predominant pulmonary regurgitation (PR) or pulmonary stenosis (PS), affects cardio-pulmonary capacity more drastically.

However, it is unknown, opinions diverge respectively, which parameter is more predictive for exercise capacity. The patients selected for this study comprise both forms of Fallot-patients and patients with ToF-like hemodynamics.
The goal of this study was to evaluate the most predicting parameter affecting exercise capacity.

Common doctrines established a strong relationship between pulmonary regurgitation, right ventricular dimensions, QRS-duration and sudden cardiac death (Gatzoulis et al. 2000a; Gatzoulis et al. 2000b; Geva 2011; Giardini et al. 2006; Holmes 2012; Lee et al. 2012; Therrien 2012). However, impaired exercise capacity has been related to PR in several studies (Carvalho et al. 1992; Frigiola et al. 2008; Giardini et al. 2006; Giardini et al. 2007; van den Berg et al. 2007).

Recent literature discussed that surgical management in early childhood often comprises valvotomy, placement of an outflow tract patch or a transannular patch to maintain flow without stenosis within the main pulmonary artery (MPA). However, this surgical correction may lead to pulmonary regurgitation. PR is accounted for being responsible for chronic volume overload of the right ventricle, which again might lead to an increase of right ventricular end-diastolic volume (RVEDV) and right ventricular end-systolic volume (RVESV). Due to dilation of the right ventricle (RV), electromechanical coupling of the myocardium is believed to be impaired, leading to oblongated QRS-duration. Again, QRS-duration, arrhythmia and sudden cardiac death are known to be positively correlated. Hence, these sequelae are ascribed to PR in the first place. *Figure 1* tries to illustrate this probably controversial relation between PR and sudden cardiac death (Gatzoulis et al. 1995b; Gatzoulis et al. 2000b; Therrien et al. 2001).

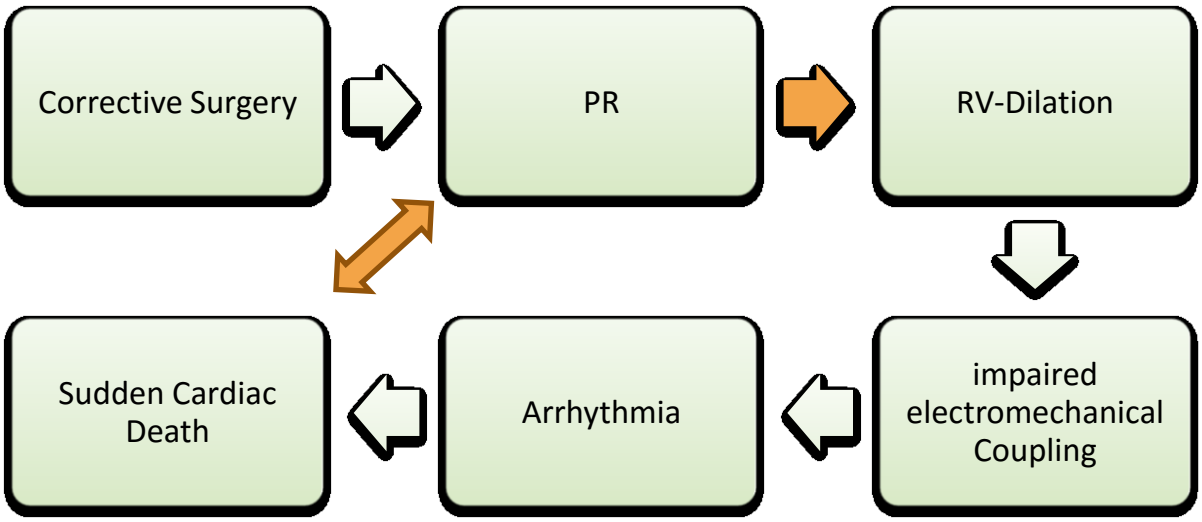


Figure 1 – PR held accountable for sequelae in patients who underwent corrective surgery; based on the thoughts of Gatzoulis and Therrien (Gatzoulis et al. 2000; Therrien et al. 2001).

Considering the relation between PR and impaired exercise capacity, a similar theory has been established. Due to chronic volume overload because of PR, the RV dilates and becomes unable to adapt to higher strain. Therefore, cardiac output and stroke volume decrease, which leads to lower pulmonary blood flow (PBF). The consequence of a lower PBF might be impaired oxygen uptake or carbon dioxide dispensary, representing the impact of PR. *Figure 2* tries to illustrate the assumed impact of PR on exercise capacity (Carvalho et al. 1992; Giardini et al. 2006).

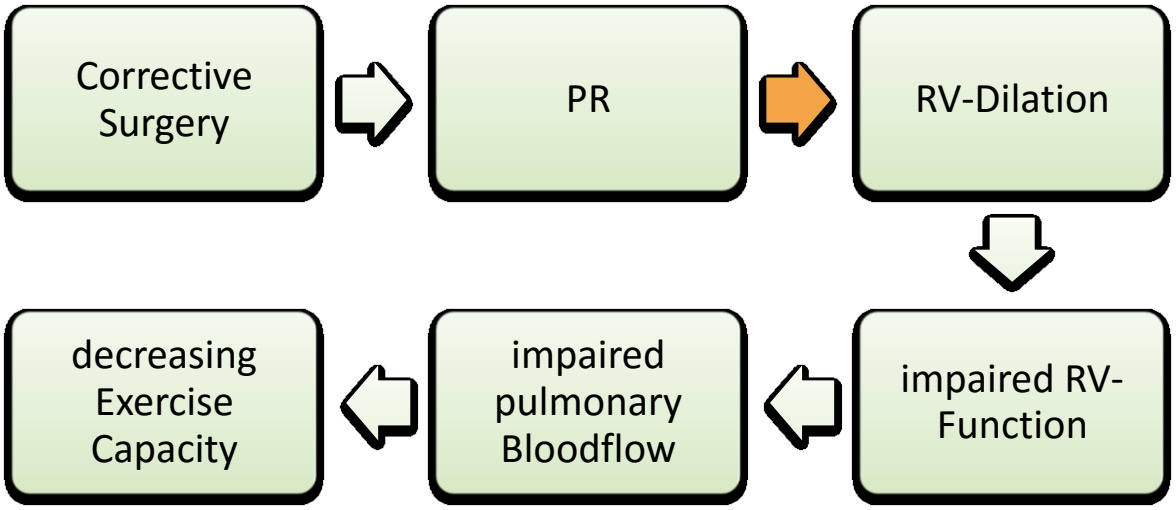


Figure 2 – assumed impact of PR; based on thoughts of Carvalho and Giardini (Carvalho et al. 1992; Giardini et al. 2006).

The importance of PR might have been overestimated due to many observations in clinical routine follow-ups.

Therefore, the aim of this study was to evaluate whether the importance of PR was really as high as previously described, and if not, which cardiac parameter affects exercise capacity.

1.1 BACKGROUND

Figure 3 – Étienne-Louis Arthur Fallot

In 1888 Étienne-Louis Arthur Fallot (1850 – 1911) described the most common cyanotic congenital heart disease, which leads to blue baby syndrome. However, it was not Fallot, who coined the eponym for the congenital heart disease, consisting of – as described by Fallot (translated from the original French) – (1) pulmonary artery stenosis, (2) ventricular septal communication, (3) rightward deviation of the aorta's origin and (4) right ventricular hypertrophy. It was Maude Abbott who first referred to "tetralogy of Fallot" in an article in 1924. From there on, the eponym found its way first into modern textbooks of cardiology and later into pediatric textbooks (Evans 2008).

Still, one should notice that Étienne-Louis Arthur Fallot was not the first scientist to describe malformed hearts of cyanotic individuals. The Danish catholic bishop and scientist Niels Stensen (1638-1686) already mentioned this very malformation in 1671(Tubbs et al. 2012):

Figure 4 – Niels Stensen

"The unusual form of the arteries arising from the heart attracted the chief attention and called for admiration. In particular, the pulmonary artery, which was much narrower than the aorta, seemed to be suggestive of something new, and hence I opened this vessel from the right ventricle to the hilus pulmonum, and then I could plainly see that the communication between the pulmonary artery and the aorta [ductus arteriosus] which usually is quite distinct in any fetus, was completely absent. When I opened the right ventricle, however, the probe that was passed forward and upward along the interventricular septum entered directly into the aorta just as readily as the probe passed from the left ventricle into the aorta. Thus, no less than three openings led into the right ventricle: one from the right atrium, the other two being connected with the arteries. The same aortic canal that was common to both ventricles, found, together with the interventricular septum, a double opening. The auricles were normal. Although in this case the arteries were of uncommon structure, the resulting effect of this was in compliance with nature, like the circulation of the blood in any fetus occurs. Just as the vena cava empties into both atria [through the foramen ovale], the right ventricle empties into both arteries; just as the left ventricle receives blood from both auricles, thus the aorta receives blood from both ventricles at the same time. So, no matter whether the blood leaving the right ventricle first passes through the pulmonary artery and then is sent through its own channel [ductus arteriosus] into the aorta, or the aorta receives the blood directly as it partly straddles the right ventricle, without the blood first passing through any other channel, the movement of the blood will be the same from the right ventricle out into both

arteries. As to the cause of this phenomenon, I have nothing to say. But, supposing that in the open thorax the pulmonary artery separates from the aorta, while in the closed thorax it receives the blood from the right ventricle and permits it to pass on to the aorta. There still remain two perplexities. It cannot be taken for granted that the arterial structure will remain obscure how an open thorax would contribute to a change in the arterial structures. There can be no doubt that the ductus arteriosus found in infanct gradually resolves itself into a ligament as the lungs expand with the establishment of respiration, and that this structure is patent only in the fetus, because all the blood coming from the right ventricle cannot pass through the pulmonary arteries. But why the blood in this case has not been able even to make its way into the pulmonary artery, but has made its way directly into the aorta, I am unable to explain. Still, no matter what the reason of this might be, I take it palinly to prove the wisdom of Nature, in as much as the effect is produced, if not in the same way, yet always somehow. Just as this fetus proves this point with regard to theat part of the blood that has to be expelled from the right ventricle in the large artery [aorta], this fetus also illustrates that the formation fo the solid parts of animals does not always proceed in the same manner even though the effect obtained remains the same" (Tubbs et al. 2012, pp. 313–314)

1.2 EPIDEMIOLOGY

Incidence and Prevalence are two epidemiologic terms that are very important in this matter and have to be defined at first.

Incidence describes the number of subjects that contracted a certain disease, considering a particular period of time or population.

In contrast, prevalence is defined as the number of patients affected at any time.

Data regarding incidence and prevalence of congenital heart disease (CHD) is scarce; thus making it difficult to assess the number of specialized physicians that should be trained (Marelli et al. 2006; Hoffman et al. 2004).

1.2.1 INCIDENCE

The Incidence of congenital heart defects fluctuates from 4 to 50 per 1000 live births (Hoffman, Kaplan 2002). This variation of reference values is dependent on which malformations are taken into account. When minor forms of congenital heart defects are included, incidence seems to be bigger. Another reason for a seemingly growing incidence might be a higher rate of detected *minor forms* of cardiac malformations, due to technical progress (better presentability and resolution in e.g. echocardiography). However, the incidence in severe CHD, including all cyanotic lesions (inter alia Tetralogy of Fallot, critical pulmonary stenosis [PS], pulmonary atresia with ventricular septal defect [PA+VSD], pulmonary atresia with intact ventricular septum [PA+IVS], hypoplastic right heart [HRH], hypoplastic left heart [HLH], transposition of the great arteries [TGA]) and non-cyanotic lesions (inter alia severe PS, large VSD, large persistent ductus arteriosus [PDA]), is rather stable, accounting for 2.5 to 3 per 1000 live births (Hoffman 1995; Hoffman, Kaplan 2002).

Baumgartner et al. reported on a Tetralogy of Fallot incidence of almost 10% of all congenital heart defects (Baumgartner et al. 2010).

There is no need in specialized cardiologic treatment in the majority of the minor forms of CHD, like the tiny VSDs or ASDs, which often close spontaneously or never induce medical conditions (Hoffman, Kaplan 2002, p. 1897).

In conclusion, under consideration of the high impact of trivial lesions, incidence of CHD seems to be stable, irrespective of time or country (Hoffman, Kaplan 2002, p. 1890).

1.2.2 PREVALENCE

Data concerning prevalence is affected by a similar variability as incidence-data. The reason for this variability is a lack of consensus among experts. Some account VSD for a congenital heart disease, which in fact is the most common congenital cardiac disorder. Others, on the other hand, exclude VSD, as it may close independently over time and, as a consequence, might not be detectable in adulthood anymore (Warnes et al. 2001).

A study by Marelli et al. presented the following prevalence (year 2000): 4.09 per 1000 adults with CHD were determined; 9 percent of those with severe lesions. ToF or truncus arteriosus accounted for 0.17 per 1000 adults (Marelli et al. 2006). On the contrary a study by Lindinger et al. displayed a prevalence of 1.08 percent in Germany, with data registration from July 2006 to June 2007 (Lindinger et al. 2010). Similar in all mentioned studies was the ascendance of women suffering from CHD; 53 percent in Germany (Lindinger et al. 2010), 57 percent in Canada (Marelli et al. 2006).

In conclusion, prevalence of adults with severe CHD is growing since 1985 (Marelli et al. 2006). Since the year 2010, adults account for two thirds of patients with severe congenital heart diseases in the general population of the Quebec CHD database (Marelli et al. 2014).

1.3 TETRALOGY OF FALLOT

The following passage describes pathology, treatment and the natural history of Fallot patients.

1.3.1 PATHOLOGY

In 1888 Étienne-Louis Arthur Fallot described the combined appearance of pulmonary artery stenosis, ventricular septal defect, overriding of the aorta and right ventricular hypertrophy (Evans 2008).

From a physiologic point of view solely two malformations are required: Right ventricular outflow tract obstruction (RVOTO) and a ventricular septal defect (VSD) large enough to equalize the pressure in both ventricles. The right ventricular hypertrophy (RVH) is a result of the RVOTO and the overriding of the aorta varies (Park 2002, p. 119). There is no correlation between the severity of the RVOTO and the degree of the dextro- and ante-positioning, overriding of the VSD respectively, of the aorta (Schumacher, Barankay 2008).

There are three types of RVOTOs depending on the development of the conus arteriosus, also known as the infundibulum, and the location of the obstruction (Park 2002):

- Infundibular stenosis (45 %)
- Stenosis at the valvular plane (10 %)
- A combination of both, an infundibular and a valvular obstruction (30 %)

The underdevelopment of the pulmonary vessels positively correlates with the degree of the RVOTO. In only 10 % of all patients, the pulmonary vessels are highly hypoplastic. The most probable reason for hypoplastic pulmonary vessels is a reduced pulmonary blood flow. In some rare cases, either the left pulmonary artery (LPA) or the right pulmonary artery (RPA) can be missing. The consequence of this malalignment is a hypoplastic lung, supplied via collateral vessels (Schumacher, Barankay 2008).

The clinical presentation of a Fallot patient reaches from an acyanotic infant (Pink Fallot) to the extreme form a Fallot patient, which is highly cyanotic. These differences in clinical manifestation depend on the degree of the RVOTO. The level of obstruction can vary widely from a mild stenosis at the planes mentioned above, to a complete pulmonary atresia (Park 2002, p. 119).

In case of the latter, pulmonary blood flow (PBF) is only maintained via systemic-to-pulmonary collaterals and a persisting ductus arteriosus (PDA). Important to understand is the fact that solely a small VSD combined with pulmonary stenosis (PS) is not Fallot. For the diagnosis “Tetralogy of Fallot” a VSD large enough to equalize the pressure in both ventricles is essential (Park 2002, p. 119).

The so called *Pink Fallot* (also *acyanotic Fallot*) can be seen as the mildest form of the Fallot-malformations. As previously explained, the degree of the RVOTO defines the direction and magnitude of the shunt. In this case, PS is mild to moderate and therefore the shunt is left-to-right. However, the magnitude of this shunt is limited by the RV-pressure. A slight increase of heart size and pulmonary vascularity, as in pink ToF present, is not capable of being distinguished to only a VSD. Therefore it can be difficult to differentiate. If there are indications in physical and x-ray examinations for one of those two malformations, one should consider findings in both, ECG and x-ray-imaging. Left ventricle hypertrophy (LVH) is a distinctive feature of a VSD (although it can also be missing). Pink Fallot presents with RVH (sometimes combined with LVH) in ECG, due to the elevated pressure in the RV. The diagnosis *acyanotic ToF* is confirmed with right aortic arch present (Park 2002, pp. 119–120).

With the stenosis becoming narrower the shunt is being turned (from left-to-right) to now, *right-to-left*. As a result to the more stenotic RVOT, less blood from the RV reaches the lungs directly. The non-oxygenized blood from the systemic venous return mixes with oxygenized blood from the pulmonary venous return in the LV. Then, the LV pumps partially oxygenized blood into the aorta, from where it is transported into the periphery on the one hand, and into the pulmonary vessels via systemic-to-pulmonary collaterals on the other hand. Because of the decreased PBF, the body is not supplied properly with oxygen and therefore impresses cyanotic. In chest x-ray films the following findings can be observed: A normal heart size, because none of both ventricles suffers from volume overload, decreased pulmonary vascularity and sometimes decreased size of the left atrium (LA) and the LV, due to the reduced pulmonary venous return. The ECG shows a RVH because of the elevated pressure in the RV. However RV-pressure does not exceed systolic aortic pressure, which is under baroceptor control. This means RV-, LV- and aortic pressure are equal. In infants, none of the chambers are under chronic volume overload, which further means that infants with ToF do not develop chronic heart failure (CHF). To distinguish between a solitary PS and ToF, auscultation can be very helpful. In ToF, the murmur audible decreases with a more stenotic pulmonary valve. That is because the right-to-left shunt increases, but shunting is silent (Park 2002, pp. 120–121).

On the other hand, is the PS mild, more blood flows through the PA (and less through the VSD) and produces a systolic ejection murmur, best audible at the mid-left sternal border (infundibular stenosis) or at the upper-left sternal border (pulmonary stenosis). These observations are contrary to isolated PS, where the intensity and duration of the systolic murmur increase with the degree of stenosis (Park 2002, pp. 120–121).

In the extreme form of ToF, the pulmonary valve is atretic which leads to a PBF solely achieved via right-to-left shunt. Multiple systemic-to-pulmonary collaterals, as well as a PDA maintain the PBF. The life of the infant depends on the patency of the ductus arteriosus, which makes administration of Prostaglandin E1 a vital element in the treatment of ToF with PA. Chest x-ray shows a small heart. As in other forms of ToF, RVH is present on the ECG (Park 2002, p. 121).

In some ToF patients at young age (around 2 months to 2 years Kothari 1992) a certain phenomenon called “hypoxic spell”, “cyanotic spell” or “tet spell” occurs. During this spell, children suffer from marked cyanosis and hyperpnoea. This can further lead to damage of the central nervous system and even death (Park 2002, p. 122).

The exact mechanism of the origin of the spell is still not definitively explained. Most probably it is a whole collective of factors that promote and /or initiate the spell. To understand the different causes for “tet spells” it is important to first explain what controls the amount of PBF. As previously described, in ToF the VSD is large enough to equalize the pressure in both ventricles. Thus, both LV and RV can be functionally seen as a single ventricle. With this in mind it is clear that either in- or decrease of both, the systemic vascular resistance (SVR) and the pulmonary resistance, affects PBF. Decrease of the SVR leads to an increase of the right-to-left shunt, resulting in decreased PBF. Contrarily, increase of the SVR leads to a decrease of the right-to-left shunt, leading to an increase of PBF. Of course not only the SVR but also the pulmonary resistance, spasm of the RVOT respectively, contributes in the amount of PBF (Schumacher, Barankay 2008; Park 2002).

1. Increase in infundibular contractility

   Along with increasing contractility of the infundibulum, the right-to-left shunt increases as well. Hence, the PBF decreases and the infant impresses hypoxic. Johnson suggested that the effect of Norepinephrine is the cause of the infundibular spasm (Johnson 1961).

Honey et al. could show that the preliminary application of beta-sympathetic blocking medication led to a reduction of the dropping arterial pO_2 under strain in many ToF-patients (Honey et al. 1964). On the contrary, Park questions the impact of RVOT-spasms on the initiation of hypoxic spells: The *"[…] infundibular stenosis, which consists of disorganized muscle fibers intermingled with fibrous tissue, is relatively nonreactive."* (Park 2002, p. 122).

Patients with the extreme form of ToF, namely ToF with pulmonary atresia, suffer from hypoxic spells as well. A temporary contraction of the infundibulum would not affect PBF in these patients at all. Therefore, SVR being one of the key factors in the origin of cyanotic spells, may be more likely.

2. Influence of systemic vascular resistance

   As described above, the SVR affects the amount and magnitude of the right-to-left shunt and therefore, the amount of blood supplying the lungs. The theory of an elevating SVR is being utilized in the therapy of hypoxic spells, namely by raising the SVR. Detailed information on possible therapeutic actions will follow below (Park 2002).

   However, controversies concerning this theory exist as well. Systolic and diastolic measurements of blood pressure during spells have not shown any alterations (Kothari 1992).

3. Tachycardia and hypovolemia

   Tachycardia and hypovolemia can lead to an increase of the right-to-left shunt. This leads to a dropping of the pO_2 and pH and an increase of pCO_2. Alterations of these parameters can also be induced by e.g. a sudden change of activity or a Valsalva-like maneuver like bowel movement or defection. These gas changes cause an activation of the respiratory center in the brainstem, leading to tachypnea. Because of an activation of the negative thoracic pump, tachypnea increases the systemic venous return, leading to an increased shunting from right to left. The arterial oxygen saturation drops further, which establishes a vicious circle that needs to be broken (Park 2002).

There are certain maneuvers that are aimed at breaking the vicious circle of hypoxic spells. The mechanism of improving PBF by assuming the knee-chest-position has been observed in the past, when children reached a certain age without surgery. After elevated physical strain, with an increase in heart rate and respiratory rate, toddlers assumed a squatting position. After only a few minutes, they recovered quickly and went on playing. There are three supposed factors that led to the improvement of their state (Guntheroth et al. 1968):

1. Reduction of systemic venous return, by trapping venous blood in the lower extremities. Thus, the right-to-left shunt is being decreased.

2. Reduction of arterial flow to the lower extremities and therefore, reduced venous washout from the leg muscles.

3. Probably squatting causes an increase of SVR, which would lead to a decreased right-to-left shunt.

The extreme form of ToF, ToF with pulmonary atresia, has been mentioned repeatedly. It is a condition that needs special attention. Overlooking of this malformation can easily lead to sudden death after physiological closure of the PDA (Park 2002). There is another condition, similar to this one, just without the VSD. It is called “Pulmonary Atresia with intact Ventricular Septum” and will be discussed below – *1.4 Pulmonary Atresia with intact Ventricular Septum*.

1.3.2 TREATMENT

Medical treatment includes the recognition and therapy of hypoxic spells. Especially the parents have to be educated by the attending physician to correctly interpret initial symptoms and start the treatment. Substitution with iron can be required to prevent the development of a hypochromic anemia. In countries where open heart surgery is not well established, oral administration of Propanolol (0.5 to 1.5 mg/kg every 6 h) is sometimes used to bridge the time gap until operative management can be arranged (Park 2002, pp. 193–194).

The oral administration of Propanolol shall remain an exception, because of a frequently favoring anatomy for surgical correction in the first year of life and the risk of reactive hypoxemic conditions after stopping the medication (Schumacher, Barankay 2008, pp. 294–295).

Surgical treatment comprises a multiplicity of different interventions, starting from catheter supported techniques to open heart surgery in multiple steps.

Balloon dilatation is primarily used in symptomatic newborns and young infants to gain time until corrective surgery is possible. Furthermore, the hypoplastic or stenotic annulus is probably being stimulated to grow and widen. If successful the rate of transannular patches can be reduced. Unfortunately, this procedure is limited to a patient collective with predominant pulmonary valve stenosis (Schumacher, Barankay 2008).

The decision whether to perform primary repair or to first apply a palliative shunt and then perform corrective surgery depends on the institution's preferences. However, there are certain situations, when a shunt operation preceding primary repair might be considered the wiser decision. These situations include premature infants, infants weighing less than 2.5 kg, a complex anatomy of the coronary arteries, ToF with PA, any anatomic constellation that requires a transannular patch for complete repair and infants with hypoplastic pulmonary arteries. There are different techniques for palliative shunt operations. The most popular procedure is the modified Blalock-Taussig-shunt. Sometimes the classic Blalock-Taussig-shunt is still used (Park 2008).

- A Classic-Blalock-Taussig shunt is an anastomose between the subclavian artery and the ipsilateral pulmonary artery. In case of a left aortic arch, the shunt is placed right-sided; a right aortic arch is handled vice-versa. The classic Blalock-Taussig-shunt is not to be used in infants younger than 3 months. Because of their small vessels thrombosis of the shunt occurs very frequently.

- The modified Blalock-Taussig Shunt is the most commonly used shunt-procedure, especially in children younger than three months of age. The modified variant differs from the classic variant, as the shunt is placed left in case of a left aortic arch and right in case of a right aortic arch. Another difference is that instead of using the subclavian artery itself, a Gore-Tex interposition is used for the connection of the pulmonary and subclavian artery.

- Other procedures, like the Waterston-Shunt or the Potts-Operation, have been performed in the past. Today, due to a higher mortality and/or complication rate, these operations are not favored anymore (Park 2002; Schumacher, Barankay 2008).

Complete surgical repair is being accomplished in dependence of the severity of the malformation. A “standard” procedure includes closure of the VSD, resection of the infundibular stenosis, pulmonary valvotomy and widening of the RVOT through a patch (subvalvular: until the pulmonary artery valve (PAV); transannular: throughout the PAV). In the purpose of widening the RVOT, placement of a fabric patch should be avoided if possible. It is more likely to achieve this goal if surgery is performed in early infancy. In case of a very narrow or hypoplastic main pulmonary artery (MPA), placement of a patch is necessary. Simultaneous implantation of a monocusp valve depends on the preferences of the center where surgery is performed. The operation is administered under cardiac arrest, cardiopulmonary bypass and hypothermia (Park 2002, 2008).

There are two main indications for surgical treatment: Manifest central cyanosis (i.e. capillary or arterial saturation <80%, hematocrit >60% or Hb >18g/100ml) or occurrence of the first hypoxic spell (Schumacher, Barankay 2008, p. 295).

As described above, unfavorable anatomic conditions like infundibular hypoplasia, constriction of the pulmonary annulus and especially hypoplasia of the PA often make a palliative shunt operation the preferred treatment (Schumacher, Barankay 2008).
On the contrary, operative enlargement of the RVOT does not constitute the risk for stenosis at the site of artery-to-pulmonary anastomoses and, moreover, enhances a symmetrical growth of hypoplastic pulmonary arteries (Sebening et al. 1984). The morbidity is high in artery-to-pulmonary shunts, which increases the rate of re-interventions. Reasons for that are thrombosed or simply too small shunts. Furthermore, shunt operations do not decrease the rate of necessary patch plastics (Schumacher, Barankay 2008).

Consideration of a balloon dilatation (in PAV stenosis), widening of the RVOT in infundibular stenosis respectively, has two possible advantages. With the increase of antegrade flow, the pulmonary arteries dilate symmetrically and a secondary pulmonary atresia could be avoided. If a secondary pulmonary atresia develops, it can be necessary to implant an extracardiac conduit to bridge the atretic part of the PA. Also positive, a patch might become gratuitous, thanks to the performed balloon dilatation (Schumacher, Barankay 2008).

Primary repair is possible, in principle, at any age under the following circumstances: The pulmonary annulus and particularly the PAs have to be large enough to carry the whole cardiac output after repair. There are two different points in time for surgical repair, each attributed to several advantages and disadvantages. Therefore, the age for elective surgery can be chosen between three and twelve months (six to eight kg body weight respectively) and between one and two years respectively. The advantage of very early surgery is the prevention of long term hypoxia, prevention of erythrocythemia and therefore, thromboembolic events, as well as the prevention of right ventricular hypertrophy (RVH). On the other hand, advantages of corrective operations at a higher age are: No need for a ventriculotomy and a transannular patch, less operative morbidity and a decreased surgical risk and rate of repeated surgery in general (Schumacher, Barankay 2008, p. 296).

Postoperative management includes long-term follow-up every 6 to 12 months, particularly in patients with ongoing unresolved issues. Children with RVH often develop arrhythmias that may lead to sudden cardiac death. Therefore it is very important to interpret symptoms like palpitations, dizziness or syncope correctly. According to current literature, treatment and meaning of pulmonary regurgitation is important (Schumacher, Barankay 2008). PR is believed to be responsible for decreased physical performance and therefore, should be corrected (Carvalho et al. 1992; Chaturvedi, Redington 2007; Frigiola et al. 2008; Gatzoulis et al. 2000b). Data regarding this very topic, collected and evaluated in our group, shows controversial results, which will be discussed later.

Morbidity and mortality are low in both, primary repair and staged approaches for ToF-correction, and both procedures are safely feasible. Today primary surgical correction at a young patient-age is the preferred option. However, recent studies showed that younger age at primary repair is a predictor of a more frequent need for the use of a transannular patch (TAP) due to the small vessel size. Long-term follow-up depicted that a TAP is associated with higher rates for re-operation, however. In order to avoid numerous redo-procedures in the future, careful patient selection for primary repair in early infancy is of great importance (Lindberg et al. 2011).

1.3.3 NATURAL HISTORY VS. TODAYS TREATMENT IN TOF

The natural history has been observed in a time when surgical possibilities and medical treatment were limited or even not available. It comprises a series of events, most of them ascribable to cyanosis due to the infundibular stenosis. In the following some examples for sequelae are presented (Park 2002, pp. 192–193):

- Acyanotic infants successively become cyanotic – the amount of cyanosis in toddlers that already are cyanotic increases as well over time. This is due to the worsening condition of the infundibular stenosis.
- Development of polycythemia due to cyanosis; with the possibility of a relative iron-deficiency (i.e. hypochromia).
- Coagulopathy as a late adverse effect.
- Hypoxic spells in infants (as described above).
- Growth retardation in case of severe cyanosis.
- Other sequelae (as in any other type of cyanotic congenital heart disease).

Immediately after birth a heart murmur may be audible. Severe cyanosis at birth is only present in patients suffering from ToF with pulmonary atresia (Park 2002, p. 190).

Today the natural history of patients born with this cardiac malformation has changed dramatically. Before the advent of surgical management in congenital heart defects, about 50% of ToF-patients died within their first few years of life. In 1955 Lillehei et al. published their first report on complete intracardiac repair of tetralogy of Fallot (Lillehei et al. 1955). Since then life expectancy constantly increased. Nowadays the adult patient-collective outnumbers children with ToF (Apitz et al. 2009; Fox et al. 2010).

Also age for surgical correction decreased throughout the years. There are clinics that operate on newborns even at the point of diagnosis. However, most centers perform surgery between 3 and 6 months of age. This age seems to be a good window, as children did not suffer too long from hypoxemia (leading to myocytical degeneration and fibrosis) but are not operated too early as well. Newborns often respond to such delicate interventions by sagging recovery (longer intensive care unit and hospital stay) and adverse effects on the neonatal brain. However, perioperative mortality is nowadays as low as approximately 1% at most centers. (Apitz et al. 2009; Fox et al. 2010)

Primary repair of ToF has been believed to be curing the disease. Unfortunately the past decades showed that a complication-free survival is possible for many years, until eventually limitations arise (Apitz et al. 2009; Fox et al. 2010).

A common complication accompanying treated ToF-patients is pulmonary incompetence. In the past 20 years awareness of the importance of the PV came up. Until the 1990s a common thought existed that preservation of the PV is secondary and that the primary goal should be the relief of the RVOT-obstruction (Apitz et al. 2009). Trivially spoken it could be argued that the PV exists for a reason; discussable RV-dilatation and probably other effects like dysrhythmia could be examples for its importance. That is why nowadays a valve preserving approach, without the use of a transannular patch is preferred whenever possible. Unfortunately this is not feasible in many cases. When PR and its influence on RV-geometry are crucial, pulmonary valve replacement might become necessary. Definitive recommendations on the type of valve, mechanical or bioprosthetic, are hard to make. The mechanical valve has a significantly longer life-period. However, the subject needs to take anticoagulant medication in order to avoid events of a thrombotic nature. This is unwanted especially in young patients, which would incur concision in quality of life, due to the danger of massive bleeding in case of, e.g. a sport-related accident. Moreover, the size of the mechanical valve is a major limiting factor. On the other hand the bioprosthetic valve has a limited life-span but without the need for anticoagulant medication. The main problem with this solution is the inevitable need for re-operation/-intervention (Fox et al. 2010).

Timing of pulmonary valve replacement (PVR) is a hot topic and probably it has to be performed on the asymptomatic patient under certain circumstances. Studies yielded that when the indexed right ventricular end diastolic volume (RVEDVi) exceeds 160 to 180 ml/m², chances for the RV to fully recover, diminish (Oosterhof et al. 2007; Therrien et al. 2005; Therrien 2012). For that reason, Geva (amongst others) published recommendations when to perform PVR in the asymptomatic patient (Geva 2011). However, there are arguments pro and contra early PVR. Early surgery may increase chances for complete normalization of right ventricular volumes; however, the chances for the necessity for redo-PVR are high. On the contrary, also in case of late intervention, volumes decreased and QRS-duration shortened, when QRS-duration was 180 ms or more prior to surgery (Fox et al. 2010; Oosterhof et al. 2007). Unfortunately, incidence for ventricular tachycardia (VT) or death may not decrease in symptomatic patients with late PVR (Harrild et al. 2009).

The electrophysiologic substrate of arrhythmia is prolonged QRS-duration. A duration of more than 180 ms positively correlates with an increased incidence of arrhythmia and sudden cardiac death (Fox et al. 2010; Gatzoulis et al. 1995b).

Given this mixed data on the outcome of early or late PVR, the best recommendation might be an individual approach under consideration of the subject's cardiac parameters, age and physical ability.

Morphologic and hemodynamic subtypes of ToF like pulmonary atresia with a VSD are often associated with even worse late prognoses. Branch pulmonary artery stenosis is common in patients with PA+VSD. If present, magnitude of PR and ventricular dilatation is bigger. Also branch pulmonary artery stenosis is an independent risk factor for late death, re-operation and PVR (Hickey et al. 2009).

In conclusion: Nowadays corrective repair of ToF is associated with early mortality rates of less than 2 percent. Therefore, a 40-year survival rate of approximately 90 percent is estimated for patients operated in the late 1980s and early 1990s (Hickey et al. 2009, p. 163). However, some key limitations still exist. First, the unresolved issue of PR, which most certainly leads to the need for PVR at some point (Fox et al. 2010). Luckily, new techniques of PVR, like the percutaneous approach (albeit not possible in every patient), might ease the decision, whether to perform the procedure or not. The second major issue is recurrent obstruction of the RVOT, which makes re-operation/-intervention necessary. Depressed myocardial function is common in the PR-/PS-patient collective. Another major complication is arrhythmia and the possible need for antiarrhythmic management, i.e. implantable defibrillator, and resynchronization therapy (Chaturvedi, Redington 2007). In this case it might be useful to synchronize both ventricles, since an impaired RV affects the LV as well (Geva 2011). Ventricular tachycardia and sudden cardiac death might be a frequent end-point when QRS-duration exceeds 180 ms (Gatzoulis et al. 2000b).

1.4 PULMONARY ATRESIA WITH INTACT VENTRICULAR SEPTUM

1.4.1 EPIDEMIOLOGY

Among all congenital heart defects, pulmonary atresia with an intact ventricular septum (PA+IVS) accounts for less than 1%. It was 0.3% in Germany, the observed period was July 2006 to June 2007 (Lindinger et al. 2010)).

1.4.2 PATHOLOGY

Patients with PA often suffer from hypoplastic right ventricles (in case of a normally developed right ventricle, the tricuspid valve is highly insufficient). The RV can be divided into three portions: inlet, trabecular and infundibular portion. Depending on the development of either all three portions (tripartite type), two (bipartite type) or even only one (monopartite type) portion, RV size and further, survival rate, varies. This morphologic classification was developed by Bull et al. in 1982 (Bull et al. 1982)

The systemic venous return has to be shunted either through an atrial septal defect (ASD) or a persisting foramen ovale (PFO). This atrial volume overload causes the dilation and hypertrophy of the right atrium (RA), notable in chest x-ray. Also the left atrium (LA) and the LV can be dilated. PBF is only maintained via the PDA and systemic to pulmonary collaterals. Still, these collaterals cannot sufficiently master the PBF and the patients are severely cyanotic. This explains why (physiological) closure of the PDA can be life threatening for an infant with PA. On the ECG the LV appears to be hypertrophied, due to hypoplasia of the RV and/or a possible actual hypertrophy of the LV. Keeping the PDA patent through Prostaglandin E1 infusion is very important to stabilize the infant's condition.

1.4.3 TREATMENT

Therapy of PA + IVS includes interventional and surgical approaches. The techniques are similar to those described above. For detailed information I would like to refer to specialist literature, e.g.

Park, Myung K. (2008): Pediatric cardiology for practitioners. 5th ed. Philadelphia, PA: Mosby/Elsevier.

and/or

Schumacher, Gebhard; Barankay, András (2008): Klinische Kinderkardiologie. Diagnostik und Therapie der angeborenen Herzfehler : mit 149 Tabellen. 4th ed. Heidelberg: Springer.

1.5 RISK FACTORS

1.5.1 NON-INHERITED FACTORS

Other than the genetic influence on cardiac malformations, which has been comprehensively surveyed over the past decade, the knowledge about non-inherited factors causing congenital cardiovascular defects (CCVD) was poor. Therefore several groups attended to this topic and epidemiological literature is currently growing in this matter. The upside in non-inherited factors leading to CCVD is that it may be preventable. The following passage describes an excerpt of (in the author's opinion important) notable risk factors. The information is taken from Jenkins, K. J.; Correa, A.; Feinstein, J. A.; Botto, L.; Britt, A. E.; Daniels, S. R. et al. (2007): Noninherited Risk Factors and Congenital Cardiovascular Defects: Current Knowledge: A Scientific Statement From the American Heart Association Council on Cardiovascular Disease in the Young: Endorsed by the American Academy of Pediatrics. In: *Circulation* 115 (23), S. 2995–3014. DOI: 10.1161/CIRCULATIONAHA.106.183216.

Vitamin Supplementation and Folic Acid

Depending on the study, numbers differ from a 25%- to 60%-risk reduction for congenital heart defects, achieved by taking multivitamin supplements containing folic acid. This risk reduction due to ingestion of folic acid potentially underlies the same mechanism as seen in prevention of neural tube defects. However, there have been other studies with different outcomes, thus a final conclusion cannot be drawn. Further studies on that subject are necessary; possible confounders have to be excluded accurately (Jenkins et al. 2007, pp. 2996–2997).

Phenylketonuria

Maternal phenylketonuria is associated with more than a 6-time higher risk for congenital heart defects, when untreated. The most common defects are VSD, patent ductus arteriosus, ToF and single ventricle. Maternal phenylketonuria is a great example for preventable CCVD, in that case by abiding by an appropriate diet (Jenkins et al. 2007, p. 2997).

Maternal Diabetes

The precise pathogenic mechanisms are still unclear, however Diabetes Mellitus is suspected to induce cardiac malformations before the seventh week of gravidity. Since the number of, especially type 2, diabetes patients is constantly growing it is of great importance to further investigate the influence of hyperglycemia on embryogenesis. Notable is the fact that gestational diabetes seems to be less associated with CCVD than pregestational diabetes. The increasing prevalence of type 2 diabetes mellitus in women in their childbearing years makes prevention a topic of high priority (Jenkins et al. 2007, p. 2997).

Rubella and other febrile Illnesses

Regressive behavior regarding vaccinations makes it important to reconsider that a maternal infection with rubella during pregnancy can lead to patent ductus arteriosus, pulmonary valve abnormalities, peripheral pulmonary stenosis and VSD. It cannot be overemphasized that rubella embryopathy is avoidable by ensuring a sufficient immunization protection. Sense of responsibility must be woken in both women and men, who act as vectors, for contributing in the prevention of rubella embryopathy.

Not only the rubella virus can cause cardiac malformations but also any other febrile infections have the potential of causing harm to the fetus. Women reporting on any febrile illness during pregnancy have a risk twice as high for giving birth to an aggrieved child. Therefore recommendations for pregnant women are to avoid contact to people with flu or other febrile infections (Jenkins et al. 2007, pp. 2997–2999).

Maternal Sociodemographic Characteristics

Maternal age is related to the likelihood of CCVD. Women of age ≥30 years have a higher risk for transposition of the great arteries and Ebstein's anomaly in the offspring. More advanced age (>34 years) goes along with an increased risk for bicuspid aortic valve and ASDs. Another study found that women becoming pregnant in an age between 35 – 40 years have an increased risk for all heart defects, tricuspid atresia and right ventricular outflow tract defects. However, young age in pregnancy (<20 years) also holds a risk for a CCVD, namely the risk of tricuspid atresia.

In case of a problematic reproductive history, the risk for ToF, atrioventricular septal defects, atrial septal defects and Ebstein's anomaly is increased.

Also maternal stress measured by maternal reports of job loss, divorce, separation or death of a close relative or friend has been associated with a higher risk of conotruncal heart defects (Jenkins et al. 2007, p. 3007).

Paternal Risk Factors

Not only the maternal age affects the risk for CCVD; newly appearing dominant mutations are more common in older fathers. Especially the risk for achondroplasia, Apert syndrome and Marfan syndrome increases with paternal age. Malformations affecting the cardiovascular system are inter alia ASDs, VSDs and PDA. Similar to women are fathers of younger age (<20 years) at a higher risk of inducing CCVDs.

Other studies could either not show any connection between paternal age and increased CCVDs or only trends were identified for older age, cigarette smoking and alcohol intake, but significance could not be proven (Jenkins et al. 2007, pp. 3007–3008).

1.5.2 INHERITED (GENETIC) FACTORS

During the past decade search for genetic association with congenital heart disease (CHD) has shown that the relation between CHD and the molecular structure of the DNA is strong. The genetic contribution has been underestimated in the past. However, especially in this field, environmental influences strongly coin the severity of the disease. Rapid progress in methods of gene discovery (e.g. cytogenetic techniques for chromosome analysis, FISH and DNA mutation analysis) highly contributed in augmenting knowledge (Pierpont et al. 2007).

There are several syndromes, but also nonsyndromic single-gene disorders, that are important to mention in congenital heart defects: DiGeorge Syndrome, Williams-Beuren Syndrome, Alagille syndrome, Noonan syndrome and Holt-Oram syndrome, as well as genetic disorders like Trisomy 21 or 18 that often comprise cardiac malformations (Pierpont et al. 2007).

Tetralogy of Fallot and its variants occur in 8 to 35 percent combined with microdeletion-syndrome 22q11. The DiGeorge Syndrome, the velocardiofacial syndrome (Shprintzen Syndrome) and the conotruncal anomaly face syndrome share this deletion as common genetic origin. The term CATCH-22 Syndrome has been used as well. CATCH in that matter is an acronym for Cardiac abnormality, Abnormal facies, T cell deficiency, Cleft palate and Hypoparathyreoidism. (Koletzko 2013; Pierpont et al. 2007)

Shinebourne et al. described that the autosomal dominant 22q11.2-deletion appears in about 15 percent of ToF-patients and sometimes accounts for a T-cell immunodeficiency (Shinebourne 2006).

If immunodeficiency is present, blood transfusions (in the context of e.g. surgery) can cause graft-versus-host-disease. Therefore it is important to screen ToF-patients for the 22q11.2-deletion and subsequently for T-cell immunodeficiency (Shinebourne 2006).

Pierpont et al. compiled a summary of recommendations when to perform cytogenetic testing for the congenital heart disease population in case of a suspected genetic origin (Pierpont et al. 2007, p. 3026):

1. Any infant or child with the apparent phenotype of a chromosomal aberration (e.g. Trisomy 21 or 18)
2. Any infant or child with a CHD and in addition
    a. Several congenital anomalies
    b. Developmental delay or mental retardation
    c. Growth retardation inadequate and not allegeable by the cardiac malformation
    d. Dysmorphic features
3. Any infant or child with a family history of repeated miscarriage or siblings with congenital defects
4. In case of prenatally documented cardiac or other visceral organ malformations

Identification of a genetic source of the disorder is helpful for both the subject suffering from the CHD as well as for the family. Parents of an affected child are able to acquire consultation in case of further family plans. An ideal follow up can also be ensured by knowing about the exact origin of the disease. The need of a multidisciplinary patient-centered care cannot be overemphasized. Ethical considerations are a comprehensively discussed issue in that matter. Especially the progress in in-vitro fertilization makes pre-implantation diagnostics a subject on which no universal agreement yet exists. In genetic testing of infants a reasonable consensus might be that a benefit should result from the testing (Pierpont et al. 2007).

1.6 DIAGNOSTIC TOOLS FOR THE EVALUATION OF CONGENITAL HEART DISEASES

Today, the gold standard in cardiac imaging is echocardiography (Mertens, Friedberg 2009). The advantages are its portability, the easy accessibility, it is non-invasive and provides physiological and anatomical information on the spot (Bailliard et al. 2008). Moreover, other than cardiac catheterization, echocardiography operates without the need for ionizing radiation.

In congenital heart diseases, echocardiography accounts as a first-line technique for reasons described above. It often allows good assessment of RV- and LV-size and -function, tricuspid regurgitation and RVSP. Furthermore evaluation of RVOTO and pulmonary regurgitation are possible with the help of echocardiography. A possible VSD, aortic regurgitation and aortic root size can be assessed. (Baumgartner et al. 2010, p. 2938)

One of the biggest disadvantages of echocardiography, however, is its user-dependency, in terms of reliability and validity of the gained data. Also, the significance of this examination is highly dependent on the acoustic-window and the patient's cooperation. (Bailliard et al. 2008)

In congenital malformed hearts, investigation of this very complex anatomy can be challenging solely with echocardiography. In that case, cardiac magnetic resonance imaging has become a powerful tool for the anatomic and hemodynamic evaluation. Especially for ventriculography, CMR is widely considered as the clinical reference standard. In the guidelines for the management of grown-up congenital heart diseases, the ESC (European Society of Cardiology) refers to CMR as the *"[…] method of choice for assessment of RV volume and function, PR, size, shape, and expansion of the PAs, the ascending aorta and the position of great vessels or conduits in relation to the sternum (resternotomy)"* (Baumgartner et al. 2010, p. 2938).

Notable limitations for echocardiography are subjects with a poor acoustic window or, as mentioned above, evaluation of the right ventricle or a single ventricle anatomy. In these situations, CMR is particularly useful and method of choice (Fratz et al. 2013a, p. 7). Besides the possibility of creating high-resolution 3D-images, CMR is able to depict intracardiac anatomy accurately and is highly reproducible. Also important, information regarding blood-flow-patterns within the great arteries can be obtained (Geva 2011).

However, CMR is an ionizing-radiation-free investigation whose availability is limited in many countries, needs a team of well-trained specialists, and is pricey (Bailliard et al. 2008).

The duration of the examination can last from 15 up to 60 minutes, which can be challenging for some patients, since one must remain almost completely motionless. In children up to a certain age, anesthesia might become necessary, in order to obtain ideal examination conditions (Bailliard et al. 2008).

While cardiac catheterization has been an important tool for pressure measurement and for the visualization of the coronary artery status, awareness of its negative impact on the subject due to ionizing radiation has become bigger. That is why today's recommendations suggest a restrictive use of cardiac catheterization. Whenever possible, the examination shall be conducted in combination with interventional procedures or in the case of inconclusive results from non-invasive methods. (Baumgartner et al. 2010)

The devices/examinations which were important for the conduction of this study (regarding data-acquisition) will be described in the following passage.

1.6.1 DOPPLER ECHOCARDIOGRAPHY – BASICS

Data concerning right ventricular pressure (RVSP) and maximal velocity throughout the right ventricular outflow tract (V_{max}RVOT) can be obtained with the help of Doppler Echocardiography. A Doppler examination provides both anatomic information and blood flow profiles of the investigated object. To depict blood flow, the different velocities of erythrocytes are used to generate a color-encoded flow pattern. Erythrocytes moving towards the transducer reflect the ultrasound beam and increase its frequency. Vice versa, the frequency of the reflected ultrasound beam decreases when it is reflected by an erythrocyte moving away from the transducer. From this change of frequency not only direction of the red blood cells but also the flow velocity can be calculated. The information about the flow is either reported as a velocity [m/s] or as pressure [mmHg]. The simplified Bernoulli equation for conversion is (Rudski et al. 2010):

$$p[mmHg] = 4 * (V_{max}[m/s])^2$$

In order to obtain the most accurate result the examiner takes multiple samples of the regurgitant jet in different alignments of the transducer. Then the highest velocity should be taken as the closest estimation. In theory the highest velocity can be gained by adjusting the transducer signal completely parallel to the blood stream. This can be hard to realize, especially in case of hemodynamic turbulences due to anatomic malformations.

1.6.1.1 INTRAVENTRICULAR PRESSURE MEASUREMENT

There are two different methods to assess right ventricular systolic pressure; depending on what is present (Park 2002, p. 75):

1. Tricuspid regurgitation jet:

$$RVSP = 4 * (V_{TR})^2 + RAP$$

Where RVSP is the Right Ventricular Systolic Pressure (in [mmHg]), V_{TR} is the tricuspid regurgitation jet velocity (in [m/s]) and RAP is the Right Atrial Pressure (in [mmHg]), which is assumed.

The assumption of the RAP is carried out indirectly via the width of the inferior vena cava (IVC). For this purpose, the patient lies in the supine position with the IVC being viewed in its long axis from a subcostal view. The width of the IVC in end-expiration allows to draw conclusions to the RAP. There are only three gradings – RAP from 0 to 5, 5 to 10 and 10 to 15 mmHg (Rudski et al. 2010). Values from 1 to 7 mmHg are considered *normal* for RAP (Beigel et al. 2013, p. 1033).

2. Ventricular septal defect jet:

$$RVSP = sSP - 4 * (V_{VSD})^2$$

Where RVSP is the Right Ventricular Systolic Pressure (in [mmHg]), sSP is the systemic Systolic Pressure (in [mmHg]) and V_{VSD} is the flow velocity across the VSD (in [m/s]).

The values for RVSP used in this study are always raw values in [m/s] of the jet velocity, converted into [mmHg] with the simplified Bernoulli-equation, without adduction of the RAP. Therefore, using the term RVSP is basically not entirely correct. However, in the face of a great investigator-dependency in the assessment of RAP, we decided to proceed in that manner. Thus, when the term RVSP is used, it is solely the converted jet velocity over the tricuspid valve – RAP was never added.

1.6.1.2 PRESSURE GRADIENT MEASUREMENT

In CHD patients, assessment of pressure gradients is often of great importance. Especially in Fallot patients the pressure gradient across the pulmonary valve, RVOT respectively, is of high interest. To estimate pressure gradients across stenotic, regurgitant or shunt lesions, one of the following two equations can be used (Park 2002, p. 74):

$$p_1 - p_2 = 4 * (V_2^2 - V_1^2)$$

$$p_1 - p_2 = 4 * (V_{max})^2$$

Where $p_1 - p_2$ is the pressure difference across to the stenosis (in [mmHg]), V_1 is the flow velocity proximal; V_2 is the velocity distal to the stenosis (in [m/s]). In case of V_1 being less than 1 m/s it can be ignored, thus the second formula is being used.

In the evaluation of RVOTO, correct localization of the obstruction is of great importance. Therefore color, pulsed-wave and continuous-wave Doppler should be used (Valente et al. 2014, p. 115). Differentiation between a dynamic obstruction within the right ventricle and a valvar/supravalvar obstruction can be accomplished by a spectral Doppler flow profile across the RVOT (Valente et al. 2014, p. 115).

1.6.2 CMR – CARDIAC MAGNETIC RESONANCE

Along with echocardiography cardiac magnetic resonance (CMR) has become the method of choice in the evaluation of complex congenital heart defects, particularly in questions regarding the right ventricle's form, function and appendant vessels (Baumgartner et al. 2010). Especially in adult patients, where the window for echocardiography becomes narrower or in patients with difficult anatomic conditions, CMR is the preferred tool for examination (Wood 2006). Absence of ionizing radiation is another great advantage, especially in the examination of children, but of course also in adults.

Today Magnetic Resonance Imaging (MRI) is a commonly known and frequently used diagnostic tool in different fields. The operating mode of this device is complex, the acquaintance requires decent training and is under no obligation trivial. Since it is used for the quantification of right ventricle volumes, function and pulmonary regurgitation, amongst others especially in patients witch corrected ToF, the following part discusses the basic functionality of an MRI-device (Valente et al. 2014, p. 113).

1.6.2.1 MRI BASICS

There are three main components that are part of every magnetic resonance imaging scanner:

- Set of main magnet coils
- Three gradient coils
- Radiofrequency (rf) transmitter coil

The object to investigate is placed within the central bore, and there into the isocenter of the scanner. The element Hydrogen acts as the cornerstone of generating images. Hydrogen holds in its core only one proton, in its atomic shell therefore one electron. Hydrogen possesses a nuclear spin that induces a small magnetic field, called magnetic moment. When applying a strong external magnetic field, hydrogen's magnetic field may be aligned in a specific fashion – within that state, Hydrogen may be imagined as a tiny bar magnet. As hydrogen occurs in every tissue in the form of water and in lipid-molecules, it is an excellent target for a device like the MRI-scanner (Biederer 2005; Ridgway 2010).

The main magnet coils generate a strong constant magnetic field, denoted B_0, which frequently is 1.5 to 3.0 Tesla in CMR (Fratz et al. 2013a, p. 3). 1 Tesla equals approximately 20.000 times the earth's magnetic field; field strengths range from 0.2 to 3.0 tesla in commercially produced MRI-systems (Ridgway 2010, p. 2). To define the magnetic field, a reference coordinate system (x-, y- and z-axis) has been established. By definition, z-axis is parallel to B_0. In the magnetic field, Hydrogen's magnetic moment arranges either towards or against the alignment of B_0, attaining a state of equilibrium. However, there is a small amount of atoms, only a few per million, that cause an excess in the alignment. This excess forms a net magnetic field or a net magnetization, tagged M. If the net magnetic field is aligned along B_0, M is denoted M_0. M is usually pictured as an arrow or a vector (Ridgway 2010).

To generate a picture, the net magnetic field has to be deflected from M_0. This is accomplished by the rf transmitter coil, which delivers energy to the protons and that way alters the angle of the net magnetization. The rf field is administered as a short pulse, called the rf pulse. By applying the rf pulse, the net magnetic field moves out of its alignment with B_0 in a defined angle (depending on the strength of the pulse) and starts to rotate around the B_0 field. The speed of the rotation is called precession (Ridgway 2010).

As soon as the net magnetic field reaches a prescribed angle, known as the flip angle, the rf pulse is switched off. Now that the rf field is gone, the net magnetization immediately goes back to its original state, equilibrium respectively. This process is called relaxation. Relaxation consists of two components. One, longitudinal relaxation along the z-axis, which is commonly known as T1-relaxation. The second component, transverse relaxation is more complex. To understand transverse relaxation one has to remember that the net magnetization results from the sum of magnetic moments of a whole population of protons. The direction where this population points to, is known as the phase angle. As long as all the protons are aligned equally, their state is called “in phase”. Due to spin-spin interactions between the atoms, the magnetic moments no longer rotate together and are moving “out of phase”. This causes a decay of the signal and is the reason for T2 relaxation. However, there is a second cause for the de-phasing of the net magnetization. Non-uniformities in the applied magnetic field lead to different rotational speeds, as the precession depends on the strength of the magnetic field. Therefore, further de-phasing appears and the signal decays more rapidly. The combination of T2 relaxation and field inhomogeneities is called T2* relaxation. Differences in relaxation times occur due to variable molecule size, which is again responsible for differing energy exchange. In the final picture relaxation times are mirrored in different contrasts (Ridgway 2010).

As a last step the spatial origin of a signal has to be encoded. This is achieved with the help of three separate gradient coils, which apply magnetic field gradients in all three axes. Defined frequencies are used for slice selection. The ability of selecting arbitrary planes makes the MRI a powerful tool, especially for the examination of complex problems, as they occur in congenital heart defects (Ridgway 2010).

1.6.2.2 SPECIAL UTILIZATION OF MRI IN CARDIOLOGY

In cine imaging, a form of data acquisition that allows to depict the collected information in the form of a movie, e.g. a movie of the beating heart, it is important to synchronize data collection points to the cardiac cycle. Therefore the cardiac cycle has to be recorded with the help of the ECG. Measurements can now be synchronized on the R-spike (marking the beginning of systole) to get a consistent picture of the desired anatomic structure. However, this requires that the patient does not suffer from arrhythmias (Ridgway 2010).

Another important factor, which can distort the investigation, is breathing. There are two possibilities to solve this problem. The easiest way is holding the breath, which causes problems in of course infants and young children, as well as in pulmonary restricted patients. Also, the average patient can hold its breath for around 15 (to 30) seconds. This should be enough for an investigation of the heart. Flow measurement duration of the vessels varies, depending on the chosen sequence. Especially when quantification of the regurgitant volume is of interest, testing time increases and can take up to two minutes. This may complicate flow measurement in breath hold under the mentioned circumstances (Kilner et al. 2007). Therefore, two different approaches were developed to maintain interference-free flow measurements. The first method uses a specialized belt around the patient's chest that registers movement of the thorax due to breathing. Scanning is then only performed in low movement breathing-phases. Another technique is to define the border between lung and liver to register breathing. Acquisition of data is only performed in a determined, so called "gating window", which allows conducting the examination in normal respiration. However duration of the scan increases (Simon 2010, pp. 28–29).

1.6.2.3 CONTRAINDICATIONS FOR MRI-EXAMINATIONS

The enormously high magnetic field inside an MRI-system bears certain risk factors that account as absolute or relative contraindications for performing an MRI-exam. Some of the most important risk factors are listed in the following passage. However, this list makes no claim to be complete. Operating with high-end technical devices like an MRI-scanner requires a reasonable and considerate acquaintance. Therefore the entire personnel need to be trained well and alert at any time.

1.6.2.3.1 ABSOLUTE CONTRAINDICATIONS

Subjects coming in contact with an MRI-device must be checked for relative and absolute contraindications. These may be amongst others (following the recommendations in http://radiology.ucsf.edu/patient-care/patient-safety/mri-safety):

- Pacemakers

  Already minimal field strengths could alter the correct functionality of a pacemaker, causing asynchronies. Even if the patient had its pacemaker removed it is important to be cautious because of accidentally left wires in the myocardium. These residual wires could heat and cause cardiac fibrillations.

- Implantable Cardiac Defibrillators

  As in pacemakers, electrodes of ICDs are placed in the myocardium. The strong magnetic field can cause heating of ferromagnetic electrodes, leading to burns. Also as described above, the electrodes can act as antennas, causing cardiac fibrillations.

Please note: Pacemakers and Implantable Cardiac Defibrillators were considered absolute contraindications in the past. This especially applies to models produced prior to the year 1996.
In 2011 the first pacemaker was declared MRI-safe by the US Food and Drug Administration. Depending on the model, some devices can now be seen as relative contraindications under certain circumstances (Lobodzinski 2012). However, controversies remain regarding the influence of pacemakers on image quality in the MRI environment. (Ferreira et al. 2014, p. 122)
For comprehensive information on this topic please check http://www.radiology.ucsf.edu/patient-care/patient-safety/mri/policy or http://www.mrisafety.com/.

Other potential contraindications, like Neurostimulators, Cochlear Implants or any other ferromagnetic device/debris appear rarely but must always be thought of, asked for respectively.

1.6.2.3.2 RELATIVE CONTRAINDICATIONS

Relative contraindications comprise a long list of factors. An excerpt from http://www.radiology.ucsf.edu/patient-care/patient-safety/mri/policy is listed in the following passage:

- Intracranial Vascular Clips

  Some aneurysm clips contain ferromagnetic components. In case of existence of such clips, MRI-examinations are contraindicated due to potential injuries that might be followed by bleeding and death.

- Coronary Stents

  Several coronary stents have shown interactions with the high magnetic field of MRI-scanners. However, these devices become incorporated within six weeks, making the examination feasible after that particular time period.

- Pregnancy

  To date there are no adverse effects known, caused by MRI. However, especially within the first trimester, dividing cells might be more susceptible to high field strengths. That is why the FDA recommends delaying the exam until after the first trimester if possible. Pregnant employees must make their own decisions, whether to work around MRI-devices while pregnant or not. Today informed decisions on magnetic safety for pregnant employees are not available yet.

- Other Relative Contraindications

  Mentionable might be penile implants, halo vests, shrapnel, pellets and bullets.

More comprehensive information regarding relative and absolute contraindications for MRI can be found under http://www.radiology.ucsf.edu/patient-care/patient-safety/mri/policy.

1.6.3 IMPORTANT INVESTIGATED PARAMETERS

There are several volumetric and flow parameters that can be determined with the help of CMR. Among them are in particular left and right ventricular volumes; usually quantified in endsystole, enddiastole respectively. Based on these volumetric parameters, every other parameter can be calculated:

- Ejection Fraction:

$$EF = \frac{EDV - ESV}{EDV} * 100$$

- Stroke Volume:

$$SV = EDV - ESV$$

- Indexed End Systolic/Diastolic Volume:

$$indexed\ ESV(EDV) = \frac{ESV(EDV)}{BSA}$$

For the evaluation of regurgitation volumes or fractions, knowledge of ante- and retrograde flow within the corresponding artery is needed. This is accomplished in a way similar to the volumetric measurements.

- Pulmonary Regurgitation:

$$PR = \frac{PA\ retro}{PA\ ante} * 100$$

Where PA_{ante} is the anterior flow through the pulmonary artery and PA_{retro} is the retrograde flow through the pulmonary artery, both assessed by CMR.

- Aortic Regurgitation:

$$AR = \frac{Ao\ retro}{Ao\ ante} * 100$$

Where Ao_{ante} is the anterior flow through the Aorta and Ao_{retro} is the retrograde flow through the Aorta, both assessed by CMR

1.7 EVALUATION OF EXERCISE CAPACITY

In order to evaluate and quantify each subject's exercise capacity cardiopulmonary exercise testing was conducted. Basics on the execution of this examination, terminology and a description of frequently used parameters are being described in the following passage.

1.7.1 CPET – CARDIOPULMONARY EXERCISE TESTING - BASICS

All the information regarding CPET is extracted from Haber, Paul (2013): Lungenfunktion und Spiroergometrie. Interpretation und Befunderstellung unter Einschluss der arteriellen Blutgasanalyse. 3. Auflage. Dordrecht: Springer.

A CPET basically comprises two examinations:

1. Testing for (maximum) exercise capacity on an ergometer
2. Testing of the cardiopulmonary-apparatus for its ability to adapt to higher strain

Assessment of exercise capacity can be achieved by exercising on either a treadmill or a stationary exercise bicycle ergometer. However, in many cases not only the maximum exercise capacity is of interest.

For a comprehensive impression of the patient's disease, the reaction of its body to stress is important. The evaluation is feasible by measuring cardio-pulmonary parameters, such as blood pressure, heart rate, ECG, blood gas and of course breathing gas. Subsequently to the CPET more differentiated examinations, e.g. catheterization of the heart, can be conducted.

(Haber 2013, p. 112)

1.7.1.1 CONTRAINDICATIONS AND INDICATIONS FOR ABORTING AN EXAMINATION

- Contraindications
  - Acute feverish/non-feverish illnesses
  - Acute myocardial infarction
  - Unstable angina
  - High-grade aortic stenosis
  - RR > 220/120 mmHg
  - Pulmonary embolism
- Indications for aborting the exam
  - Objective indications
    - Dysrhythmia
    - RR > 260/130 mmHg
    - Dropping of RR, despite increasing strain
  - Subjective Indications
    - Prostration
    - Pain
    - Vertigo

(Haber 2013, pp. 112–113)

1.7.1.2 ERGOMETERS

There are two commonly used ergometers – the bicycle ergometer and the treadmill. Important to note is that the VO_2max mostly reaches higher levels on the treadmill, which means that bicycle ergometer and treadmill cannot be compared directly.

Usage of a bicycle ergometer provides a set of advantages, such as

- less ECG-artifacts
- additional measurements (RR, venipuncture) are easy to accomplish, without the need for pausing the examination
- test is well standardizable, due to a specified pedaling cadence
- Exercise capacity is being measured in physical unit Watts

For clinical use, the treadmill provides no advantages compared to the bicycle ergometer.

(Haber 2013, pp. 115–116)

1.7.2 PROTOCOL

There are two different protocols – the step protocol and the ramp protocol.

1.7.2.1 STEP PROTOCOL

Starting with only little load, power is being increased stepwise, e.g. 25 W/min. In clinical use, load is being adapted to the individual's exercise capacity. The recommended test duration lies between 8 and 16 minutes (Haber 2013, p. 118).

1.7.2.2 RAMP PROTOCOL

A ramp wise increase of load is feasible since the invention of electronically controlled ergometers. Power increases continuously, thus the body can never reach a form of steady state, which makes it difficult to assess submaximal strain. This is especially important in cases of strain-induced hypertension (Haber 2013, pp. 119–120).

1.7.3 DESCRIPTION OF USED PARAMETERS

In the following passage four CPET-parameters VO_2max, VO_2max%, Wmax and VE/VCO_2 Slope will be described more specifically.

1.7.3.1 VO_2MAX [L/MIN]

VO_2 stands for oxygen-uptake per minute and is the physiologic definition of the physical term Power. VO_2 increases linearly with the equivalent strain on the ergometer. Thus, a directly proportional relation between power and VO_2 exists. Maximum O_2-uptake correlates with the cardiac output. The higher the maximum reachable CO, the higher is the resulting VO_2max. VO_2max is reached when, despite increasing power on the ergometer, VO_2 does not increase anymore. One of the biggest "problems" of VO_2max is the dependency on the so called anthropometric variables, namely sex, weight, height and age. In women VO_2max is around 20% less than in men of the same weight. VO_2max positively correlates with height and weight, active body mass respectively. Increasing age leads to a decrease of VO_2max, though the velocity of the decrease is not equal in men and women. VO_2max in absolute terms is not very meaningful as it strongly depends on the body mass. That is why VO_2max/kg is a widely spread and often used parameter. However, relating VO_2max to the bodyweight still does not help in objectifying it, as it is still dependent on the residual anthropometric variables. Hence, it is very reasonable to describe VO_2max in percentage of a reference-value, VO_2max% (Haber 2013, pp. 128–130).

1.7.3.2 VO_2MAX%

The initial idea behind this value was to introduce a reasonable parameter that displays the maximum O_2-uptake, which is independent from anthropometric variables (i.e. sex, age, height, weight). VO_2max% is a value denoted in percent of VO_2max. The advantage of VO_2max% is that the variables sex, weight, height and age are already considered in the reference value. Therefore, a normal VO_2max% is regarded *normal* in every patient; thus it is easy to interpret (Haber 2013, p. 130).

1.7.3.3 WMAX

W_{max} is a highly variable and individual parameter. It strongly depends on the subject's physical condition and limitations like immobilization (Haber 2013, p. 124). However, in patients with a primary cardiac disorder, the achieved W_{max} may not represent the potential actual output. W_{max} in this scenario may not be represented by maximum load due to prostration of the skeletal muscle but may represent the cardiac limitation to sufficiently master the required cardiac output. Therefore W_{max} has to be interpreted individually with knowledge of the subject's condition and constitution.

1.7.3.4 VE/VCO_2 SLOPE

VE stands for respiratory minute volume; VCO_2 means carbon dioxide exhalation per minute. VE/VCO_2 means respiratory equivalent and it is a dimensionless parameter. It represents the respiratory economy, referring to CO_2-exhalation. In resting state the CO_2-expiration is relatively low; hence the VE/VCO_2 reaches high values. With increasing strain the respiratory equivalent is becoming lower until it reaches a state, where it does not change anymore because VE is dependent on VCO_2 (Haber 2013, p. 139).

1.7.3.5 APPLIED FORMULAS IN THIS STUDY

The following formulas for the calculation of reference values for VO_2max have been described by Cooper and Storer in: Cooper, Christopher B.; Storer, Thomas W. (2001): Exercise testing and interpretation. A practical approach. Cambridge, U.K.,, New York, NY, USA: Cambridge University Press.

In this work, the formula is extracted from Muller, J.; Christov, F.; Schreiber, C.; Hess, J.; Hager, A. (2009): Exercise capacity, quality of life, and daily activity in the long-term follow-up of patients with univentricular heart and total cavopulmonary connection. In: European Heart Journal 30 (23), S. 2915–2920. DOI: 10.1093/eurheartj/ehp305, since the author of this publication was responsible for the collection of the CPET-data.

Maximum oxygen uptake per minute (peak VO_2/VO_2max) varies in different age groups. According to these changes, corresponding formulas have been established before. (Cooper, Storer 2001; Muller et al. 2009)

For patients greater than or equal to 18 years of age, the following formula was applied (Muller et al. 2009, p. 2916):

Females:

$$peak\ VO_2[\frac{\frac{ml}{kg}}{min}] = 5.8 + \frac{(62.2 * height\ [m] - 45.5) * (37.03 - 0.371 * age\ [years])}{weight\ [kg]}$$

Males:

$$peak\ VO_2[\frac{\frac{ml}{kg}}{min}] = 5.8 + \frac{(71.6 * height\ [m] - 51.8) * (44.22 - 0.394 * age\ [years])}{weight\ [kg]}$$

For patients 12 to 17 years of age, the following formula was applied (Muller et al. 2009, p. 2916):

Females:

$$peak\ VO_2[\frac{\frac{ml}{kg}}{min}] = \frac{22.5 * height\ [cm] - 1837.8}{weight\ [kg]}$$

Males:

$$peak\ VO_2[\frac{\frac{ml}{kg}}{min}] = \frac{42.6 * height\ [cm] - 4547.1}{weight\ [kg]}$$

For patients younger than 12 years of age, pooled data from both sexes was used (Muller et al. 2009, p. 2917):

$$peak\ VO_2[\frac{\frac{ml}{kg}}{min}] = \frac{37.1 * height\ [cm] - 3770.6}{weight\ [kg]}$$

1.8 QUALITY OF LIFE

In the past, certain impairments in daily life have been ascribed to patients with congenital heart diseases as their hereditary burden. These impairments are supposed to be regarding issues such as physical activity, employment and pregnancy (Lane 2002). However, recently conducted studies on patients with corrected ToF and/or conduit dysfunction have investigated quality of life (Mueller et al. 2013; Müller et al. 2014):

- In a selected cohort of patients with PR and/or PS, QoL significantly improved in physical domains six months after PPVI (Müller et al. 2014)
- Quality of life in ToF-patients and healthy subjects is comparable (Müller et al. 2014; Walker et al. 2002)
- Peak oxygen uptake (VO_2max) and self-reported physical well-being showed a significant positive correlation (Müller et al. 2014)
- Peak oxygen uptake (VO_2max) and total score of the KINDL-R questionnaire showed a significant positive correlation (Müller et al. 2014)

  However
- Self-estimated physical ability is significantly overestimated (objectified in CPET) by the KINDL-R questionnaire in ToF-patients (Müller et al. 2014)
- The KINDL-R questionnaire does not sufficiently reflect the actual (impaired) physical ability of the study-population (Müller et al. 2014)

  Therefore
- It is advised to use exercise tests and QoL-instruments in a complementary manner, in order to avoid crucial self-misinterpretation of the actual exercise capacity (Müller et al. 2014)

Some aspects that might have an influence on QoL like sports and exercise or giving childbirth are worth mentioning. Asymptomatic patients do not underlie certain restrictions in their freedom of performing sports or exercising (Baumgartner et al. 2010, p. 2939).

Risks of arrhythmia and right heart failure in pregnancy in repaired ToF-patients are dependent on the individual's hemodynamic situation. The risk is low in case of good hemodynamic status but may increase with residual lesions present. The risk for recurring congenital heart disease is approximately three percent. When microdeletion 22q11 is present, there is an increase in risk to 50 percent. (Baumgartner et al. 2010, p. 2939)

2 METHODS

2.1 PATIENTS

This study was designed as a retrospective single-center study, using preexisting cardiac MRI- and CPET-data. Search for subjects was accomplished using the database of the department of pediatric cardiology and congenital heart diseases of the Deutsches Herzzentrum München (German Heart Center Munich), university hospital of the Technische Universität München (Technical University of Munich – TUM). Search for matching subjects was accomplished from November 2005 to May 2011. At that particular time the database consisted of around 4500 examinations that were scanned for the following parameters: Fallot, ToF, PA+VSD, PA+IVS, PS, prä-Melody. *Table 2 – Inclusion and Exclusion Criteria* gives an overview of the applied criteria:

No.	Criteria	Subcriteria	Inclusion
1	**CMR and CPET**	Data available from both	X
2	**Time between CMR and CPET**	< 183 days	X
3	**Diagnosis**		
3a		ToF	X
3b		PS	X
3c		PA+VSD	X
3d		PA+IVS	X

Table 2 – Inclusion and Exclusion Criteria

The scan of database mentioned above provided 416 cases. These were cross-referenced with patient data of the CPET, leaving 264 cases that fulfilled Criteria #1. *Table 2* shows that a time of 183 days, six months respectively, must not have been exceeded between those two examinations, in order to ensure comparability. 17 cases had to be excluded for that reason, leaving 247 cases after the application of criteria #2. In case of multiple MRI-examinations on the same subject, only the latest examination was included, under the condition of a CPET having taken place contemporarily. If interventions have occurred, the same patient has been accounted for two different cases (altered hemodynamic situation before and after the intervention).

The following clinical and demographic data was collected retrospectively from the patient's most recent medical reports: Date of birth, gender, date and age at MRI/CPET, diagnose, weight and height.

After deducting non-usable and multiple cases, the collective consisted of 132 cases. Of the 132 cases, 73 were male and 59 were female. The median age was 28 years (range 13 – 66 years), the median age at both MRI- and CPET-examination was 24 years (range 9 – 64 years). The median weight was 64 kilograms (range 28 – 127 kg), the median height was 1.7 meters (range 1.32 – 1.92 m) and the median body surface area (BSA) was 1.72 square-meters (range 1.01 – 2.56 m^2).

Regarding diagnosis and particularly hemodynamics, three groups were formed:

1. ToF or PS – "native" – procedures performed, such as: RVOT-patch, resection of the infundibulum, Brock procedure, etc.

2. corrected ToF, PA+VSD or PS – correction includes allograft (AG), homograft (HG), xenograft (XG)

3. PA+IVS

Figure 5 shows the distribution of the three groups:

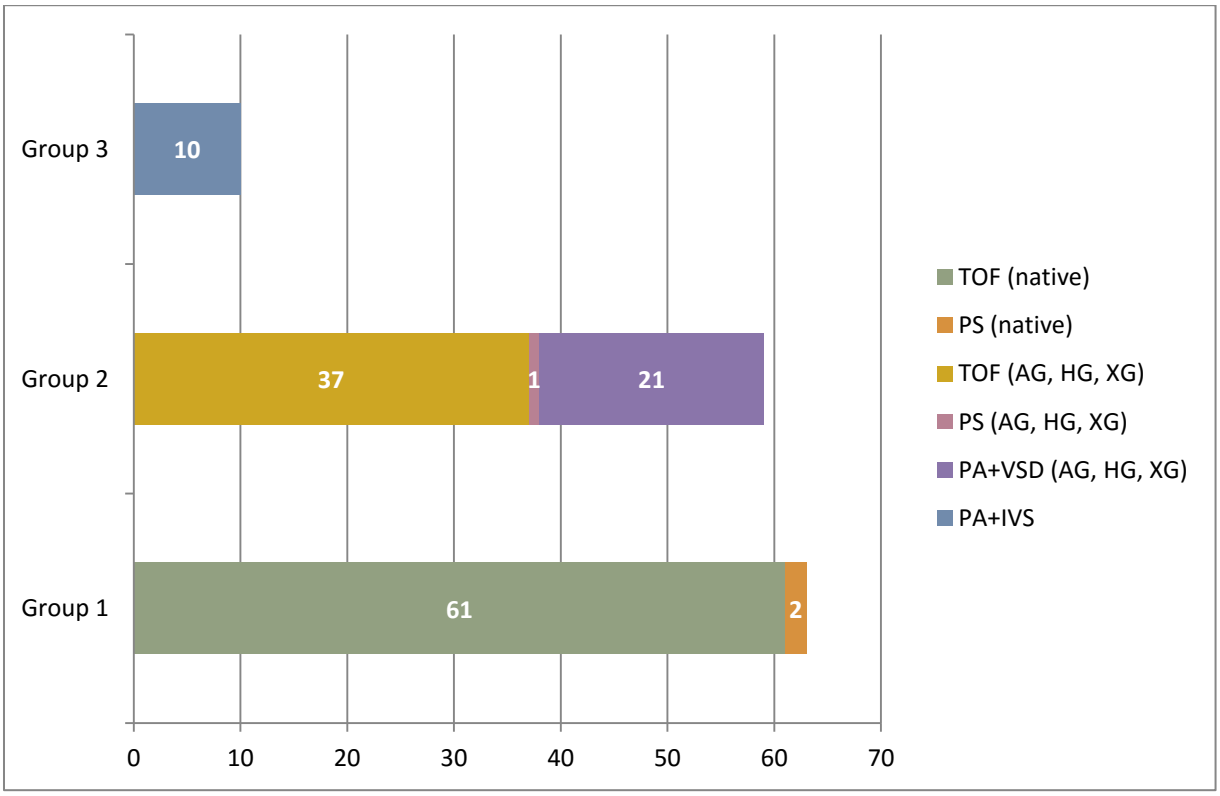


Figure 5 – Distribution of different Diagnoses

Group 1 comprises patients with Tetralogy of Fallot and isolated Pulmonary Stenosis, who have undergone procedures like RVOT-patch, infundibular resection, Brock procedure or etc. Group 1 accounts for 48 percent of the total.

Group 2 consists of Fallot-patients, patients with Pulmonary Stenosis and patients with Pulmonary Atresia combined with a Ventricular Septal Defect. Every subject within group 2 underwent a conduit implantation. Group 2 accounts for 45 percent of the total.

Group 3 contains all patients with Pulmonary Atresia and Intact Ventricular Septum and accounts for seven percent of the total.

The collective represents standard values regarding median, standard deviation and range. *Table 3 – Descriptive Statistics* gives an overview of the biometric parameters:

Parameter	Median	Mean	SD	Min	Max
Age [y]	24	26	11	9	64
Weight [kg]	64	65	17	28	127
Height [cm]	170	168	12	132	192
BSA [m²]	1,72	1,74	0,27	1,01	2,56

Table 3 – Descriptive Statistics

2.2 APPLICATION OF ECHOCARDIOGRAPHY IN THIS STUDY

2.2.1 ACQUISITION PROTOCOL

Two-dimensional and Doppler transthoracic echocardiography was applied, using a commercially available ultrasound system (Vivid 7; General Electric, Vingmed, Horten, Norway), as previously described (Groh et al. 2013; Kühn et al. 2013). In brief, recording of the tricuspid regurgitation jet was conducted with the patient in the supine position. Whichever provided the higher tricuspid valve jet velocity, either the parasternal or the apical window was used. In order to ensure the most exact results, special attention was paid to a strictly parallel alignment of the Doppler beam to the tricuspid jet. A mean of three consecutive cardiac cycles was taken as the final result to account for variations due to respiration. In case of a VSD present, an analogous approach was conducted. The simplified Bernoulli equation was applied on the obtained jet velocities.

In order to evaluate the degree and site of the RVOT obstruction, color, pulsed wave and continuous wave Doppler echocardiography has been used. Examination of the RVOT is feasible in the long axis and short axis planes, as well as in the inflow-outflow view, especially in young patients with a good subcostal window. In older patients the parasternal long and short axis view has been favored, as recommended by previous authors (Valente et al. 2014, p. 115).

Right ventricular pressure can be measured by either analyzing tricuspid regurgitation jet velocity or analyzing the jet velocity of a VSD (Park 2002, p. 75). Consequences of the first approach are that in the absence of tricuspid regurgitation, non-invasive pressure assessment is hardly, or even not at all, feasible. The second method for determining systolic RVSP, using the VSD-flow leads to similar problems. Since presence of a VSD is neither desired nor guaranteed, assessment of RVSP can be challenging.

A general limitation in echocardiography is its dependency on the examiners expertise (Baumgartner et al. 2010, p. 2919), which makes it a potentially error-prone technique. The most accurate result can be obtained, when the transducer signal is aligned strictly parallel to the jet (Groh et al. 2013, p. 6). Because of the angle-dependency of velocity measurements, it is recommended to perform the examination in different alignments and use the highest jet velocity as final result (Rudski et al. 2010, p. 698).

Congenital malformations or anatomic alterations due to surgery taken place prior to the echocardiographic examination are possible confounders. Visualization of certain parts of the right heart, quantitative and functional assessment, as well as evaluation of valvular lesions can be challenging. From child- to adulthood the echocardiographic window consecutively becomes narrower. Therefore, for the accurate assessment of RV size and function, additional modalities like CMR become of greater necessity. (Valente et al. 2014, p. 115)

When RVSP is evaluated by quantifying the tricuspid regurgitation jet velocity, the simplified Bernoulli equation is used:

$$RVSP = 4 * (V_{TR})^2 + RAP$$

In this equation right atrial pressure (RAP) is a possible confounder, as it is only assumed. There doesn't exist a non-invasive method for the exact evaluation of the RAP. The pressure is usually assumed at around 3 (0-5 mmHg), 8 (5-10 mmHg) or 15 (5-10 mmHg) mmHg, according to the width of the inferior vena cava and the presence of inspiratory collapse (Rudski et al. 2010). Pressures higher than 15 mmHg are unusual in the absence of severe cardiac malformations (Kumar 2012).
However, in this study, estimated values for RAP have not been added to the converted tricuspid jet velocity. Thus, as already stated in *1.6.1.1 Intraventricular Pressure Measurement*, when using the term RVSP, only the tricuspid jet velocity is meant. Calculations and statistical models have been executed with these "raw" values.

2.3 APPLICATION OF CMR IN THIS STUDY

2.3.1 ACQUISITION PROTOCOL

For cardiovascular magnetic resonance (CMR) a standard cardiac 1.5 Tesla CMR-scanner (MAGNETOM Avanto®, version software VB15, Siemens Healthcare, Erlangen, Germany) and a standard cardiac 12-channel coil was used. Patients were examined in the supine position and (with breath-holding in expiration for flow measurements). For determination of the ventricles and the great arteries, the sessions were initiated with steady state free precession localizing views in the three orthogonal planes.

2.3.1.1 VENTRICULAR VOLUME MEASUREMENTS

Volume analysis was performed in a supine position with breath holding in expiration as previously described (Alfakih et al. 2004; Fratz et al. 2009; Fratz et al. 2013b). In brief, acquiration of axial slices was conducted from the coronal and sagittal localizing images. In order to capture the heart in its entire dimension from a plane just below the diaphragm to the pulmonary bifurcation, a stack of orthogonal slices was planned.

In patients suffering from CHD, ventricular conduction delay is very common. Thus, end-systole and end-diastole may not be within the same cardiac frame for both the LV and the RV (Fratz et al. 2013a, p. 10). Therefore, definition of end-systole and end-diastole should always be accomplished visually and manually according to the observer's evaluation. In doing so, end-systole should be defined visually as the phase with the smallest volume; therefore end-diastole should be defined as the phase with the largest volume. The phases for end-systole and -diastole chosen automatically by the software are based on the ECG-triggering. Unfortunately this technique is error-prone because ECG recordings in CHD-patients are often not as accurate as required. If bad ECG-triggering is the case, the suggested first phase might be incorrect, further leading to under- or overestimated ESV/EDV. That is why Fratz and Stern recommend to always perform the phase-selection individually, manually and visually (Fratz, Stern 2012).

Patients with congenital heart defects are likely to suffer from poor ventricular function. This is expressed by only little movement of the ventricles in the cine MR imaging. In that case it is very difficult to determine a certain phase as end-systole, end-diastole respectively. In order to define the correct phase, positioning of mitral and tricuspid valve can be taken into account. (Fratz et al. 2013a)

Another difficulty that very likely occurs is the assessment of the endocardial borders within a non-hypertrophied RV. (Fratz et al. 2013a)

2.3.1.2 FLOW MEASUREMENT

Flow measurement within the great arteries has been described before (Fratz et al. 2008; Schuhbäck, Annika Renate Christina 2011; Fratz et al. 2013a). In brief, flow measurement was maintained as follows: Phase velocity (PV) CMR in non-breath-hold technique was used for flow measurement within the great arteries. A phase sensitive gradient echo sequence in a strict double-oblique plane perpendicular to the vessel of interest was used. Flow-measurement of the aorta was carried out at the level of the sinutubular junction, which is located after the origin of the coronary arteries. Flow through the MPA was measured between the pulmonary valve and the pulmonary branch bifurcation (LPA and RPA). For each vessel the set of measurements was individually planned and matched with the subject's anatomy. Furthermore, each of these measurements was adjusted to flow velocity and direction. Under certain circumstances flow measurements had to be repeated, for example if the velocity encoding setting was not smaller than 50 cm/s than the maximal velocity measured. In order to gain the most accurate and precise result, the slice of interest was placed exactly in the isocenter of the magnet. The vectorcardiographic ECG was monitored with great care during acquisition and for further improvement of the results, the acquisition was aborted, when extrasystoles were present. Therefore, scans had to be repeated until correct ECG-triggering throughout the whole acquisition was achieved. The following parameters were used:

Typical acquisition times of around 3 minutes in free breathing with retrospective ECG-triggering, the velocity encoding was chosen by the investigator in assumption to the jet velocity from 200 – 550 cm/s, slice thickness was 5 mm, repetition time 36.7 ms, echo time 3.09 ms, flip angle 30°, averages 3, segmentation 3, number of phase-encoding steps 192, receiver bandwidth 31.25 kHz, rectangular field of view 260 to 330 × 330 mm, matrix 256 × 256, phase partial Fourier off. Each examination provided 30 magnitude (anatomic) and phase (velocity-mapped) images per cardiac cycle. All measurements were automatically adjusted to the attendant gradient effects. (Knesewitsch et al. 2013, p. 2)

There are certain limitations and confounders that can complicate and distort measurements:

- ECG-Triggering: It is important to perform flow measurements in retrospective, rather than prospective ECG-gating, in order to inclose the whole diastolic portion of the cardiac cycle. Scans can be executed in free breathing. If incorrect ECG-triggering occurs, the scan should be aborted and repeated. (Fratz et al. 2013a, p. 10)
- Spatial resolution, number of planes and velocity range: To ensure reproducibility and accuracy the spatial resolution has to be high enough to avoid partial volume effects (Tang et al. 1993). Also a number of at least 20 non-interpolated planes is recommended. In order to avoid aliasing, the velocity range has to be adapted to the expected flow velocity. Especially in stenotic areas, flow velocity can exceed the primarily expected velocity, which should lead the operator to an adjustment of the velocity range and repetition of the scan. (Fratz et al. 2013a, pp. 10–11)
- Correct positioning of the patient: It is of great importance to put the desired vessel of investigation precisely into the isocenter of the scanner. Furthermore, to guarantee accuracy of velocity the imaging plane has to be aligned accurately perpendicular to the blood stream. (Fratz et al. 2013a, p. 11)

2.3.2 IMAGE POSTPROCESSING

Standard analysis post-processing software (ARGUS, Syngo MultiModality Workplace, Siemens Healthcare, Erlangen, Germany) was used to evaluate the gathered (volume- and flow-) material.

2.3.2.1 VOLUME

Ejection fraction (EF), end-systolic volume (ESV) and end-diastolic volume (EDV) were calculated according to the contours drawn by the observer. To maximize measurement accuracy, end-systole and end-diastole were defined independently for the RV and LV. The phase with the largest volume was defined visually by the observer as end-diastole, equally the phase with the smallest volume as end-systole. The endocardial contours of the RV and LV in end-systole and end-diastole were traced manually in every slice in which the myocardium of the ventricle was visible.

Considering papillary muscles and trabecula parts of the myocardium, they were excluded from the volume measurements. The software computed the end-diastolic volume (EDV) and end-systolic (ESV) volume. The stroke volume (SV) was calculated by deducting ESV from EDV.

Depending on age and general capability to hold ones breath, volume measurement was performed with the breath-hold technique. In order to achieve accurate results, the subject was instructed to hold its breath in full expiration. Several studies have shown an increase in accuracy, less ghosting artifacts and clearer cardiac boundaries (Sakuma et al. 1993), (Plathow et al. 2006).

However, breath holding is not always possible. Some patients are simply too young to follow the instructions, others are not able to hold their breath due to dyspnea. In case of low intellectual capabilities or mentally handicapped patients, following the given instructions can also be problematic. In these cases scans were performed in free breathing.

2.3.2.2 FLOW

The images of flow measurements were processed similar to the volume-evaluation of the ventricle, by manual contour segmentation in all phases of the cardiac cycle. Blood flow parameters were collected for the Aorta, main pulmonary artery (MPA), left pulmonary artery (LPA) and right pulmonary artery (RPA). However, LPA and RPA are only mentioned in the interest of completeness, since those parameters where not important for our study. Differences in the signal amplitude (brightness) of each voxel are representing different velocities (Fratz et al. 2013a). In this manner, the software calculated antegrade and retrograde flow in the vessel of interest. Net flow results from deducting antegrade from retrograde flow. The regurgitation fraction is the result of dividing retrograde by antegrade blood flow.

In many softwares, automated contouring of the vessel is rather inaccurate because of movement and often non-physiologic morphology of the vessel. That is why it is recommended to review each image and adjust the borders according to the actual anatomic conditions. (Fratz et al. 2013a, p. 13)

2.4 APPLICATION OF CPET IN THIS STUDY

All patients underwent symptom-adapted CPET (CardioPulmonary Exercise Test) in an upright position on a bicycle ergometer according to international guidelines (Washington et al. 1994; Gibbons et al. 2002). At least one educated investigator was present at any time.

The examination followed a defined protocol, starting with 3 minutes time of observing baseline values. Patients were then given 3 minutes time for warm-up without load. After the warm-up phase, a stepwise increase of 5, 10 or 15 W/min of load was applied, depending on the individual's expected exercise capacity, estimated by the investigator. The goal was 8 to 12 minute exercise duration. The end of the examination was marked by symptom limitation and was followed by a 5-minute-period of recovery without cycling.

"The exercise test featured a breath-by-breath gas exchange analysis using a metabolic chart (Vmax; SensorMedics, Viasys Healthcare, Yorba Linda, CA, USA). Peak $\dot{V}O2$ was defined as the highest mean uptake of any 30 s time interval during the exercise." (Muller et al. 2009, p. 2916)

As a reminder: Formulas for reference values were calculated as described in *1.7.3.5 Applied Formulas in this Study*.

Collected parameters were amongst others:

- VO_2max (peak VO_2)
    - Therefrom VO_2max% was derived
- VCO_2max
- VE/VCO_2 Slope
- Wmax

These are the parameters that were of importance in this study, hence the other collected CPET-data will not be discussed.

The outcome of the CPET, especially when considering VO_2max, strongly depends on the chosen ergometer. When performing the CPET on a treadmill, VO_2max reaches higher levels compared to the bicycle ergometer, because a larger mass of musculature is active (Cooper, Storer 2001, p. 25). This does not rate one method superior to the other but means that once a method has been selected, it should not be changed, since the outcome is simply not comparable. In this study, every CPET was performed on a bicycle ergometer.

2.5 STATISTICS

Statistical analysis of the collected data was conducted in collaboration with the Institute of Medical Statistics and Epidemiology – IMSE – at the Klinikum rechts der Isar of the Technische Universität München (Technical University of Munich – TUM). In order to get a first impression of our data and the parameter's relations among each others we conducted univariate analyses. Hence, we investigated linear correlations between continuous variables (cf. *Table 4 – Overview of Variables* for details on the investigated parameters). In order to evaluate variable importance in percent of a predicted VO_2 (VO_2max%), random forests with conditional variable importance were used (Breiman 2001; Hothorn et al. 2006; Strobl et al. 2008).

Missing values in the sections *RVSP* and *VmaxRVOT* were imputed using multivariate imputation by chained equations (MICE) (van Buuren, Groothuis-Oudshoorn 2011).

In the following section, the statistical methods will be described more comprehensively.

2.4.1 RANDOM FORESTS

„Random forests are one of the most popular statistical learning algorithms […]" (Strobl et al. 2009, p. 14). Random forests have the ability to deal with large numbers of predictor variables, even when complex interactions between these variables are present. That is why this method is applied in many scientific fields. (Strobl et al. 2009, p. 14)

In 2001 Leo Breiman developed an algorithm for random forests which is based on the thoughts and methods by Tin Kam Ho from 1995 (Breiman 2001; Tin Kam Ho). In this work Breiman describes random forests as *"[…] a combination of tree predictors such that each tree depends on the values of a random vector sampled independently and with the same distribution for all trees in the forest"* (Breiman 2001, p. 5).

Random forests are basically based on decision trees. Decision trees operate in a dichotomous fashion, which means that a certain constraint can be either fulfilled or not. Depending on whether the constraint is fulfilled or not, either the left or the right branch of the tree is being chosen. Accounting for the uncertainty of one tree, the random forest algorithm comprises many decision trees. It would be unreasonable to construct every tree the same way. (Lüthy 2009)

That is why the random forest algorithm randomly chooses a certain limitation applied on the variables every time a new tree is being constructed. The limitations are chosen independently for every newly generated tree, the distribution however stays the same. All trees “vote” for a certain value – the value, which got the most votes resides in the end (“The winner takes it all”-principle) (Lüthy 2009).

Random forests are a robust and valid technique using the so called Bootstrap-method: In every step of the analysis a so called bootstrap-grab-sample, the exact same size as the original data set, is used for building a new tree. A single subject can now appear more than once in this newly generated data set, since sampling is conducted with replacement. This recently built tree is being cross-referenced with the variables not included in this data set – do predicted value and true value match, and if so, how well do they match?. From this revision a ranking regarding the importance of each variable can be created. Therefore, random forests display a validated outcome, referred to the grab sample from existing data.

Detailed information on this topic can be found in Breiman, Leo (2001): Random Forests. In: *Machine Learning* 45 (1), S. 5–32.

2.4.1.1 INCLUSION AND EXCLUSION CRITERIA

In order to generate a random forest model, to clarify which cardiac parameter has the strongest influence on exercise capacity prediction, data had to be collected and arranged in a reasonable fashion. Depending on the target variable, certain parameters had to be either in- or excluded. *Table 4 – Overview of Variables* depicts these criteria.

Variable	Random Forest Model	
	Inclusion	Exclusion
Age [y]		X
Sex [f; m]		X
Weight [kg]		X
Height [cm]		X
BSA [m²]	X	
BMI [kg/m²]	X	
RVEF [%]	X	
RVEDVi [ml/m²]	X	
RVESVi [ml/m²]	X	
LVEF [%]	X	
LVEDVi [ml/m²]	X	
LVESVi [ml/m²]	X	
PR [%]	X	
RVSP [m/s]	X	
VmaxRVOT [m/s]	X	
VO_2max%	X	
VO_2max [ml/kg/min]		X
VE/VCO_2 Slope		X
Wmax [W]		X

Table 4 – Overview of Variables

The parameters Age, Sex, Weight and Height have been excluded from the calculations, since they are already considered in VO_2max%.

2.4.2 CONDITIONAL VARIABLE IMPORTANCE

Random forests became a frequently used tool for non-parametric regression in the past few years. The conditional variable importance was developed for the special case of highly correlating variables when using a random forest model. By approaching a random forest model with the classic marginal procedure, the *"[…] variable importance measures show a bias towards correlated predictor variables"* (Strobl et al. 2008, p. 1). Strobl et al. found two reasons for that circumstance: (i) During the tree building process, correlated predictors are being preferred and (ii) the unconditional permutation scheme is responsible for further favoring of correlated predictor variables.

Based on these findings a new approach for the computation of the variable importance measure, called conditional permutation scheme, was developed. Thus, the resulting conditional variable importance represents the effect of each predictor variable more reliably than the standard marginal approach. For more information, see Strobl, Carolin; Boulesteix, Anne-Laure; Kneib, Thomas; Augustin, Thomas; Zeileis, Achim (2008): Conditional Variable Importance for Random Forests. In: *BMC Bioinformatics* 9 (1), S. 307.

2.4.3 MULTIPLE IMPUTATION

Imputation per se describes the technique of "filling in" missing values in an incomplete data-set. There already existed methods for replacing missing data before Rubin developed the idea of multiple imputation (MI) in 1987 (Schafer, Graham 2002). When applying multiple imputation, the major goal is to preserve structure and uncertainty about this structure within the data-set (van Buuren 2007, p. 219).

Missing values were imputed using multivariate imputation by chained equations (MICE) (van Buuren, Groothuis-Oudshoorn 2011). Van Buuren describes the stepwise procedure as follows: A data-set may comprise of a variable number of missing values. Each missing value is being replaced by a plausible synthetic value. These synthetic data values are the so called imputations. Specification and generation of imputations is the first of three steps in MI. The second step generates a number of plausible complete data sets (m), usually around 3 – 10 (m=3 – 10). This is accomplished by *"[…]analyzing each imputed data set by a statistical method that will estimate the quantities of scientific interest"* (van Buuren 2007, p. 219), resulting in m data-sets, each being different due to varying imputations (van Buuren 2007; van Buuren, Groothuis-Oudshoorn 2011).

In this work m=10 was chosen, meaning there were 10 newly generated data sets. Each of the ten was different to the others, because of diversely imputed values. A random forest analysis was conducted on each imputed data set. The variable importance measure was calculated by averaging the result of these 10 analyses.

3 RESULTS

Goal of this study was to assess cardiac parameters that influence exercise capacity. It was possible to show that right ventricular pressure (RVSP) was the strongest and most influencing variable of VO_2max%-prediction in our collective. It had the biggest effect on exercise capacity. The random forest model shows a ranking of the different parameters and their influence on VO_2max%-prediction.

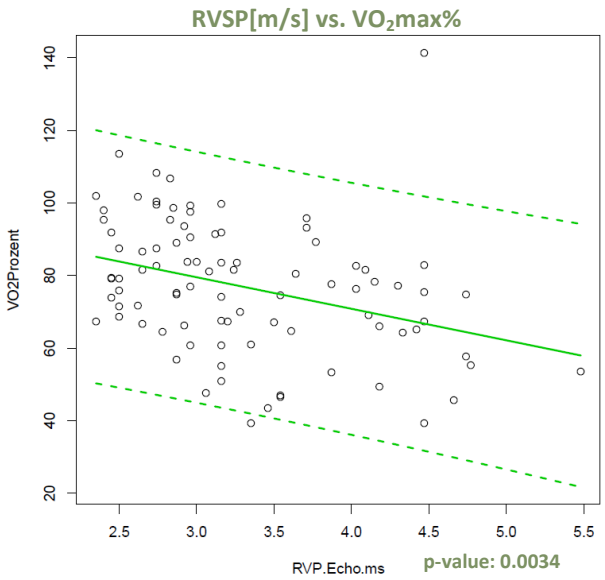
Before conducting the random forest analysis, linear regression models were applied to variables of interest. This way we tried to gain a first understanding of the relations between certain parameters. Unfortunately we realized that linear regression models could not sufficiently provide the answers we were looking for. They in fact acted as a good tool for getting a first rough understanding of our study-population; however the parameters are highly correlating among each others. The random forest model, especially when applying the conditional variable importance method, has been developed especially for these kinds of problems. Thus, with the competent expertise of trained statisticians, we were able to deduct this promising study.

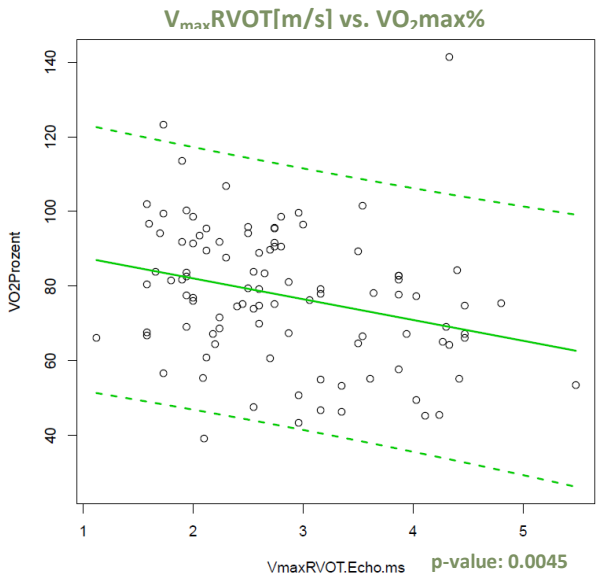
Table 5 gives an overview of important descriptive results:

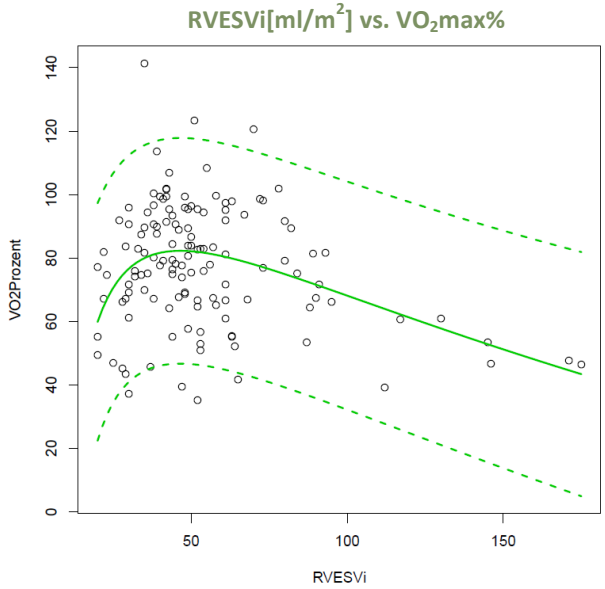
Parameter	Median	Mean	SD	Min	Max
RVSP [mmHg]	40	46	21	22	120
VmaxRVOT [$\frac{m}{s}$]	2,6	2,8	0,9	1,1	5,5
RVEF [%]	54	52	11	18	72
RVEDVi [ml/m²]	104	108	33	53	234
RVESVi [ml/m²]	48	54	27	20	175
LVEF [%]	59	58	8	26	76
LVEDVi [ml/m²]	73	74	19	28	166
LVESVi [ml/m²]	30	32	13	7	123
PR [%]	20	20	15	0	52

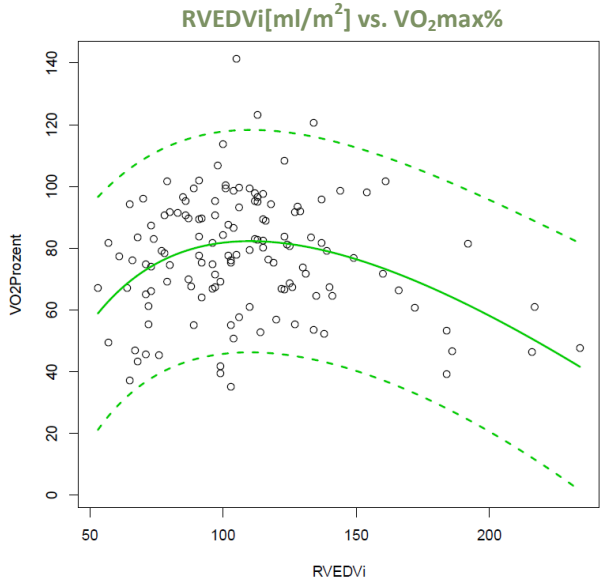
Table 5 – Descriptive Results

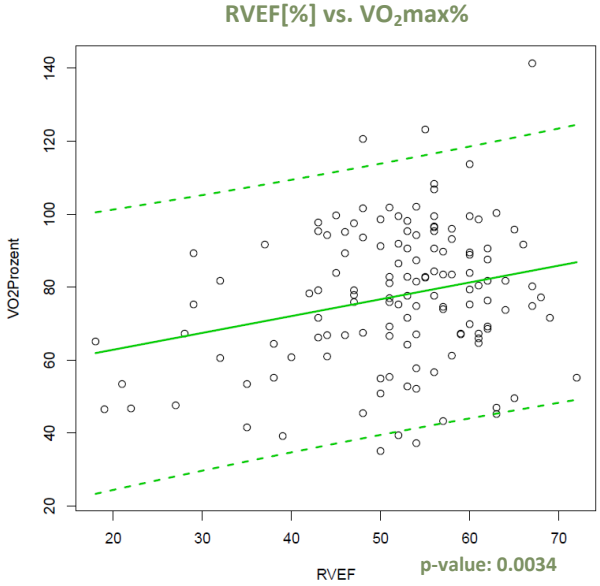
3.1 UNIVARIATE ANALYSES

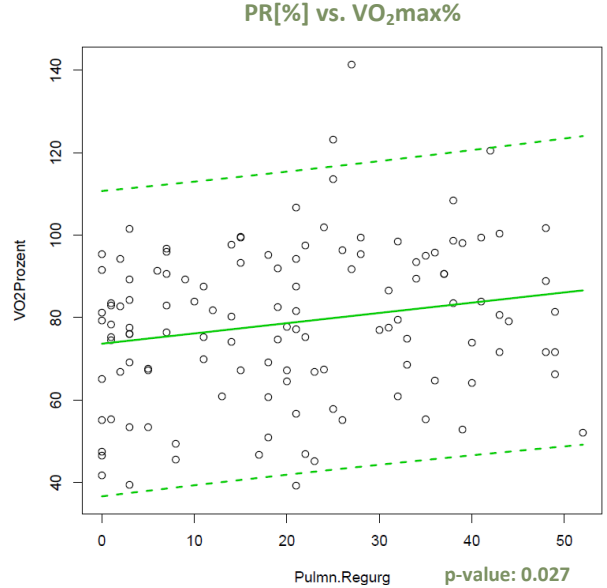












The figures show correlations between important cardiac parameters and VO_2max%. The intention of those graphics is to give an impression in which direction the following results might be leading.

The univariate models yield an impression towards the results of the random forest model. In this study it is important to note that the parameters are strongly related to each other – that is why univariate analyses are most likely not able to depict the underlying complex correlation in this survey.

3.2 RANDOM FOREST ANALYSES

The following graphic shows a ranking related to the importance of variables and their influence on VO_2max%, resulting from the random forest model. Since VO_2max% is already adjusted to anthropometric variables (Sex, Age, Height, Weight), these are excluded from the model.

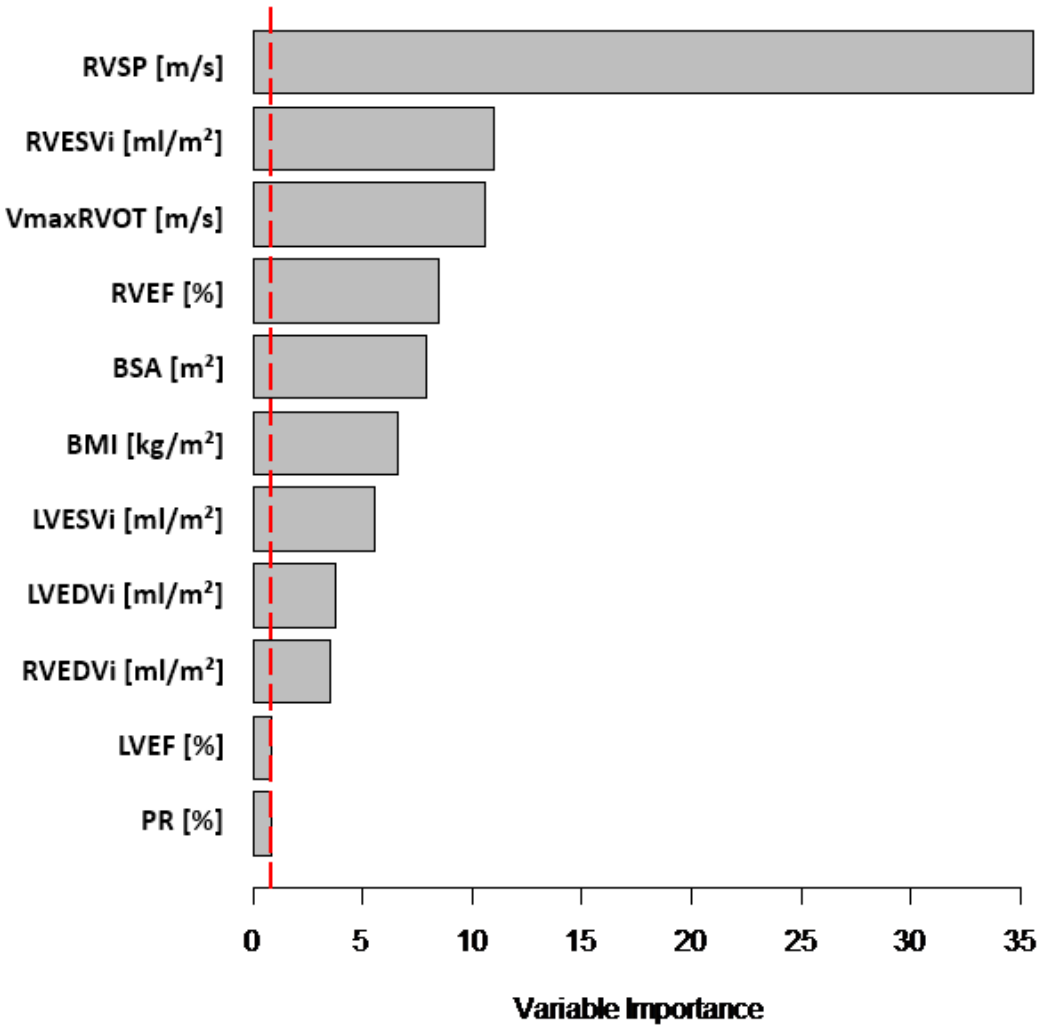


Figure 6 – Influence of Variables on VO_2max%

RVSP strongly sets itself apart from every other cardiac parameter. The resulting variable importance cannot be interpreted as an absolute number but as a comparison amongst all variables included in the model – the higher the assigned value, the greater the influence on the prediction of the target variable. Unimportant variables fluctuate around zero.

The random forest analysis as the keystone of this study yielded the following results:

- RVSP has the biggest influence on VO_2max%
- PR has no influence on VO_2max%
- The influence of the remaining parameters varies; however none comes close to the importance of RVSP.

4 DISCUSSION

4.1 RESULTS

The main question this study should answer was which cardiac parameter has the most pronounced impact on exercise capacity in ToF patients.

Basically there are two different theories: The first one describes elevated RVSP due to stenotic lesions within the RVOT as the pivotal factor, ultimately leading to an impaired exercise capacity (Lurz et al. 2010; Lurz et al. 2012).
However, the second theory for a decreasing exercise capacity in ToF-patients, got much higher levels of attention and has been comprehensively surveyed especially in the past decade. It describes PR as the cornerstone of sequelae, such as dilation of the right ventricle, elongation of the QRS-complex, arrhythmia and sudden cardiac death and of course deterioration in quality of life due to impaired exercise capacity. Among others, these authors sustainably contributed in developing this frequently supported theory: (Abd El Rahman et al. 2000; Carvalho et al. 1992; Chaturvedi, Redington 2007; Frigiola et al. 2008; Gatzoulis et al. 2000a; Gengsakul et al. 2007; Giardini et al. 2006; Shimazaki et al. 1984; Therrien 2012).

However, our results do not fit the second theory, as we could only show a weak correlation between PR, RVEDVi, RVESVi or RVEF and exercise capacity in linear models. Moreover were we able to show that RVSP has a significant impact on exercise capacity.
Other than the left ventricle and the systemic circulation, the right ventricle and the pulmonary circulation are part of a low-pressure-system (Haddad et al. 2008). RVOTO is present in every native and possible in any corrected Fallot-patient. This leads to a general hemodynamic alteration within the right-heart circulatory-system, namely a pressure elevation inside the right ventricle. When surgical correction is performed on ToF-patients, it is aimed at eliminating the RVOTO by a single or a combination of the following procedures: Valvotomy and patching of the RVOT, insertion of a conduit or balloon dilatation of the pulmonary stenosis. However, surgical treatment of the RVOTO does not ensure lifelong freedom of obstruction or re-formation of a pressure gradient. Pertinent literature considers RVSP-levels ≤2.8 to 2.9 m/s, ≤35 to 36 mmHg, assuming normal RAP-levels (3 to 5 mmHg), respectively, as normal values (Rudski et al. 2010, p. 698). In our collective pressure levels in the right ventricle were elevated in about two thirds of the available data (64 to 72%), depending on the adducted reference value [2.8 vs. 2.9 m/s]).

Even though these patients received surgical correction in childhood, pressure levels were as high as 3.3 m/s, 46 mmHg respectively, on average.

It is known that pressure work consumes more oxygen than volume work (Suga et al. 1982). A ventricle under constantly elevated pressure load hypertrophies depending on e.g. the amount of stenosis within the RVOT. This cannot only be observed in ToF but also in other cardiac malformations such as isolated pulmonary stenosis, the prime example of pressure overload (Fogel, Rychik 1998).

In case of a high pressure load, the RV wall can thicken in an amount that a sufficient blood supply cannot be accomplished anymore. This may even lead to infarction of the papillary muscles or the subendocardial layers, especially in infants and children (Franciosi, Blanc 1968). Subsequently, this state may lead to an impaired RV function, but may also affect the LV.

The impact on the LV can be explained due to RV-LV-interactions. The myocardial fibers of each ventricle cannot be seen isolated or as two independently working chambers but their structure is enmeshed. Therefore, if RV myocardial fibers perish, the myocardium of the LV is affected as well. This phenomenon is called the “reversed Bernheim effect”. It is tagged “reversed” because the dependence of RV-function on LV-function and -size was named “Bernheim effect” (Geva 2011, p. 5). The second cause for interaction is the actual size of the RV, which anatomically besets the LV and compromises it in its degree of free motion. This further leads to diastolic dysfunction of the LV. For those reasons, impaired RV function may ultimately lead to an overall impairment of the cardiac function (Voelkel et al. 2006).

Volume overload lesions may result in an enlargement of the affected ventricle. In ToF-patients the RV-volumes often exceed normal values and by becoming larger, they also affect the LV. This is due to the structural change in the myocardium. As RV and LV “share” the interventricular septum, the LV’s function and movement is disturbed (Voelkel et al. 2006; Frenneaux, Williams 2007). Thus, it is conceivable that the exercise capacity suffers from LV-incompetence, originating in the RV. Right ventricular compliance determines the development of the volume overloaded RV, caused by pulmonary insufficiency. ToF-patients with a restrictive RV physiology benefit from their diminished RV compliance by having smaller PR-fractions and a better forward flow within the pulmonary artery (Fogel, Rychik 1998). Gatzoulis et al. furthermore described improved exercise capacity and less cardiomegaly in those patients (Gatzoulis et al. 1995a). That is why a collective of authors suggests pulmonary valve replacement in accordance to RVEDVi, RVESVi respectively (Buechel et al. 2005; Oosterhof et al. 2007; Therrien 2012).

Mean indexed right ventricular volumes in our patient collective were 108 ml/m² for RVEDVi and 54 ml/m² for RVESVi. According to existing recommendations, indexed volumes shall not exceed 160 ml/m² (RVEDVi), 82 ml/m² (RVESVi) respectively, so that normalization of RV volumes after PVR is possible (Oosterhof et al. 2007). From these data, one could hypothesize that within a collective of patients with elevated, but not exceeding values for ventricular volumes, the impact of RVSP is crucial. This impact may change, as further processes in terms of RV dilation take place.

4.1.1 IMPACT OF RIGHT VENTRICULAR SYSTOLIC PRESSURE (RVSP)

We conducted this study to evaluate if the RVSP has a much higher influence on exercise capacity than PR. Our ideas are based on the following considerations: Adaption to higher strain requires the ability of the heart to increase cardiac output (CO). CO is defined by stroke volume (SV) multiplied by heart rate (HR), which means the heart can raise the CO by either increasing SV, HR or both. In normal and healthy subjects the increase in CO can be accomplished by positive inotropy (increased SV and EF), positive chronotropy (increased HR) and a recruitment of preload, by e.g. increasing end-diastolic volume (Frenneaux, Williams 2007, p. 254). Magnitude of CO-augmentation is in accordance to the work being performed (Lurz et al. 2012).

In comparison to the LV, the RV responds more sensitive to an increase in afterload. Afterload in that matter describes a combination of static and dynamic elements of the pulmonary vascular impedance on the one hand, as well as possible restrictive lesions within the RVOT, pulmonary valve respectively, on the other hand. (Haddad et al. 2008, p. 1438)
Under these conditions, the potential for raising CO through positive inotropy may diminish in case of obstructions. The RV's geometry is built to maintain circulation in a low-pressure system (Haddad et al. 2008, p. 1438) – that is why its reserves to adequately adapt to increased afterload may be limited. Therefore, when exercising, the pressure loaded RV may not be able to sufficiently increase SV. CO might be raised predominantly by an increase of HR (Lurz et al. 2012).

The situation is quite different when PR is the primary lesion. Naturally, regurgitation occurs only in diastole. When exercising, duration of systole is becoming relatively longer at the expense of diastole-duration. With the reduction of diastole-duration, PR-fraction becomes smaller as well, or in other words: the regurgitant volume is less under strain. Also, the systemic venous return increases and pulmonary vascular resistance decreases during exercise. Roest et al. described the decrease of PR under stress in the past (Roest et al. 2002).

With the RV being under volume load, it is important to differentiate between a physiologic and a pathologic filling. Under physiologic conditions, an elevated filling of the RV should lead to an increased myocardial contraction, according to the Frank-Starling mechanism. When the RV volume loading exceeds the physiological range, the mechanisms of ventricular interdependence and compression of the LV (through the RV) may lead to an overall impairment of the cardiac function (Haddad et al. 2008, p. 1439). Respecting these circumstances, a patient predominantly suffering from PR should still be able to elevate CO by increasing both, HR and SV, i.e. positive inotropic and chronotropic rise of CO (Lurz et al. 2012), as long as a certain threshold for RV dilatation has not been exceeded.

With this in mind, exercise capacity seems to be sustainably affected by RVSP. Our results support this hypothesis. A mentionable work regarding this topic has been published in 2012 by Lurz and co-workers: 17 children and young adults (age 19.2 ±- 6.1 years) with clinical indication for percutaneous pulmonary valve implantation (PPVI) were investigated; nine suffering predominantly from PS (PR-fraction ≤ 25%) and eight with PR as the primary lesion (PR-fraction ≥ 25%). An exercise test was performed within one month prior to PPVI and again within one month after the interventional procedure. To measure cardiac parameters under strain by CMR, a specialized ergometer that allows exercising while remaining in the supine position was used. (Lurz et al. 2012, pp. 2434–2435)

The PS-group showed significant changes post-PPVI in the following parameters: RV systolic pressure and the PA to RV pullback-gradient decreased; RVEDV and RVESV decreased at rest; RVSV and RVEF increased during exercise. Pre-PPVI RV and LV volumes/function did not change. The change of magnitude in left ventricular cardiac output (LVCO) while exercising was similar pre- and post-PPVI. However, pre-PPVI, LVCO was mainly driven by HR, while post-PPVI LVCO raised because of both left ventricular stroke volume (LVSV) and HR. The peak HR was lower post-PPVI. (Lurz et al. 2012, pp. 2436–2437)

The results in the PR-group reflected the theoretical considerations discussed before as well: Before PPVI no significant changes in RVEF or RV volumes were observed. However, at peak exercise a reduction of PR-fraction >50% was present, leading to a distinct increase of right ventricular stroke volume (RVSV). Therefrom resulted a higher peak LVCO compared to the PS-group; the higher LVCO was driven by HR and increased effective RVSV. Insertion of a competent PV led to (almost) an elimination of PR, a reduction of RV volumes and therefore, a reduction of RVEF as well. RVSV and RVEF increased significantly from rest to exercise, however the augmentation in effective RVSV was similar to the situation pre-PPVI. (Lurz et al. 2012)

"Although there was an increase in biventricular SV at peak exercise after PPVI in both the PS and the PR group, this increase was significantly higher after reduction [of] RVOT obstruction than after reduction in PR. (Δ8.2±4.1 in the PS group vs. Δ2.9±4.1 mL/m² in the PR group, p=0.01[…])" (Lurz et al. 2012, p. 2437).

The major findings of this study are summarized below:

1. Patients with PR- or PS-malformations were unable to elevate *total* RVSV under strain (Lurz et al. 2012, p. 2437)
2. Patients with PR were still able to elevate *effective* RVSV, since PR reduces under strain. This led to an increase in LVSV (Lurz et al. 2012, p. 2437)
3. After PPVI, both the PR- and the PS-group showed an elevation of SV during exercise. However, effective RVSV augmentation was similar before and after PPVI in the PR-group (Lurz et al. 2012, pp. 2437, 2439)

In conclusion, patients with fixated PS benefited from the procedure because it significantly reduced afterload on the RV. Peak LVCO and therefore exercise capacity should improve, due to newly gained reserves (i.e. RVEF) of the RV. This could be shown by an increased peak VO_2 after PPVI. (Lurz et al. 2012, p. 2439)

Patients with PR, however, have "physiological" valve competence, which means that PR-fraction significantly reduces under strain. Thus, despite marked PR at rest, submaximal exercise capacity should not show significant differences pre- to post-PPVI. Also LVCO should remain unchanged and therefore VO_2, which in fact was the case. Although physical valve competence does not improve exercise capacity, patients do benefit from the procedure as RV-volumes reduce. Therefore, measuring exercise capacity by CPET after PV-restoration in patients that primarily suffered from PR cannot be used as a parameter of success or failure of the procedure. (Lurz et al. 2012, pp. 2439–2440)

4.2 PVR – PULMONARY VALVE REPLACEMENT

Nowadays congenital cardiac defects like ToF are correctable by surgery with often very satisfying outcomes. That is why today a whole new collective of patients is alive. These are adult patients with corrected ToF that have to cope with the sequelae of surgery performed in the past (Apitz et al. 2009). Easy to observe is the very common pulmonary insufficiency as a result of the correction of pulmonary stenosis, RVOTO or both in childhood. The right ventricle seems to tolerate PR very well throughout the first two decades of life; later in the third decade of life mortality rates start to increase (Holmes 2012). Ventricular volume enlargement combined with impaired RV function is ascribed to PR. For that reason the idea of PVR came up. It has been stated that shortly after PVR ventricular volumes decrease (Buechel et al. 2005) and functionality improves (Vliegen et al. 2002). However the threshold when to perform surgery, so that the patients benefit from the operation, is still not resolved definitively. The suggested RVEDVi reaches from 150 ml/m² to 180 ml/m², depending on study, author and measuring method (Frigiola et al. 2008; Therrien 2012).

These suggestions may need further discussion because the results after surgery/intervention are not without any doubt. There have been patients in different studies that may not have satisfyingly benefited from PVR since the incidence of ventricular tachycardia and arrhythmia as well as exercise capacity did not improve, although PR-fraction decreased and although these patients underwent surgery while they were within the suggested limits (Gengsakul et al. 2007). Another study by Harrild et al. did not show any difference in the frequency of ventricular tachycardia or sudden cardiac death compared to a matched control group. Also there were no significant alterations in the width of the QRS-complex (Harrild et al. 2009). Therefore, considering freedom of life threatening events such as ventricular tachycardia or sudden death as a major objective, PVR may not represent the sample solution (Gengsakul et al. 2007; Harrild et al. 2009).

A meta-analysis performed by Cheung et al. in 2007 showed similar results to those stated above (Cheung et al. 2010): Both RVEDVi and RVESVi, as well as PR-fraction showed a significant reduction after PVR. However RVEF and QRS-duration did not change significantly after PVR. When interpreting the reduction of RV volumes, concomitantly performed surgical procedures have to be taken into account. Removal of aneurysmatic parts of the RVOT for example leads to an extraordinary reduction of RV volumes. Gatzoulis et al. described a significant correlation between enlarged RV-volumes and prolongation of the QRS-complex (Gatzoulis et al. 1995b).

This meta-analysis however could not show any reduction of QRS-complex-width although a significant reduction of the RV-volumes was present (Cheung et al. 2010). Uebing et al. suggested that a widened QRS-complex rather results from a malformed RVOT than from abnormal RV-volumes and that this could be the reason for consistently elongated QRS-complex widths albeit decreasing RV-volumes (Uebing et al. 2007).

The question whether reduction of atrial or ventricular tachycardia can be ascribed to PVR stays controversial. Reports about decreased events of tachycardia often exist in situations where PVR was not the only procedure performed, but in combination with for example cryoablation (Therrien et al. 2001).

In a recent publication by Therrien, the following approach is suggested: *"If PR begets RV dilatation and RV dilatation begets RV dysfunction, and if significant morbidity and mortality relates to RV size and RV dysfunction, why would you not replace a PV for severe PR when the RVEDV reaches 170–180 cc/m2, knowing that an RVEDV>170–180 cc/m2 carries a dire prognosis and that by replacing the PV at that RV threshold you will (a) restore the RV to a normal size again and (b) preserve its function?"* (Therrien 2012, p. 2). There are a few statements worth discussing. PR has been made responsible for RV dilatation many times (Cheung et al. 2010; Therrien 2012) but the relation between RV dilatation and RV dysfunction is still not fully understood. It was not possible for the author to find a publication that denies the relation between RV dilatation and RV dysfunction. However, it has been stated that late PVR does not lead to long-term benefits regarding reduction of incidence of ventricular tachycardia or death (Harrild et al. 2009). Even more complicated is the statement that significant morbidity and mortality relate to RV size and RV dysfunction. The impact of PR depends on many factors, e.g. type of surgical repair, surgical approach, individual's constitution, accompanying syndromes and much more (Apitz et al. 2009). That is why the statement within the title, *"Pulmonary valve replacement based solely on right ventricular size is appropriate in the asymptomatic tetralogy patient"* (Therrien 2012, p. 31) may need critical reconsideration.

The above cited approach is, in the author's opinion, too unidirectional and relies on hypotheses that are not fully confirmed. The last passage might be misleading for the reader, making him believe that restoring the RV to a normal size is equivalent to preserving the function of the RV. Unfortunately, this circumstance is still not entirely understood and needs further investigation (Cheung et al. 2010).

When considering pulmonary valve replacement, it is important to know that it is not without risks. Cheung et al. listed pooled data on early and late mortality rates as well as on redo-rates for PVR. They compiled a series of pediatric patients and a series of adult patients. *Table 6* gives an overview of the pooled data (Cheung et al. 2010, p. 554):

Series	Early Mortality (%)	Late Mortality (%/patient-year)	Redo-PVR (%/patient-year)
Pediatric	2.7 (0.9-7.5)	0.4 (0.0-1.0)	1.2 (0.2-2.2)
Adult	1.8 (0.8-4.1)	0.5 (0.2-0.8)	2.2 (1.5-2.9)
Total	2.1 (1.1-4.0)	0.5 (0.2-0.8)	1.9 (1.3-2.5)

Table 6 – Pooled Outcomes in Pediatrics and Adults (Cheung et al. 2010, p. 554)

Although the rates for early mortality, late mortality and redo-PVR are low, finite lifetime of grafts are an issue. Frigiola et al. suggest an early and relatively aggressive PVR-policy. They report on normalization of VE/VCO_2 when PVR was performed prior to the age of 17.5 years. VE/VCO_2 is considered a surrogate parameter for submaximal exercise capacity and therefore, everyday strain.
Müller et al. observed similar improvements regarding VE/VCO_2, primarily in a patient group with predominant PS (Müller et al. 2014).
PVR was also associated with better LV filling and CO in this younger age group. Furthermore it is stated that the improvement in CO and LV-filling is bigger, probably because of a less fibrosed ventricle which might be more capable of recovering after PVR than a ventricle in older patients. Performing PVR on such young patients is unfortunately associated with a higher frequency of re-operation throughout a patient's life (Frigiola et al. 2008, pp. 187–189).

A study by Lee et al. gives a good impression of the complications caused by PVR: Most of the events during the follow-up-period were redo-PVR. 75% freedom of redo-PVR at 10 years follow-up seems acceptable; however freedom of valve failure and dysfunction was 50% at 10 years. Further investigations showed that approximately 80% of all bioprosthetic valves would have needed replacement – or manifest valve dysfunction would have followed by a 10 year lifespan (Lee et al. 2012). In the face of missing improvement between PVR- vs. non-PVR-groups, regarding the frequency of ventricular tachycardia and sudden cardiac death (Gengsakul et al. 2007; Harrild et al. 2009), the results by Lee et al. might be analyzed even more critically. The question that needs to be answered is whether the impact and improvement in quality of life legitimates a surgical procedure that is likely to be performed again after approximately ten years.

Of course the newly developed techniques of percutaneous PVR complicate this debate, as one could argue that reoperation is not an issue, like it has been before. However, today percutaneous PVR is bound to a certain geometry of the RVOT. For example, presence of an RVOT-aneurysm may complicate percutaneous PVR. That is why most transcatheter procedures are performed on patients with a conduit-repair (Geva 2011). With future developments in this handy technique, the question of restoring the PV might be easier to answer. In a study from 2011, Eicken et al. performed transcatheter PVR on 102 patients, which showed a low complication rate – one patient died, 5% stent fractures occurred, one percutaneous valve had to be removed due to bacterial endocarditis and in 9% a re-dilatation of the valve was necessary (Eicken et al. 2011). The events took place during a median follow-up time of 352 days. This implicitly shows that the PPVI-procedure has to give proof of its effectiveness and benefit for the patient over mid- and long-term observations.
At present a large number of PVR is still performed surgically. High re-operation rates require elaborate planning and justifying indications with a balanced risk-to-benefit ratio (Geva 2011).

Geva published recommendations, especially for PVR in patients with repaired ToF or Fallot-like hemodynamics with a pulmonary regurgitation fraction ≥ 25%. Geva suggests early PVR because by postponing the procedure until the point where patients become symptomatic (progressive exercise intolerance, heart failure symptoms, syncope, ventricular tachycardia), the damage might be irreversible. (Geva 2011)

Both the ESC as well as Geva list an elevated RVSP in the face of a RVOTO as an indication for PVR in the asymptomatic patient (Baumgartner et al. 2010; Geva 2011). However, performing surgery on an asymptomatic patient necessitates sufficient education of the subject, especially in the face of unresolved questions like the long-term effect of PVR and redo-rates (Cheung et al. 2010).

The possibility of a relief of the RVOTO by balloon dilatation is not an issue in both manuscripts, but may be considered in symptomatic and asymptomatic patients. The findings of Lurz et al. underline the importance for the abolishment of a (residual) RVOTO. They observed a correlation between a reduction of RVSP and improved peak oxygen uptake, even in patients with PR being the primary lesion. In patients with an increase of the RVOT gradient after PPVI, the peak oxygen uptake decreased. These findings emphasize the influence of a RVOT gradient and its elimination. That is why they treat residual RVOT gradients by high pressure balloon dilatation, in order to ensure a gradient <10 mmHg after PPVI. (Lurz et al. 2010, p. 726)

Percutaneous pulmonary valve implantation is feasible with good results, as recent studies have shown (Bonhoeffer et al. 2000; Eicken et al. 2011). However, revision of the RVOT and investigation for a residual gradient appears to be of great importance (Lurz et al. 2010).

In our study group, we were not able to show a correlation between PR-fraction and exercise capacity, RVEF or RVEDVi. However, our results could show that RVSP strongly influences exercise capacity. This finding may underline the observations made by Lurz et al. that a RVOTO is of importance, in terms of peak oxygen uptake (Lurz et al. 2010). Impact and importance of RVSP might have been strengthened through another recent study by the same author (Lurz et al. 2012).

PR has often been referred to as a malignant lesion with deleterious effects on exercise capacity, QRS-duration and right ventricular parameters (Abd El Rahman et al. 2000; Carvalho et al. 1992; Geva 2011; Giardini et al. 2006; Therrien et al. 2001). Although the literature doesn't show a definitive result on the question of the impact of PR, a study conducted by Shimazaki et al. is often cited because it seems to be showing that PR in fact is the lesion that eventually leads to certain cardiac limitations. In this study, 72 patients with isolated congenital pulmonary valve incompetence were investigated. 17 patients (24%) developed symptoms throughout their lives. Freedom of symptoms was 77% at 37 years, 50% at 49 years and 24% at 64 years. Shimazaki considered tachycardia or palpitations, effort intolerance, dyspnea and new onset peripheral edema symptoms (Shimazaki et al. 1984). However, these symptoms are not unlikely in subjects of the above the mentioned age groups, given that 76% of the collective were symptom-free, despite suffering from this cardiac lesion.
Discussing this study shall not rise the impression of denying the influence of PR. The intention is to critically reflect upon the actual influence, which clearly needs further investigation.

Another lately published study by Müller et al. shed light on an interesting topic, namely quality of life in patients with similar hemodynamic situations like our study population before and after PPVI (Müller et al. 2014). In this survey 59 patients with dysfunctional conduits have been examined. 46 patients (78 %) had predominantly PS, 13 subjects (22 %) had PR as the primary lesion. According to short form 36 – SF36, significant improvements in quality of life were notable in six out of nine domains of the questionnaire in the PS-group, but only in two out of nine domains within the PR-group. Therefore, patients may profit of PPVI, not only in terms of an increased exercise performance but also in quality of life. (Müller et al. 2014)

An interesting result regarding quality of life provided a nationwide study of the German competence network for congenital heart defects by Mueller et al. (Mueller et al. 2013). This study investigated health related quality of life (KINDL-R questionnaire) with self-estimated physical ability in 168 children (age 8 to 16 years) after ToF-repair. To objectify exercise capacity, a CPET was performed.
The result of the questionnaire showed similar or even better quality of life (QoL) in the study-population, compared to a standard population. However, objective exercise capacity was lower and impressed impaired in the study-population (Mueller et al. 2013).

4.3 PATIENT GROUP

This study comprises a patient group consisting of 132 cases with multiple diagnoses (cf. *Figure 5 – Distribution of different Diagnoses*). However, considering the hemodynamic situation, the study group becomes very homogenous. Almost three quarters (74%) of the patients had ToF as diagnose (therefrom 62% “native” ToF, 38% ToF with AG/HG/XG). The residual 26% of patients had Fallot-like hemodynamics (PS, PA+VSD, PA+IVS), allowing an inclusion of those patients in this study. The data regarding median, standard deviation and range are close to the common borders (Alfakih et al. 2003b; Buechel et al. 2009), what makes our data very comparable and reduces chances for bias (cf. *Table 3 – Descriptive Statistics* and *Table 5 – Descriptive Results*).The large number of 132 cases (therefrom 98 ToF-cases) makes this study robust and significant. Strict exclusion criteria were applied in order to ensure a homogenous cohort.

4.4 METHODICAL LIMITATIONS

CMR and CPET underlie several influences that could alter the outcome of the measurements. These possible confounders will be discussed in the following section.

4.4.1 CARDIAC MAGNETIC RESONANCE

Image post processing was accomplished as described in *2.3.2 Image Postprocessing*. Image analysis has been described multiple times by different authors (Helbing et al. 1995a; Helbing et al. 1995b; Pattynama et al. 1995; Rominger et al. 1999; Alfakih et al. 2003a; Alfakih et al. 2003b; Fratz et al. 2009; Clarke et al. 2012; Fratz, Stern 2012). However, there are slight differences in the contouring-process of the ventricles between other study groups and our workgroup. One of the major differences is displayed in *Figure 7*:

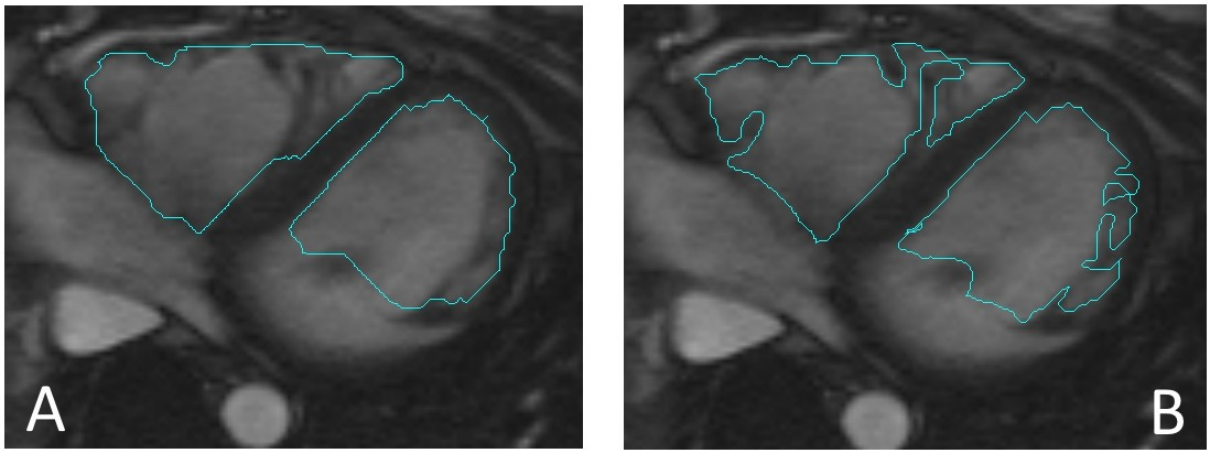


Figure 7 - Differences in the Contouring Process

Figure 7 shows a variation in the practice, how contouring of the ventricles can be accomplished. Figure 7A displays a more reproducible way of contouring, since it is only slightly adapted to the software's automated endocardial tracing. Figure 7B shows how the contouring is carried out in our workgroup. Clearly Image B displays a more accurate way of contouring the endocardial boundaries of a ventricle. There are procedural variations regarding the processing of the papillary muscles (Sievers et al. 2004). While the LV mostly provides clear endocardial boarders, the RV has a more complex structure due to its trabeculations. Papillary muscles and trabecles may be considered part of the myocardium and could therefore be excluded from the blood pool. However, complete exclusion of the trabeculations may not be the correct approach, since a significant part of blood volume may be "trapped" in the apical trabecular meshwork of the RV (Fratz et al. 2013a).

By contouring in a similar fashion as suggested in Figure 7B, papillary muscles and trabeculations are considered myocardial tissue. This technique yields smaller ventricular volumes, but little changes in ejection fraction and stroke volume. The second approach may display a more precise image of the actual anatomic situation. However, though more accurate in theory, it may reduce data reproducibility. Another limitation may be the higher time consumption and, at present, no automated protocol (Fratz et al. 2013a, p. 10).

The effect of partial volume might be of greater influence when using axial slices instead of short axis slices (Alfakih et al. 2003a; Fratz et al. 2009). Difficulties occur because the blood-myocardium-boundaries might be harder to identify in axial slices. The influence of partial volume is even bigger within the right heart. Attention must be paid again in the basal slices to exclude a sufficient amount of atrial volume. Using SteadyStateFreePrecession imaging on axial slices may reduce the partial volume effect. Axial slices may also allow a better distinguishability between atrium and ventricle within the right heart (Alfakih et al. 2003a). Therefore, Fratz et al. recommended axial slices as the orientation of choice for ToF-patients (Fratz et al. 2009).

One of the biggest problems in volumetry of the heart is that there does not exist a reliable method to determine the actual blood volume in vivo (Clarke et al. 2012). The recommendation for use of axial slices instead of short axis slices is, among other reasons, based on the better inter- and intraobserver variance (Fratz et al. 2009). Contrary to the LV, the trabeculated meshwork of the RV might complicate the demarcation of the endocardial borders and the surrounding fat tissue (Pattynama et al. 1995). These difficulties increase with a more complex and malformed anatomy of the RV (Clarke et al. 2012).

Cardiac MRI scans for volumetry can be performed in two different ways: Normal breathing while the scan is running or in breath hold. Unfortunately normal breathing may lead to artifacts, reduction in image quality, through-plane movement error and blurring (Bellenger et al. 2000, p. 416). That is why this method is only used in young patients and in patients who are having trouble holding their breath due to physical or mental limitations. If possible for the subject, scans are recommended to be conducted in breath hold (Fratz et al. 2013a). To reduce chances of bias due to breath holding, the patient should hold its breath in end-expiration, and therefore the diaphragm in the same position in every single scan (Plathow et al. 2006). It has been observed that many heart failure patients could not manage to hold their diaphragm in a steady position (Bellenger et al. 2000, p. 416).

Especially axial slices are vulnerable for inconsistent breath holding, leading to wrong volumes because of slices either measured twice or not at all. To avoid unsteady breath holding and minimize the error-rate, all the scans are performed in end-expiration after taking several deep breaths.
Another possibility for increasing the quality of the scan is the application of prospective navigator-echo gating. This is especially useful in patients, who are challenged by breath-hold commands (Bellenger et al. 2000, p. 417).

CMR has not only become the reference standard for the evaluation of ventricular volumes and dimensions in congenital heart defects (Clarke et al. 2012), but also flow measurement of the cardiac and pulmonary vessels by CMR are today widely used in clinical routine (Stalder 2009). In this study, special interest was spent, amongst others on PR, which is assessed by blood flow measurements with CMR. Limitations and confounders that can complicate and distort measurements require knowledge and understanding of these constraints. The supervising physician needs to be aware of pitfalls like inappropriate setting of the velocity range, non-observance of turbulent flow or incorrect partial volume averaging, just to mention a few. In case of inconsistencies within the collected data, it is recommended to always check for limitations, cf. *2.3.1.2 Flow measurement*. (Fratz et al. 2013a)

Complex cardiac aberrations as present in our patient collective may complicate measurements and can be challenging for the investigator. However, knowledge of the limitations and conduction of flow and volume measurement is excellent in the operating personnel. Also an expert physician in the field of congenital heart defects with special expertise regarding technical background-information was present at any time, supervising the examination.

4.4.2 PREDICTION OF INTRACARDIAC PRESSURE AND PRESSURE GRADIENTS ACROSS THE PULMONARY ARTERY

Pressure measurement is carried out with the help of echocardiography. A general problem in echocardiography is its dependency on the examiners expertise (Baumgartner et al. 2010, p. 2919). This makes it a potentially error-prone technique.

Examiner dependency is not the only limitation in the assessment of RVSP. Presence of multiple stenotic lesions throughout the RVOT causes difficulties in evaluating the contribution of each stenosis (Baumgartner et al. 2009, p. 21). The peak RVSP might be overestimated in patients with such serial lesions or in patients with tubular stenoses (Baumgartner et al. 2010, p. 2935).

Another recent finding by Groh et al. delineates a limitation of Doppler echocardiography (DE) especially in children with elevated right heart pressure. The study could show that DE inaccurately represents RVSP, with both, under- and overestimation occurring. (Groh et al. 2013)

These findings concur with a study of an adult cohort of patients with pulmonary hypertension. Both under- and overestimation of pulmonary artery systolic pressure occurred. The reference measure was right heart catheterization in both studies. (Rich et al. 2011)

These results should be taken into account when interpreting RVSP measurements by Doppler echocardiography.

4.4.3 STATISTICAL METHODS

In this study, statistical algorithms were applied that are quite new in medicine. This is due to the fact, that they are rather new, compared to frequently used statistical techniques, like linear regression models. Nonetheless, the methods are robust, valid and approved as outstandingly reliable tools for prediction (Strobl et al. 2007; Strobl et al. 2008).

4.4.3.1 RANDOM FORESTS AND CONDITIONAL VARIABLE IMPORTANCE

In the early days of random forests, Leo Breiman described them as *"[…] an effective tool in prediction"* (Breiman 2001, p. 29). In the following years, the initial method by Breiman has been enhanced and extended to cope with different scenarios.

In pertinent literature, random forests have been described as *"[…] one of the most popular statistical learning algorithms […]"* (Strobl et al. 2009, p. 14). By introducing the conditional variable importance, random forests have become an even more robust technique in the face of highly correlated predictor variables. That is why random forests have been suggested as prediction tools in the field of genetics (microarray data, DNA sequencing), but also clinical medicine (Strobl et al. 2007). A key feature of random forests, compared to univariate analyses, is its ability to, on the one hand, take each predictor variable's influence *individually* into account, and on the other hand, consider *multivariate interactions* with the remaining predictor variables. (Strobl et al. 2008)

Initially, we tried to depict our hypothesis by a univariate and linear approach. Unfortunately, the collected data from CMR and CPET underlies complex interactions among each other. Many parameters are calculated from other directly collected/measured parameters. Others include biometric parameters like weight or height.

We realized that simple linear regression models were not the ideal method to depict, but moreover consider these interactions.

The fact that we were not able to show a significant linear correlation between RVSP and VO_2max%, in terms of a big R^2, should not lead to a distorted conclusion of no actual association. The R^2 only reflects the linear correlation between two variables, while a true, more complex correlation may be underlying. The linear model is most likely unable to picture such complex correlations between these two variables. However, the random forests analysis may also solely show a correlation and an influence on a target variable. Causality yields neither a linear model nor a random forests analysis.

In many cases, multivariate analyses are adducted, when a large number of variables has to be processed. One of the major problems with multivariate models is that they are prone to depict wrong interactions/correlations when the data set comprises of highly correlating variables.

The close collaboration with statisticians at the IMSE made this study feasible, as they applied the random forests analysis in combination with the conditional variable importance. Though still new in our field, this model is almost tailored to our data set. Finally we were able to correctly depict every predictor variable from CMR and its influence on the target variable VO_2max% from CPET in a single model, adapted to the question, namely finding of a cardiac parameter that influences the target variable (VO_2max%).

4.4.3.2 MULTIPLE IMPUTATION

When collecting the data we had to face the problem of missing values in different categories. Due to the cardiac malformations, especially echocardiography sometimes maxed out. Assessment of several parameters was not feasible in those patients. In order to conduct the chosen random forests model, complete data sets were essential. That is why the method of multiple imputation was applied on the parameters that contained missing values. *Table 7* – Missing and Imputed Values gives an overview of the valid and missing data:

Parameter	Valid n	Missing n
RVSP	90	42
VmaxRVOT	99	33
LVESVi	131	1
LVEDVi	131	1
LVEF	131	1
PR	123	9

Table 7 – Missing and Imputed Values

Since we were working with partly incomplete data sets, the question for significance of the imputed data necessarily comes up. To answer this question it is important to understand, that in order to generate the missing values (e.g. in section RVSP), the remaining complete values of the data sets are adducted. The conclusion of this fact is that also potential outliers are taken into account, since their data are partly existent. *Figure 8 – Valid and Imputed Data Sets* may give a better understanding of the data set after imputation. Also, it will depict the distribution of the imputed data:

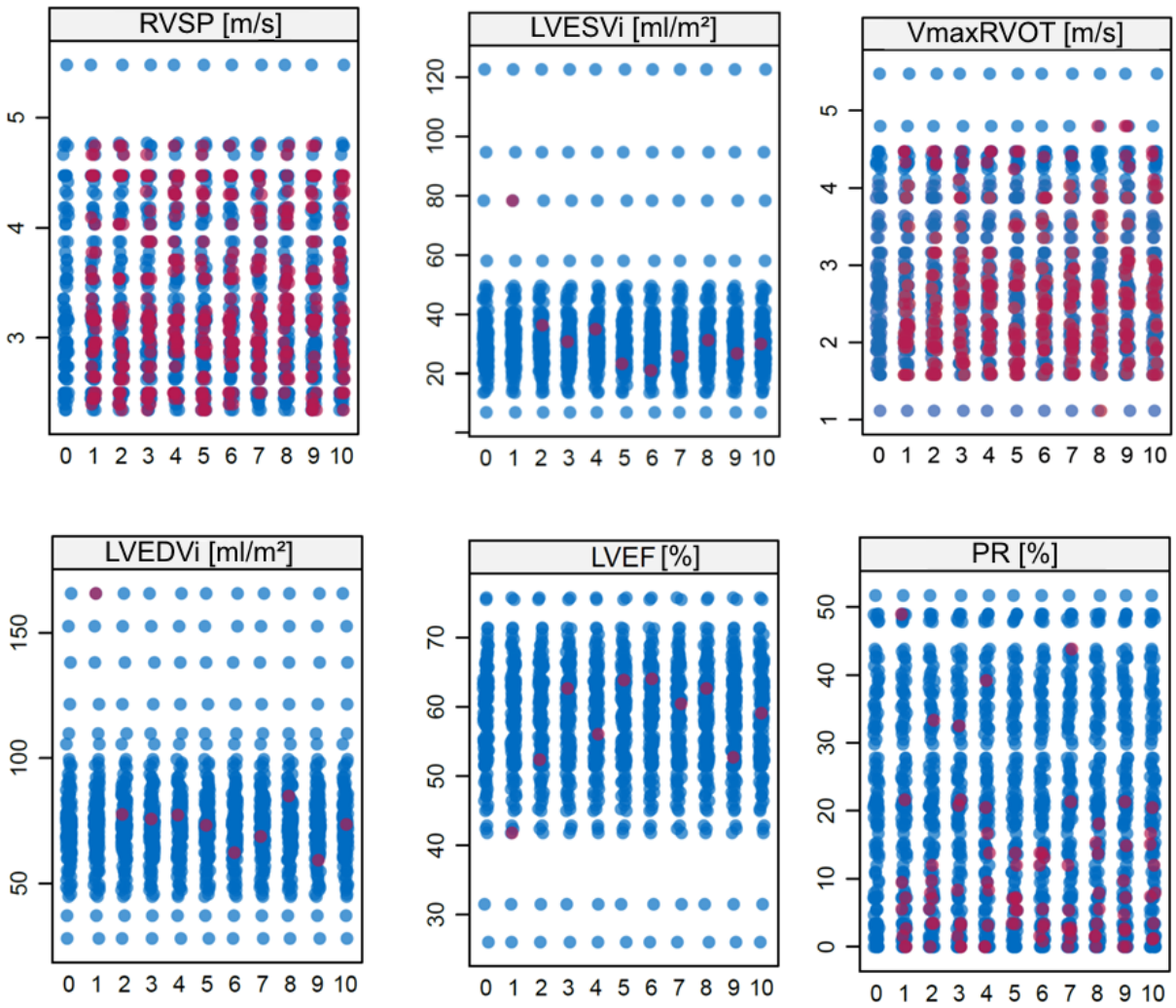


Figure 8 – Valid and Imputed Data Sets

Column "0" (left in each graph) displays the data set and the distribution of its values before imputation. Column 1 – 10 are the resulting newly generated and, now new and complete data sets. It is important to note the distribution of the imputed values (red dots).

As one can easily observe, the imputed data fits the big picture. Moreover, not one but ten new and different data sets were computed. These data sets provide the basis for conducting the random forest analysis, as every new data set (1 – 10) forms the basis of an own random forest model. The results of the random forests analyses are then combined to one final result.

4.5 CONCLUSION

This study aimed at identifying the cardiac parameter that has the biggest impact on peak oxygen uptake in percent of a reference value (VO_2max%) in patients with ToF, PS, PA+VSD and PA+IVS. The result shows that the magnitude of the jet velocity over the tricuspid valve, RVSP respectively, is the dimension that sustainably affects VO_2max%, which was adducted as surrogate parameter for exercise capacity. Furthermore, this study showed that in terms of exercise capacity, amount of pulmonary regurgitation fraction was not the limiting factor. The magnitude of PR showed at best a weak correlation with VO_2max% in linear regression models. Moreover, the random forest analysis could not show any influence of PR on exercise capacity.

Observations of the influence of RVSP-reduction have been made before (Lurz et al. 2010; Lurz et al. 2012; Müller et al. 2014; Vezmar et al. 2010). Percutaneous pulmonary valve implantation has proven to be feasible (Eicken et al. 2011; Vezmar et al. 2010). Further observations of a relief of RVOT obstructions with PPVI as a relatively new and handy technique may strengthen our study outcome of the importance of a RVSP-reduction.
In the 1970s and 1980s PR was referred to as a benign lesion by some authors (Geva 2011), however this has changed dramatically. Today, surgeons at most centers favor valve-sparing techniques, in order to minimize pulmonary regurgitation (Fox et al. 2010). The adverse effects of highly incompetent or even absent pulmonary valves could be observed in the past decades and it became clear that pulmonary insufficiency and ventricular arrhythmia, dysfunction and RV volume overload are associated (Chaturvedi, Redington 2007; Gatzoulis et al. 2000b; Giardini et al. 2006).

However, neither stenotic, nor regurgitant lesions alone might be responsible for the deleterious effects observable in the history of CHD-patients. Nevertheless, the results of this study suggest that there is a correlation between a pressure loaded RV and the physical ability. This should be considered in decision making.

5 SUMMARY

Tetralogy of Fallot is the most common cyanotic congenital heart defect. The congenital malformations comprise of right ventricular outflow tract obstruction(s), a ventricular septal defect, an overriding of the aorta and a right ventricular hypertrophy. The obstruction of the right ventricular outflow tract may affect the infundibulum, the pulmonary valve or a combination of both. The supravalvular segment and the branch pulmonary arteries may be affected by stenotic lesions as well. These obstructive lesions lead to right ventricular hypertrophy.
About 15 percent of patients with Tetralogy of Fallot have a microdeletion-syndrome 22q11. When present, a heredity transmission occurs with a probability of 50 percent, due to its autosomal dominant heredity process.

The progress in surgical possibilities makes early repair of Tetralogy of Fallot in infants feasible and today, the adult collective outnumbers children with this congenital heart defect. The 35-year survival rate is roundabout 85 percent (in comparison: non-operated Tetralogy patients died in more than 95 percent before 40 years of life), which is responsible for the observation of long term sequelae. Late complications may include residual obstruction(s) of the right ventricular outflow tract, right ventricular hypertrophy, elevated right ventricular pressure, pulmonary regurgitation, dilation of the right ventricle, congestive heart failure, arrhythmia and sudden cardiac death.
Quality of life in patients with Tetralogy of Fallot is comparable with healthy subjects and exercise capacity is often limited in this patient collective.

This study aimed at finding the pivotal cardiac parameter in patients with Tetralogy of Fallot, Pulmonary Atresia with Ventricular Septal Defect, Pulmonary Atresia with Intact Ventricular Septum and Pulmonary Stenosis that extensively affects peak oxygen uptake in percent of a reference value – VO_2max% – which serves as means of exercise capacity. By conducting a random forests analysis, it was possible to excerpt right ventricular pressure as the cardiac parameter that has the biggest impact on exercise capacity.

Other findings were that pulmonary regurgitation showed no impact on exercise capacity in the random forests analysis. Conducted linear regression models yielded at best a weak correlation between pulmonary regurgitation and VO_2max%.

The main result – high impact of right ventricular pressure on VO_2max% – fits recent observations that the abolishment of right ventricular outflow tract obstructions and therefore a reduction of right ventricular pressure, leads to an increase in exercise capacity.

6 ZUSAMMENFASSUNG

Die Fallot Tetralogie ist der häufigste zyanotische kongenitale Herzfehler. Diese angeborene Malformation umfasst eine oder mehrere Obstruktionen des rechtsventrikulären Ausflusstraktes, einen Ventrikelseptumdefekt, eine (auf dem Ventrikelseptumdefekt) reitende Aorta und eine Rechtsherzhypertophie. Die Obstruktion des rechtsventrikulären Ausflusstraktes kann dabei das Infundibulum, die Pulmonalklappe oder beides betreffen. Das supravalvuläre Segment und die Äste der Pulmonalarterie können ebenfalls von Stenosen betroffen sein. Diese obstruktiven Läsionen führen zu Rechtsherzhypertrophie.
Etwa 15 Prozent aller Fallot Patienten haben gleichzeitig ein 22q11-Mikrodeletionssyndrom. Liegt dieses vor, kommt es mit einer Wahrscheinlichkeit von 50 Prozent zum Wiederauftreten der Fallot Tetralogie aufgrund des autosomal dominanten Vererbungsmodus.

Der Fortschritt chirurgischer Möglichkeiten macht die Frühkorrektur der Fallot Tetralogie bereits bei Säuglingen möglich. Heutzutage ist die Erwachsenenpopulation mit Fallot Tetralogie bereits größer als die Kinderpopulation mit dieser Erkrankung. Die 35-Jahre-Überlebensrate liegt bei ungefähr 85 Prozent (zum Vergleich: nicht operierte Fallot Patienten erreichten in weniger als fünf Prozent das 40. Lebensjahr). Dies ist der Grund für die Beobachtung von Spätfolgen der Erkrankung. Spätkomplikationen können unter anderem sein: residuelle Obstruktion(en) des rechtsventrikulären Ausflusstraktes, Rechtsherzhypertrophie, erhöhter rechtsventrikulärer Druck, pulmonale Regurgitation, Dilatation des rechten Ventrikels, (globale) Herzinsuffizienz, Arrhythmien und plötzlicher Herztod.
Die Lebensqualität von Fallot Patienten ist vergleichbar mit der von gesunden Patienten. Allerdings ist die Leistungsfähigkeit bei Fallot Patienten oft vermindert.

Diese Studie zielte darauf ab, den ausschlaggebenden kardialen Parameter bei Fallot Patienten, Patienten mit Pulmonalatresie und Ventrikelseptumdefekt, Patienten mit Pulmonalatresie und intaktem Ventrikelseptum sowie bei Patienten mit Pulmonalstenose ausfindig zu machen, welcher die vorhergesagte maximale Sauerstoffaufnahme in Prozent eines Referenzwertes – VO_2max% - weitreichend beeinflusst. VO_2max% wurde als Messwert der körperlichen Leistungsfähigkeit herangezogen. Mit Hilfe einer Random Forests Analyse konnte der rechtsventrikuläre Druck als jener Parameter identifiziert werden, welcher den größten Einfluss auf die körperliche Leistungsfähigkeit hat.

Weitere Ergebnisse der Studie waren, dass die Höhe der pulmonalen Regurgitationsrate keinen Einfluss auf die Leistungsfähigkeit nimmt. Auch in linearen Regressionsmodellen konnte bestenfalls eine schwache Korrelation zwischen pulmonaler Regurgitationsrate und VO_2max% gesehen werden.

Die Hauptaussage der Studie – großer Einfluss des rechtsventrikulären Druckes auf VO_2max% - passt gut zu aktuellen Beobachtungen: Die Beseitigung von Obstruktionen des rechtsventrikulären Ausflusstraktes und damit verbunden, die Reduktion des rechtsventrikulären Druckes, führt zu einer Verbesserung der körperlichen Leistungsfähigkeit.

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8 FIGURES

9 TABLES

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