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Treatment of right ventricular outflow tract dysfunction: a multimodality approach

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The right timing to replace the pulmonary valve in a patient with dysfunction of the right ventricular outflow tract is unknown. Both percutaneous pulmonary valve and surgical prosthesis are suitable options. In every patient, the right ventricle (RV) remodels and recovers differently after pulmonary replacement. Therefore, it is difficult to identify the best treatment option and to predict the long-term results. In the last few years, we focused our research on optimizing the characterization of these patients through advanced cardiovascular imaging in order to find possible variables, parameters, and reproducible measurements that can help us in the decision-making process. The aim of the present article is to present our ongoing research lines that focus on the characterization and optimal treatment approach to the dysfunction of the RVOT.

Introduction

In some congenital heart disease, in particular in conotruncal cardiovascular defects, such as tetralogy of Fallot, pulmonary atresia with ventricular septal defect, and truncus arteriosus, the right ventricle outflow tract (RVOT) is underdeveloped. During the correction of the disease, the surgeon has to reconstruct the continuity between the right ventricle (RV) and the main pulmonary artery. Similarly in patients who undergo Ross operation, the pulmonary valve is used as autograft in the aortic position and the pulmonary valve is replaced with a prosthetic material. Depending on patient age, anatomy, and other factors, a variety of techniques, prosthetic materials, and valves are used to reconstruct the RVOT, but essentially all become dysfunctional over time causing pulmonary stenosis (PS), pulmonary regurgitation (PR), or both.

One of the biggest challenges of managing these patients after previous surgery is to balance the risks of the PR or stenosis against the risks and benefits of replacement of the pulmonary valve. All is complicated by the fact that any prosthesis used for the replacement has a limited lifespan that is shorter than the life expectancy of the patient, so the problem will recur again.

In the last decade, we have started a new therapeutical programme introducing the percutaneous implantation of the pulmonary valve that now allows us along with the surgical options to choose the best solution for the treatment of the RVOT dysfunction tailored to the patient's anatomy, age, and clinical history.

From 2008 to 2015, we have implanted 70 percutaneous pulmonary valves and surgically replaced almost 120 pulmonary valves with bioprosthesis. A comprehensive preoperative clinical and multimodality imaging assessment of the cardiovascular state was performed in all patients who were candidates for pulmonary valve replacement. A similar approach was also applied in the follow-up evaluations. Imaging techniques such as transthoracic echocardiography and cardiovascular magnetic resonance (CMR) were extensively used with an integrated approach to provide information on function, size, and morphology of

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the RV that are known to be strong influencing factors on morbidity and mortality in this group of patients.

Since the beginning of the programme, we noticed that in every patient the RV remodels differently to PR or PS, as well as recovers differently over time in response to the treatment. Therefore, it is difficult to identify the best treatment option and to predict the long-term results. This is why we focused our research on finding possible variables, parameters, and reproducible measurements that can help us in the decision-making process in order to do the best for our patients.

The aim of the present article is to present our ongoing research lines that focus on the characterization and optimal treatment approach to the dysfunction of the RVOT.

Echocardiographic imaging

The RV has anatomical and functional features that are difficult to study with echocardiography: the asymmetric and highly variable shape and the location behind the sternum necessitate distinct approaches and multiple echocardiographic windows to assess the inflow and outflow structures. Standards echocardiographic measurements, as reported in the 2010 ASE guidelines,[1] use M-mode or 2D imaging for linear measurements that in patients with dilated or anatomically malformed ventricle are not always reliable and are difficult to reproduce. Ventricular volume and function are indirectly calculated applying geometrical assumption derived from the left ventricle and therefore should be carefully weighted taking into account the pre-load and after-load conditions and the ventricular interdependence. Many limitations of conventional echocardiography to evaluate RV volume and function can be obviated with new non-geometrical parameters such as TAPSE Doppler flow analysis, Tissue Doppler Imaging (TDI) and 2D Strain and Strain Rate that better characterize the RV and its remodelling based on loading conditions.

Tricuspid annular plane systolic excursion (TAPSE) measures the systolic excursion of the RV annular plane towards the apex. TAPSE must be interpreted with caution: in patients with severe RV hypertrophy radial contraction becomes the prevalent direction of RV systolic deformation and TAPSE may underestimate the real systolic function. On the other hand, TAPSE is strongly pre-load dependent and in the case of severe PR and RV volume overload TAPSE may show high values masking mild systolic dysfunction.

Continuous wave and Color Doppler of the pulmonary flow and of the tricuspid regurgitation allows us to estimate the severity of PS and PR offering various information on the RV systolic function and diastolic pressure.

The ventricular strain measures the contractile deformation of the ventricle. Since 2009 we have worked with Esaote in the development of a 2D strain software (XStrainTM Esaote) and published our reference values in paediatric and adult population.[2] Once established our control group, we continued to use this system to avoid errors due to the well-known inter-vendor variability. This system uses a smaller region of interests by combining ultrasound speckle information with border tracking. When applied to the interventricular septum, it is possible to study the deformation of the right or left longitudinal fibres independently. Recently, we focused our interest to the application of this method to the evaluation of the RV.[3,4] Since none of the available 2D strain software includes a template for the study of RV, we use in our laboratory the template designed for the left ventricular apical 4-chamber view and arbitrarily divide the RV lateral wall into basal, mid, and apical segments.[3] High values of longitudinal strain and strain rate are observed only on the right lateral wall in young patients with severe PR; in these patients, both strain and strain rate normalize 24 h after the valve substitution. In patients with long-standing PR and severely dilated RV, the longitudinal strain and strain rate present lower values that correlate with the degree of RV dilatation, severity of PR, and QRS duration. The group with the more severe reduction of this deformation indexes are those early operated for ToF or pulmonary atresia who presented with dilated RV and stenosis of the pulmonary artery conduit. In the latter group of patients, a combination of pressure and volume overload causes stress on a previously dysfunctional RV with various degree of fibrosis and induces an evident after-load mismatch with very low values of longitudinal strain and strain rate (*Figure 1*). Improvement of longitudinal strain and strain rate are indexes to be considered at the follow-up of these patients as indicators of recovery of systolic function. The improvement of the longitudinal deformation correlates with the reduction of the RV volume, but never reaches normal values, with exception of patients who have a percutaneous pulmonary valve implanted in a stenotic RV-to-PA conduit previously positioned during a Ross operation. In the latter group of patients, the post-operative deformation indices are close to normal, presumably because the RV does not have congenital abnormalities and did not undergo any direct surgical procedure.

In case of severe RV hypertrophy and restrictive physiology, the systolic function of the RV is switched from a most prevalent longitudinal to radial deformation. Consequently, RV longitudinal strain and strain rate as well as TAPSE or TDI of the right lateral wall become less reliable and may underestimate the real function. In this case, a more correct quantification of RV systolic function can be done by measuring RV transversal strain that measures the systolic thickening of the RV myocardium directly on the dedicate RV long axis view.

Real-time 3-dimensional echocardiography (RT3DE) allows a better detail of the RV anatomy, in particular of the pulmonary valve and RVOT (*Figure 2*). However, in our population with poor acoustic windows the applicability of the transthoracic RT3DE for anatomical study is not encouraging. On the other hand, the introduction of the new software for off-line analysis of RV volumes and ejection fraction opens the possibility to obtain these data in those situations where MR is not feasible or not available. The principal limitations of RT3DE are the low spatial and temporal resolutions that limit significantly its applicability in severely dilated ventricles, where it becomes very difficult to acquire in a single 3D volume of the whole RV including the RVOT. In our experience, once the RV diastolic volume measured by MR is >200 mL or the volume rate of the acquisition it is lower than 25 volumes per second, RT3DE underestimates the RV end-diastolic volume and ejection fraction.

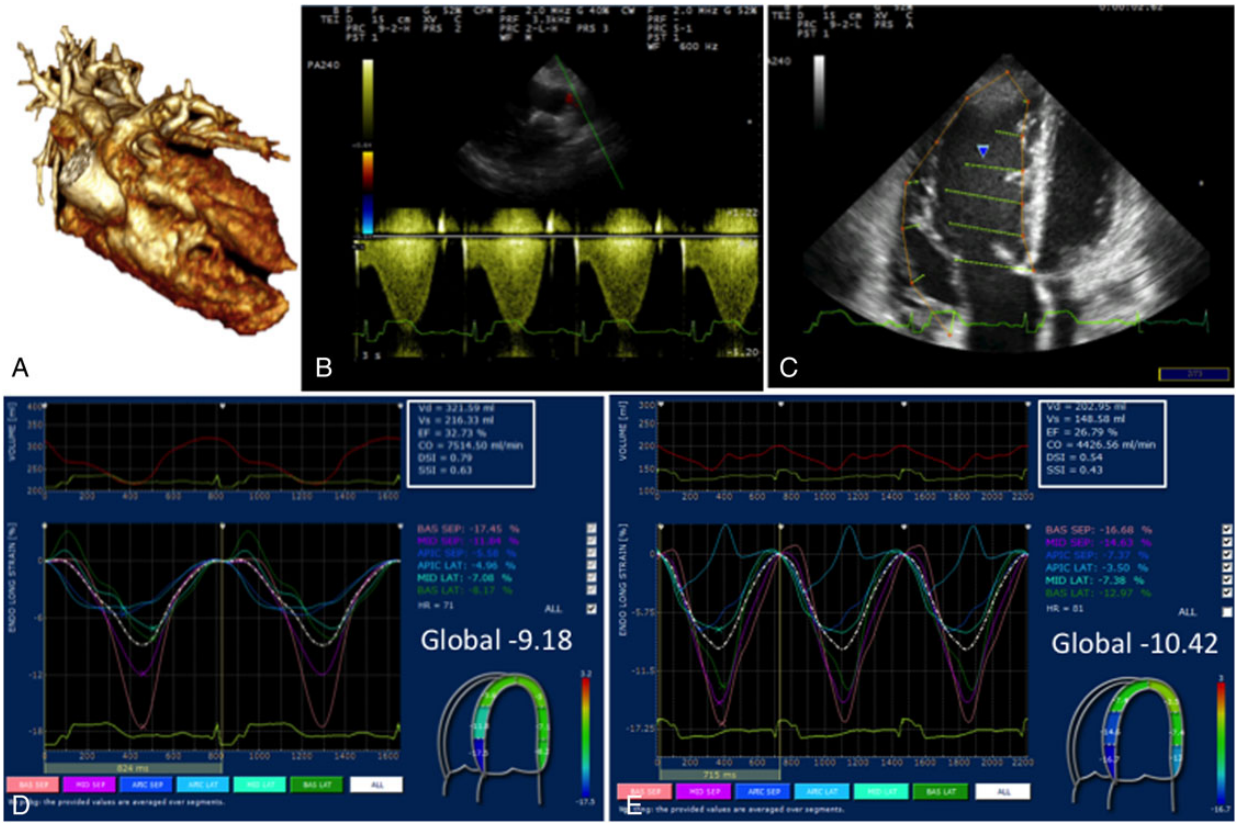

Figure 1 Right ventricular longitudinal strain in a 30-year-old patient with stenosis of the RV-to-PA conduit. (*A*) 3D reconstruction of the heart. (*B*) Echo Doppler shows severe conduit stenosis. (*C*) Tracking points position on subendocardial fibres to analyse the strain. (*D*) Report of strain values by segments before implantation of a pulmonary valve into the conduit. (*E*) Report of strain values by segments 3 days after implantation of a pulmonary valve into the conduit. Strain values are ordered according to a left ventricle four-chamber template for which the label of septal segment refers to lateral wall and those of the later wall refer to septal segments. In patients with RVOT stenosis, the strain values are very low and do not change much after pulmonary valve replacement in the short-term follow-up; however, quantitative data showed significant reduction of RV volume and normalization of the cardiac output (see white box).

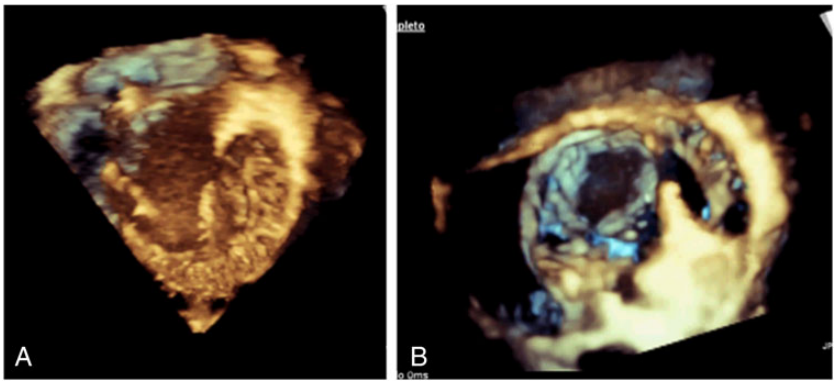

Figure 2 3D echocardiography of the RV. (*A*) Long axis 3D reconstruction of the RV. (*B*) Tricuspid valve seen from above (atrial prospective).

Advanced imaging—cardiac magnetic resonance

CMR is the gold standard for the assessment of RV dimensions and function due to its ability to image in any plane, its excellent blood-tissue contrast, its capability to depict even small wall motion abnormalities and its proven reproducibility.[5] CMR provides both anatomic and functional information that are complementary and essential for a proper evaluation of the RVOT dysfunction.

We are conducting a study to evaluate the medium and long-term impact of pulmonary valve replacement on biventricular function as assessed by CMR. We analysed the data of 33 patients (median age 20 $\pm$ 8 years) who underwent percutaneous pulmonary valve implantation (PPVI), and 16 patients (median age 30 $\pm$ 11 years) who underwent

surgical pulmonary valve replacement (SPVR). A conotruncal disease was present in 59% of the patients; the remnants had undergone Ross operation. CMR was performed before and after an average of 10 months (range 3–15) from the pulmonary valve replacement. Independently from the type of procedure used to replace the valve, in both groups the RV end-diastolic volume decreased significantly, while the RV ejection fraction increased more in the SPVR group compared with the PPVI patients. To confirm the importance of the ventricular–ventricular interaction, changes in the RV caused an increase in the LV end-diastolic volume and in the LV stroke volume after the procedure in both groups. Interestingly, we noticed an inverse correlation between the RV and LV end-diastolic volume: as the RV end-diastolic volume decreased at follow-up, the LV end-diastolic volume increased. These preliminary data confirmed that improvement of RVOT function is associated with reduction of RV volume and positive effects on ventricular–ventricular interaction. So far, the medium-term follow-up showed beneficial effect of pulmonary valve replacement in both groups.

Another interesting study that we started recently concerns the RV-pulmonary arterial coupling in our patients with dysfunctional RVOT. The concept of ventricular-arterial coupling was originally studied for the LV in patients with hypertension or heart failure.[6,7] In the literature, only few articles studied the RV-pulmonary arterial coupling in pulmonary hypertension[8,9] and one in patients with PR.[10] Ventricular-arterial coupling is defined as E_a/E_{max}. E_a is the effective arterial elastance and an index of the post-load and includes vascular resistances, vessel compliance, vascular impedance, systolic and diastolic time intervals. E_{max} is the maximal systolic ventricular elastance and a load-independent index that occurs at the end of the systole. Translating the information from the literature and simplifying the mathematical equation underneath the concept, we defined E_a/E_{max} = RV end-systolic volume/RV stroke volume. Optimal ventricular-arterial coupling is when $E_a/E_{max} = 1$. The objective of this study was to evaluate by cardiac magnetic resonance (CMR) the right ventricular-arterial coupling before and after surgical or transcatheter pulmonary valve implantation in subjects who had PR. We included 34 patients (age 23 $\pm$ 21 years; BSA 1.61 $\pm$ 0.5) treated for tetralogy of Fallot who have PR and/or PS and underwent SPVR in 15 cases or PPVI in 19 patients. CMR studies were performed before and 12 months after the procedure. The E_a/E_{max} ratio changed significantly between the pre-operative and the post-operative period (pre 1.42 $\pm$ 1.06 vs. post 1.02 $\pm$ 0.43; $P = 0.027$). Interestingly, no relationships were found with age at procedure, age at evaluation, sex and group of treatment. Once again our data suggest that both procedures of pulmonary valve implantation normalize the RV-pulmonary artery coupling at 12 months of follow-up with benefits for the patients.

3D cardiac models: planning is better

With the advent of high-resolution cardiac imaging, three-dimensional (3D) printing technology is successfully utilized to create heart prototypes of congenital cardiac defects.[11] The use of 3D cardiac models allow for previously unavailable visualization, understanding, handling, and analysis of anatomy of complex heart disease. We had recently a challenging case of pulmonary conduit stenosis, where the calcified conduit had an oval shape and we were not confident that we could safely implant a pulmonary valve percutaneously. Therefore, we decided to print a 3D model of the patient's RVOT in order to better understand the situation and to plan properly the type of intervention in that patient. The patient, a young lady, 21 years old, had a diagnosis of pulmonary atresia and ventricular septal defect that was corrected surgically in infancy with a RV to pulmonary artery conduit. During the last few years, the conduit became stenotic and severely incompetent, and the anatomy of the pulmonary branches was distorted creating a mild stenosis at the origin of the right pulmonary artery. After the team discussion, we decided that this patient was a good candidate for percutaneous pulmonary valve replacement. In October 2014, we performed a cardiac catheterization to implant a covered stent in the conduit and a second stent at the origin of the stenotic right pulmonary artery. Later on a 3D cardiac model was printed (*Figure 3*). The 3D model

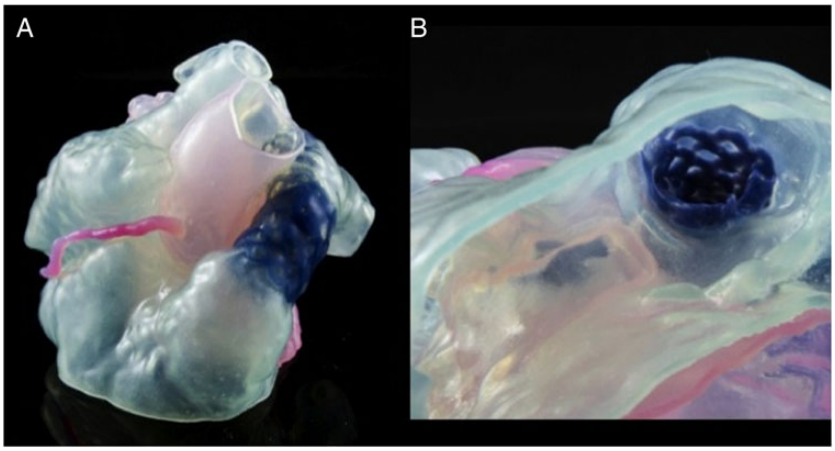

Figure 3 3D printed patient-specific model. (*A*) RVOT showing the stent (coloured in blue), the aorta and both coronaries that have been coloured in pink to make them evident in relation to the position of the stent. (*B*) Closed view of the stent in the RVOT.

afforded key information for planning the procedure: it helped us to understand the relationship between the stent in the main pulmonary artery and the left coronary artery. With this model, we confirmed the indication of a PPVI and simulated a catheter laboratory scenario to enhance our team discussion and decision-making as well as to exclude any potential surprises. The patient was consulted using the 3D-model aiming to give her a better understanding of the disease, and the complications could have occurred during the procedure.[12]

After this positive experience, we have started a research project aiming to evaluate the impact of 3D-printed models for an improvement in the quality of care and the interaction between surgeons and cardiologists.

Conclusions

Echocardiography is the examination routinely performed in the follow-up of patients with RVOT dysfunction. Use of the validated echocardiographic indexes based either on the conventional echocardiography and the newest technologies such as 2D strain and 3D echocardiography allow us to integrate the usual subjective observational information with a new set of parameters useful to quantify RV function. The analysis of the RV longitudinal strain allows us to recognize dysfunctional ventricles regardless of the load variations and to study the intrinsic ventricular function determined by the characteristics of the native ventricle and the chronicity of the lesions present. Despite that, CMR still represents the gold standard for non-invasive quantitative assessment of the RV and gives us important prognostic information to consult the patient.

The advent of high-resolution cardiac imaging allows the creation of 3D models of complex cardiac malformation that can be successfully used to visualize and understand the anatomy, and to assess, planning and trying *in vitro* interventions.

Conflict of interest: none declared.

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