The right ventricle under acute and chronic overload: early detection of right ventricular dysfunction
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SUMMARY AND CONCLUSIONS: RIGHT VENTRICULAR FUNCTION IN CONGENITAL HEART DISEASE: NONINVASIVE QUANTITATIVE PARAMETERS FOR CLINICAL FOLLOW-UP

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INTRODUCTION

Adult patients with congenital heart defects represent a continuously growing population owing to improvements in medical care, advances in surgical techniques, and postoperative care. Current surgical standards make mortality the exception in many diseases, and results are judged more in terms of morbidity, residual defects, freedom from reoperation, and long-term functional outcome. Closer follow-up of these patients becomes mandatory, and non-invasive modalities are increasingly being recommended and used.

In a substantial number of patients with congenital defects the right ventricle (RV) is in a functionally or anatomically abnormal position, thereby exerting a state of chronic pressure or volume overload. This includes patients with transposition of the great arteries (TGA), congenitally corrected TGA (ccTGA), tetralogy of Fallot (TOF), and certain subsets of double outlet right ventricle (DORV).

Except for qualitative data (clinical status, functional classification, and echocardiography), there are few other possibilities to diagnose deterioration of RV function. Although these established diagnostic modalities allow in most instances for appropriate medical therapy adjustment or surgical timing in symptomatic patients or those with obvious myocardial impairment, this is not so in more subtle situations. Newer non-invasive quantitative diagnostics would be of particular value in asymptomatic or minimally symptomatic patients with borderline RV function, for whom the therapeutic dilemma currently exists. Management of these patients would be improved by establishing accurate quantitative determinants of RV function and by relating them to the already existing qualitative ones (Table 1). The combined information could thus be implemented in daily clinical practice.

This article delineates the various states of RV functional overload in certain congenital heart diseases, and presents noninvasive quantitative data obtained in our institution for RV function assessment applicable to clinical follow-up in these patients.

CONGENITAL HEART DEFECTS WITH RV OVERLOAD

TETRALOGY OF FALLOT
Residual lesions after repair of tetralogy may include suboptimal relief of right ventricular outflow tract (RVOT) obstruction or residual pulmonary artery stenosis, leading to a state of chronic pressure overload (Figure 1). After repair and in particular with transannular patch, various degrees of pulmonary valve insufficiency may create volume overload and eventual dilation of the RV.

Double outlet RV with subaortic VSD and pulmonary stenosis schematically follows this physiology, and is surgically corrected similar to a complete repair of TOF. The long-term fate of the RV may therefore be diagnostically considered and followed in the same manner.
TRANSPOSITION OF THE GREAT ARTERIES

There remains a large cohort of young adults who underwent an atrial switch procedure of the Senning or Mustard type in childhood. After the atrial switch, RV functions as a systemic ventricle leading to long-term problems of chronic RV pressure overload, and to tricuspid valve (systemic atrio-ventricular valve) regurgitation with RV volume overload (Figure 2). Refractory atrial dysrhythmias due to multiple incisions and suture lines in the atria may also induce or exacerbate RV failure. Finally, atrial baffle obstructions or leaks may respectively lead to systemic or pulmonary venous obstruction, and left-to-right shunts. The morphology of the RV in Senning or Mustard patients is analogue to that in patients with unoperated ccTGA, where the RV is round and the interventricular septum is convex towards the left ventricle.

CONGENITALLY CORRECTED TRANSPOSITION OF THE GREAT ARTERIES

Although the natural history of ccTGA may allow asymptomatic survival into adulthood, the majority of unoperated patients face long-term consequences of RV failure and dilatation, tricuspid valve (systemic atrioventricular valve) insufficiency, and complete heart block (Figure 3). The etiology of RV failure is multifactorial, and probably leads to RV dysfunction that worsens in relation to the development of tricuspid valve insufficiency and/or complete heart block. This remains true after physiologic, also called “classical” repair of ccTGA, where the RV remains in the systemic circulation.
RV FUNCTION DIAGNOSTIC POSSIBILITIES

Traditional parameters:

**History/Symptoms:** NYHA class, specific activity scale

**Echocardiography:** Ejection Fraction, tricuspid and pulmonary artery flow pattern, RVSP

**Exercise capacity:** Peak VO₂, walking distance

**Central haemodynamic:** pulmonary hypertension

**ECG:** Arrhythmia's

"New" parameters:

**MRI:** reliable quantitative RV function assessment

**Neurohormones:** brain and atrial natriuretic peptides

**Autonomic dysfunction:** heart rare variability

**Echocardiography:** 3 dimensional, MPI

Table 1. NYHA, New York Heart Association; RV Right, Ventricle; RVSP, Right Ventricular Systolic Pressure; MRI, Magnetic Resonance Imaging; MPI, Myocardial Performance Index.

QUANTITATIVE DIAGNOSTIC METHODS FOR NONINVASIVE ASSESSMENT OF RV FUNCTION

**ELECTROCARDIOGRAM**

A 12-lead ECG may give considerable insight into the degree of pressure and/or volume overload, and allows a simple and inexpensive first glimpse at RV function after repair of various congenital heart lesions.

A retrospective study, including 48 patients with chronic RV pressure overload after surgical correction of various congenital lesions was performed in our institution. The main inclusion criterion was chronic RV pressure overload (RVSP > 35 mm/Hg assessed by echocardiography) after surgically repaired congenital heart disease without important additional hemodynamic lesions in asymptomatic or minimally symptomatic patients (NYHA I or II). Patients were classified into 3 groups according to their diagnosis: 1) patients with ccTGA; 2) patients after atrial switch procedures according to Mustard or Senning for TGA, and 3) patients with a subpulmonary pressure overloaded RV. The last group was divided into 2 subgroups: a) patients with TOF and b) patients with RV pressure overload due to other congenital heart disease. Our study showed a gradual prolongation in QRS duration and QRS dispersion in patients with chronic RV pressure overload, regardless of the nature of congenital heart disease (Figure 4). In
the studied population, RV end diastolic volume, RV mass, and brain natriuretic peptide (BNP) were increased compared to the known reference values for healthy volunteers. A significant correlation was found between QRS duration and RV end diastolic volume in patients with a subpulmonary RV submitted to chronic pressure overload. With this study, we also demonstrated a significant correlation between QRS duration and RV mass in TOF patients. Several other studies also described the importance of QRS duration and dispersion as a predictor of malignant tachycardias and sudden death in patients with congenital heart disease\textsuperscript{10-12}. Gatzoulis et al. found that in TOF patients $\text{QRS}>180$ ms is a strong predictor for malignant ventricular tachycardias and also introduced QRS dispersion as a marker for inhomogeneity of ventricular depolarization\textsuperscript{10}. These studies were limited on specific types of cardiac lesions\textsuperscript{10-12}. Our study showed changes in ECG markers over time in patients with chronic RV pressure overload regardless of the nature of congenital heart disease. According to the findings of these studies, the increase in QRS duration and dispersion in patients with chronic pressure overload, as described in our study, could have important clinical implications concerning the risk of development of malignant VTs.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Changes in ECG markers during follow-up in patients with chronic RV pressure overload. ccTGA, congenitally corrected transposition of the great arteries; TOF, tetralogy of Fallot; TGA, surgically corrected transposition of the great arteries; rest: 9 patients with residual pulmonary valve stenosis, 4 with peripheral pulmonary hypertension, 1 with primary pulmonary hypertension, subpulmonary: all patients with TOF and all patients of the rest group. A) changes in QRS duration, B) changes in QRS dispersion.}
\end{figure}

**MAGNETIC RESONANCE IMAGING (MRI)**

MRI provides the diagnostic noninvasive technique of choice for the evaluation of RV function in congenital heart disease by its potential to obtain both anatomic detail and flow quantification. MRI is useful in detecting intracardiac and homograft conduit obstruction following cardiac surgery in complex congenital heart disease\textsuperscript{13-16}. Good accuracy and superior reproducibility of
MRI are setting a new gold standard for the quantification of RV ejection fraction (EF), cardiac output, myocardial mass and wall thickness\textsuperscript{13,17}.

Technical advantages of MRI in comparison with other techniques are the excellent spatial resolution, the characterisation of myocardial tissue, multi-plane versatility, and the potential for three-dimensional imaging\textsuperscript{18}.

Cardiac MRI allows an accurate noninvasive functional assessment of the RV and further development of this diagnostic method needs to be done in a multidisciplinary fashion amongst cardiologists, radiologists, physiologists, software scientists and MRI producers.

**MRI DOBUTAMINE RESULTS IN PATIENTS WITH TETRALOGY, ccTGA, AND ATRIAL SWITCH TGA, COMPARED TO CONTROLS**

We explored the effect of dobutamine stress and its possible clinical implications in different groups of asymptomatic patients with chronic RV overload due to congenital heart disease\textsuperscript{19,21}.

Asymptomatic and minimally symptomatic patients (NYHA I and II) with chronic RV pressure overload were studied: 29 patients with a systemic RV (16 after atrial switch for transposition of the great arteries (TGA) (Mustard or Senning), and 13 patients after physiologic repair of ccTGA), 22 patients with chronic pressure overloaded subpulmonic RV, and 11 age and sex-matched healthy volunteers. MRI was applied both at baseline and during dobutamine stress to determine RV volumes and ejection fraction.

Compared to the left ventricle of healthy controls, all patient groups had larger RV volumes. This study showed a clear heterogeneity in response to MRI dobutamine stress between different groups of patients with chronic RV pressure overload. We found decreased RV end diastolic volume suggesting impaired filling and decreased stroke volume stroke volume in patients after atrial switch for TGA. In a few recent studies the group of Redington\textsuperscript{22,23} using invasive techniques, also observed reduced diastolic filling and RV stroke volume in response to dobutamine stress test in patients with surgically corrected TGA. Based on their results they speculated that the capacitance and conduit function of the abnormal, often calcified, intra-atrial pathways may be responsible for the failure of stroke volume augmentation during exercise\textsuperscript{23}. During dobutamine stress a remarkable decrease in RV stroke volume, accompanied by both failure to augment RV EF and impaired RV filling were noticed in our TOF population. In a recent study Roest et al. including 15 asymptomatic TOF patients, using MRI imaging, described no significant EF change during physical exercise\textsuperscript{24}. However, different to our results, the authors described a minimal increase in RV end diastolic volume and stroke volume during exercise. Two reasons might declare the differences between these two studies: 1) In our study we used pharmacological stress (dobutamine), while Roest et al. used physical stress (bicycle ergometer) and 2) our patients were markedly older 27 (5), compared to 17.5(2.5), and therefore had less compliant RV due to long term overload and hypertrophy. Similar to our results Gatzoulis et al. using radionuclide angiography in 95 TOF patients (NYHA I – III) noticed failure of the RV to increase its EF during physical exercise. The authors interpreted their findings as indicative of early RV dysfunction\textsuperscript{25}. The RV in TOF is subject from birth to hypoxia and pressure overload. This results in structural and functional changes, such as: hypertrophy, interstitial fibrosis, cellular atrophy and myofibrillar disorganization marked as possible cause for an inappropriate response to stress in asymptomatic patients with TOF\textsuperscript{22}.

Patients with ccTGA showed an appropriate response to dobutamine stress. RV function determinants of unoperated ccTGA patients were closer to controls than patients with
physiological repair. MRI dobutamine may help to define the subgroups of ccTGA patients with favorable anatomy, whereby asymptomatic adult survival could be anticipated without need for surgery. Dobutamine stress MRI may facilitate the follow-up of RV (dys)function in patients with chronic RV pressure overload due to congenital heart disease. This was the first study addressing the cardiac reserve determined by MRI dobutamine stress test in different asymptomatic and minimally symptomatic patient groups with chronic RV pressure overload.

**Echocardiography**

Echocardiography is the most used imaging technique for the RV, doppler echocardiography can provide morphologic and hemodynamic information through segmental analysis of most congenital heart defects. Also, echocardiography provides indirect documentation of pulmonary artery hypertension and estimation of severity by the presence of RV dilatation and/or hypertrophy, the presence of tricuspid or pulmonic valvular regurgitation, and by Doppler estimation of RV systolic pressure.

More recently the myocardial performance index has been proposed as a geometry-independent index for global RV function. Myocardial performance index is derived from the time intervals obtained via Doppler echocardiography of the inflow and outflow of either ventricle. It reflects the isovolumetric activity of the ventricle in relation to the ejection time, and shows a good correlation with catheter-derived parameters of ventricular function such as peak dP/dt and Tau. This index does not distinguish between systolic and diastolic function, but rather reflects global performance.

We examined the possible correlation of myocardial performance index with RV ejection fraction (determined by MRI) in 29 consecutive patients with chronic RV pressure overload. We found a significant inverse correlation between RV myocardial performance index and RV ejection fraction \( r = -0.87, p<0.001 \). These data suggested that myocardial performance index might be used in clinical practice as determinant for global RV function in patients with congenital heart disease.

In the clinical practice cardiologists and echocardiographic technicians are faced with wide variety of RV lesions, caused by congenital heart disease. It is likely that they might recognize something abnormal but they might not recognize all the characteristics of the congenital heart lesion. For that reason and considering that echocardiography is still the first diagnostic choice in patients with congenital heart disease it is necessary that both the interpreting cardiologist and the echocardiographic technician have special competencies in congenital heart disease.

**Plasma Neurohormones**

Recent publications have shown that plasma concentrations of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are elevated in patients with asymptomatic systolic dysfunction, and that these parameters are highly accurate for the detection of heart failure. BNP is a marker for ventricular dysfunction and is secreted in both atria and ventricles, especially in failing ventricles. BNP has potent diuretic and systemic vasorelaxant properties.

In normal subjects ANP is synthesized and secreted almost exclusively in the atrium, whereas patients with congestive heart failure have increased ANP production in both atria and ventricles in response to increased atrial stretch. Although previous studies suggest that neurohumoral markers not only play a role in LV dysfunction but also in RV dysfunction their clinical applicability in the detection of RV dysfunction is not yet established. Speculation as to their
usefulness in noninvasive detection of RV failure in patients with congenital heart defects is all but too tempting.

We measured BNP and ANP levels in 21 asymptomatic or minimally symptomatic patients with chronic RV pressure overload due to a congenital heart disease and in seven healthy volunteer RV ejection fraction was determined using MRI. RV ejection fraction of the volunteers was significantly higher than RV ejection fraction of the patients. Between patients and volunteers there was a significant difference in the plasma concentrations of BNP and ANP. RVEF was inversely correlated with BNP and ANP (Figure 5). In a recent paper Bolger et al. found a highly significant stepwise increase of neurohumoral activation according to New York Heart Association class and systemic ventricular function. The authors interpreted these results as a state of chronic heart failure in adult patients with congenital heart disease relating to symptom severity and ventricular dysfunction and not necessarily to the underlying anatomic substrate. Our study was focused on asymptomatic or minimally symptomatic patients with chronic RV pressure overload, but basically both studies showed similar results: elevated BNP and ANP levels in the patient population versus healthy controls and a strong correlation between RV function and neurohumoral activation.

The results of the recent studies involving RV neurohumoral activation are encouraging clinical implementation of plasma neurohormones and BNP in particular as quantitative marker for RV function. It is very realistic that in the near future BNP might serve as a marker for the efficacy of treatment in patients with RV dysfunction, such as that after acute or pulmonary embolism, or after various repair of congenital heart disease placing the RV under strain.

![Figure 5](image_url)

**DISCUSSION**

The fate of the RV in congenital heart disease is an increasing source of concern and debate, both with regard to follow-up modalities and management issues. The long-term prognosis of these patients is open ended, and is mainly dependent on RV function, the eventual occurrence of RV failure and rhythm disorders. Because of the growing population of adults with congenital heart disease, operated or not, new modalities of noninvasive follow-up are required which are accurate, reproducible, and allow earlier detection of pressure or volume overload of...
the RV before the occurrence of failure or irreversible myocardial damage. Early detection of RV failure may permit better medical management and a better insight in optimal timing for preventive surgery.}

Patients with atrial switch operations for TGA or for DORV with subpulmonary VSD (Taussig-Bing) generally show reduced exercise tolerance, which has been attributed to factors such as abnormally low heart rate response, filling abnormalities of the RV and systolic dysfunction. Intrinsic myocardial damage of the RV in the systemic position, systemic or pulmonary baffle obstruction or leaks, and rigidity of the baffles in the heart may all contribute to this picture. Failure to increase stroke volume during dobutamine stress was confirmed as the primary hemodynamic abnormality in patients with TOF. Failure to increase RV EF and the significant decrease in RV end diastolic volume during dobutamine stimulation suggested impaired systolic and diastolic function in these patients.

In patients with ccTGA, the natural history of RV pressure and/or volume overload allows adult survival, but the possibility of RV failure, and the almost inevitable tricuspid valve insufficiency mandate accurate and reproducible diagnostic imaging to improve management of the patient and surgical timing. MRI undoubtedly provides the best imaging modality for preoperative assessment, and gives a comprehensive visualization of intracardiac pathways allowing for optimal surgical strategy.

MRI has become an established diagnostic modality for follow-up, as well as for preoperative assessment of patients with congenital heart disease requiring first time surgical intervention or reoperations. Broadening indications for the use of plasma neurohormones, such as BNP and ANP, may reveal to be promising future quantitative markers for the early detection of RV dysfunction in asymptomatic patients with congenital heart defects.

CONCLUSION

Although substantial knowledge has been gained about RV function in various congenital heart defects, both in the native state and after surgery, there is much left to do. Imaging and noninvasive quantitative parameters already play a role in the diagnostics of RV function; these diagnostic modalities will gradually take an even more important part in clinical practice. Implementation of reliable and reproducible parameters for RV function will enable a more aggressive follow-up tailored to the individual patient.
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Chapter 14

GENERAL CONCLUSIONS AND FUTURE RECOMMENDATIONS

Right ventricular function is of great importance in patients with both acute and chronic ventricular overload. The early detection of right ventricular dysfunction may facilitate possibilities, to prevent or delay further functional deterioration of the right ventricle.

In patients with right ventricular overload due to congenital heart diseases, MRI dobutamine stress test, ECG changes, and plasma brain natriuretic peptide (BNP) concentrations are very suitable parameters for the early detection of ventricular dysfunction, and should therefore be used in the follow-up of these patients.

Concerning patients with pulmonary embolism, we advocate the combined utility of BNP and cardiac troponine T for the risk stratification of right ventricular failure, especially in cases when echocardiography is not available or not possible.

It is apparent that no single measurement of anatomy or function can ever adequately describe the form or performance of the right ventricle. Rather, we should be looking more towards an integrated approach of different parameters for right ventricular function, and the quantitative parameters described in this thesis can serve this purpose. The strong correlation found between these non-invasive and independent parameters encourages their clinical implementation.