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Editorial

Repaired isolated pulmonary valve stenosis: living happily ever after?

Reparación de la estenosis aislada de la válvula pulmonar: ¿es curativa?

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Isolated pulmonary valve stenosis (PVS) is a rather common congenital heart disease with an incidence of 6.5% to 7.1%.[1,2] It comprises a spectrum of disease, ranging from critical stenosis in the newborn to lifelong asymptomatic mild stenosis.[3] Galian-Gay et al.[4] reported follow-up data from 158 patients with isolated PVS who underwent either surgical treatment or percutaneous balloon valvuloplasty in their tertiary referral center. These authors should be congratulated for this work: the reported group is relatively large for adult congenital heart disease, clinical data including symptoms, electrocardiograms, echocardiograms, hemodynamic data and, importantly, long-term outcome data are provided with a follow-up of decades. Determinants of outcome are defined: age at PVS repair and the presence of cyanosis before repair were predictors of cardiovascular complications.

The authors resisted the temptation to increase patient numbers by including those with tetralogy of Fallot. These patients also have PVS as part of the congenital anomaly, but often have a more complex anatomy in terms of morphology of the right ventricular (RV) outflow tract and the presence of a ventricular septal defect. They require a different approach and a different timing of repair, undoubtedly affecting outcome. In contrast to tetralogy of Fallot and timing of pulmonary valve replacement (PVR), which has been extensively studied in the past 20 to 30 years, there are few data on long-term outcome after PVS relief in isolated PVS.

It would be a mistake, however, to apply the long-term Fallot data to the isolated PVS group. Patients with tetralogy of Fallot have worse right and left ventricular ejection fractions, their QRS width is substantially wider—related to ventricular arrhythmias, risk of sudden death and to RV size and function—and they more often undergo pacemaker or defibrillator implantation.[5] These factors are considered in the timing of reintervention, especially PVR, in Fallot patients, and should not be used in clinical decision-making in the PVS group. Again, the study by Galian-Gay et al. shows, even more clearly than most previous studies, that the long-term outcome and "natural" history after relief of PVS at a young age is substantially better than in the Fallot group.

The follow-up described by the current report is rather long, with an average of 27 years. The major part of the initial cohort was included in the follow-up. The survival of these patients with repaired PVS was very good: there was only 1 death, leading to a survival rate of 99.4%. This is in agreement with numbers known from the literature reporting on long-term follow-up and thereby describing patients who reached adult age, varying from 90% up to 98.4%.[3,6,7]

Apart from the well-deserved praise for the study, a few criticisms can be made about the study by Galian-Gay et al. A minor criticism concerns the one quarter of patients who were not included in the follow-up. This is not uncommon for relatively mild congenital cardiac defects that were treated, almost cured, by an intervention in childhood; we see this in virtually all studies from all over the world, dealing with follow-up of similarly mild defects. In the limitations section, the authors suggest that this may be due to the good clinical status of these patients, which made them feel that no further outpatient visits were needed. This is probably true, but it remains speculative. There is even a chance that some of them died, explaining why they were no longer seen for follow-up. No baseline characteristics of the excluded patients were provided, so we do not know if they differ from those in the included group. If their baseline characteristics were indeed better, indicating a milder form of the disease, the authors' explanation might be more legitimate.

More important is the way the authors report functional class. They did not provide many data on clinical function except for New York Heart Association (NYHA) class. This class has been proven to be of limited value for adult patients with congenital heart disease. As an illustration, some follow-up studies of Fontan patients, having a single ventricle physiology, reported that a large proportion were in NYHA class I.[8] Apart from reporting of NYHA class, exercise testing, preferably using VO_{2max} testing, would provide the data needed to assess the actual functional class of these patients, in other words, what they may be able to do and their limitations. This is the reason why it has been incorporated in the European Society of Cardiology and the North American guidelines: structural follow-up of adult patients with congenital heart disease requires the inclusion of serial exercise testing.[9,10] This will provide information on how moderate to severe pulmonary regurgitation (PR) and RV dilatation, common in this group of patients, are tolerated functionally over the years. Such data are necessary to guide us in clinical decision-making on when to intervene and when to consider PVR in patients treated for isolated PVS, without (unjustifiably) borrowing data from the Fallot population. Nevertheless, despite these minor flaws that are inherent to almost all retrospective follow-up studies, this study does enhance our knowledge of the long-term outcome of patients with repaired PVS.

The most important data from this study are those on the excellent survival for the duration of the follow-up, the fact that half of the patients have moderate to severe PR, a quarter of them have substantial RV dilatation, and that more than one third of the

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patients had undergone reintervention. For a long time, PR was considered to be innocuous,[6] but doubts have arisen about whether this is true.[11] In this study, as in the few other long-term follow-up studies,[3,7,12] a substantial subset of patients underwent late reintervention after 30 to 40 years of follow-up because of severe PR. Probably those who had PVR were the worst cases; in this study—as in all other follow-up studies—details about exact indication for PVR are missing, because they cannot be retrieved. Interventions in these patients are performed because they are expected to lead to a better outcome. In the short term, there is evidence that RV function improves, not only in Fallot patients but also in patients with isolated PVS.[13] The question is whether this is superior to a conservative approach in the long run, but so far there are no data to elucidate this question. The results of a conservative approach in the long run are not known either. The study by Galian-Gay et al. has a follow-up of up to 42 years after intervention. That is one of the longest ever reported, but is still not enough to answer the important question of whether the approach so far will lead to the best life expectancy and the best quality of life. How severe PR will be tolerated when patients are 50 or 60 years old and whether PVR at that age, when patients become symptomatic or when RV function deteriorates, will yield good results, is still completely unknown. Therefore, with the very relevant cohort that the Barcelona group has under structural follow-up now for so many years, we would like to encourage the authors to report the outcomes of this particular cohort in the future again, 10 and 20 years from now. Understanding what happens over the years will answer our patients' questions: do I have a normal life expectancy, what are my risks related to pregnancy, and will I be able to play (competitive) sports?

Over the past decades, various strategies have been applied to identify optimal timing of PVR. In the early days, when reoperation with PVR had a perioperative risk of nearly 10%, the threshold for referral for valve replacement was high. Only when patients developed signs of right heart failure they were referred to surgery. There are no reliable data on survival after PVR in this era in this specific diagnostic group, so it is not known whether it was truly a successful approach. Following considerations on the timing of PVR in tetralogy of Fallot, there has been a tendency to operate on patients with severe PR, with isolated PVS as the primary diagnosis, to prevent deterioration toward RV failure and to preserve RV function. It remains questionable whether that approach is justified. Recently Bokma et al.[13] reported that RV remodelling in the group with severe PR, who had isolated PVS as the primary diagnosis, was significantly better than in the Fallot group. Waiting for symptoms of RV failure to prompt PVR might be a good option for these patients.[13] Together with the recently reported doubts on the efficacy of early PVR in tetralogy of Fallot patients—early PVR does result in higher complication rates than conservative treatment, while mid-term outcome is not improved by early intervention[14]—there seems to be a justification to follow-up patients with moderate to severe PR and RV dilatation without intervention, and repeatedly examine them every 3 to 5 years. A structured follow-up should be provided, including assessment of functional capacity, and results should be published, because doubts remain about the health status of these patients in their sixth or seventh decade. Survival is the hardest and most important endpoint, but quality of life in correlation with the extent to which patients are limited by their cardiac condition, is also important.

The RV plays an important role in exercise. Even in healthy individuals with normal pulmonary vascular function, the hemodynamic load on the RV increases relatively more during exercise than that of the left ventricle. Exercise-induced increases in pulmonary artery pressures can exceed RV contractile reserve (so-called arterioventricular uncoupling), resulting in attenuated cardiac output and exercise intolerance.[15] Most, if not all, functional data reported in patients with PVS, are obtained during rest. What exactly happens during exercise in the presence of moderate to severe PR is not yet fully understood. One might argue that the higher heart rate on exercise will reduce the relative duration of diastole, which may reduce the extent of PR. In that case, it would not be a relevant factor in limitation of exercise capacity. On the other hand, if combined with RV dilatation and depressed RV function, it might result in an inability to increase cardiac output enough to meet the demands. Hopefully future investigations will illuminate this still largely unknown territory.

Better understanding of RV function during exercise also has implications for pregnancy, when cardiac output has to increase by approximately 40%. The current study reports very good pregnancy outcome: 46 pregnancies were registered in 31 women and the only complication found was a restrictive RV pattern. This outcome is better than those reported by previous, large registries. In the ZAHARA risk score, PR is a predictor of adverse outcomes during pregnancy, as well as for noncardiac complications such as hypertension.[16] In general, women with normal RV function do well during pregnancy. However, women with severe PR and RV systolic dysfunction or hypertrophy are at higher risk for developing right heart failure.[17] Furthermore, the ROPAC registry (Registry of Pregnancy and Cardiac Disease) described a case of sudden cardiac death during caesarean section in pulmonary stenosis, although it was not apparent whether this stenosis was treated before pregnancy or not.[18] All in all, to date, we do not have sufficient data to be sure about the risks of pregnancy, especially in the case of PR or RV dilatation. Despite the positive outcome in the pregnancies reported in the study by Galian-Gay et al., we should conclude that pregnancy in women with repaired PVS might become complicated, and that these women warrant extra medical attention during pregnancy, depending on prepregnancy cardiac function. This again necessitates follow-up in all centers to collect more data on long-term follow-up, including pregnancies.

If we continue collecting data in the conventional way, it will be very difficult to ever have enough data to provide sufficient evidence for every day clinical decision-making. Artificial intelligence might be a very important tool to achieve this goal. Diller et al.[19] have shown that it is feasible even in complex congenital heart disease in the setting of a single tertiary referral center. The best way to collect data on long-term follow-up in our patients with congenital heart disease would be a national, or even an international database. Automatic data collection and extraction from routine clinical care on a large scale is technically feasible, but there remain many obstacles, especially in terms of privacy regulations, the absence of consensus in terms of nomenclature of congenital heart disease, and limited consistency within centers in the use of the same nomenclature.[20] We hope these barriers can be solved in the coming years and that this will be our near future: to fulfil the need for data on adult congenital heart disease and finally have enough information on which to base our everyday clinical decisions and to be able to inform our patients in the right manner. Before we reach this utopia, we consider that we are on the right track with data as provided by Galian-Gay et al.: a dedicated long-term follow-up from a specialized center.

CONFLICTS OF INTEREST

All authors declare no conflicts of interest.

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