The Fourth Decade After Repair of Tetralogy of Fallot:

Taking Aim at Moving Targets

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This year marks the 60th year since the first successful intracardiac repair of tetralogy of Fallot (TOF). The repair, largely unchanged over decades, consists of VSD closure and the relief of variable forms of right ventricular (RV) obstruction, usually with a trans-annular patch (TAP), and usually resulting in free pulmonary insufficiency (PI). Early in the experience with TOF repair, attention was on quantity of life - lifting the early dip in the survival curve. Palliative shunts were widely used, to permit repair at a safer, older age. The dividends from a full relief of obstruction included excellent function for decades for patients formerly suffering morbid or lethal disease. In this issue of Circulation, Cuypers and colleagues report findings of the third decennial follow up of a cohort of early TOF repairs, the longest prospective study of this population to date. As such longitudinal evidence accrues, we are continually called upon to reexamine both ends of the treatment timeline, though it is a wobbly yardstick that attempts to inform today’s best practices by measuring the sequelae of yesterday’s.

Early mortality after TOF repair is now very low, and 10-20 year follow up was encouraging. But, in the third post-repair decade, the Kaplan-Meier curve droops with progressive exercise intolerance, arrhythmia, right heart failure, and sudden death. Evidence points to ventricular scarring, chronic PI, RV hypertrophy, declining left and right ventricular performance as interrelated contributing factors. Some late risk may be modified at the front end, during infant repair. The progression of late sequelae also pushes the question of how to do a better job at the back end, with proactive strategies to preempt the onset of late morbidity.

At the Front End

Early and long-term evidence supports the modern practice of repair in infancy, with near 0% mortality and excellent early physiology, irrespective of a higher incidence of TAP with earlier repair. Echoing prior studies, Cuypers, et al. show that older age at primary repair and prior
shunt are independent predictors of late morbidity or death.\textsuperscript{2,5,6} Of note, very few patients were repaired in infancy in the Rotterdam cohort. Among other 3-4 decade series, the youngest age at repair was beyond infancy, and a palliative shunt was used for up to 40\% of cases, compared with contemporary series when repair is seldom performed beyond the first half of infancy and the shunt has all but vanished.\textsuperscript{6,7} The populations are not comparable, in fact, by age and method of repair, they are nearly mutually exclusive, challenging a meaningful translation of 40-year data to the present. Repair in early infancy still awaits data about the 3\textsuperscript{rd} post-repair decade.

Strategies to avoid TAP and to spare the pulmonary valve have enjoyed variable enthusiasm and mixed outcomes. Early successes are reported, but durable valve competence is limited to valves with milder dysplasia at the outset, and valve-sparing approaches yield shorter freedom from re-intervention than TAP.\textsuperscript{8} Twenty-year data is emerging for a valve-sparing approach, with encouraging freedom from ventricular arrhythmia, but era differences make comparison difficult.\textsuperscript{9} The Rotterdam data strengthens evidence that TAP is a factor predicting late dysfunction, arrhythmia or death, which finds support in other, but not all series.\textsuperscript{2,7,10}

At the Back End

Whereas the 40-year data presented today may questionably foresee the fate of today’s infants, it represents what is exactly relevant to today’s adults, who make up the drooping tail of the Kaplan-Meier curve, and who account for a large proportion of adult congenital interventions today. Neither morbidity nor mortality plateaus in the 4\textsuperscript{th} decade. Cuyper’s group shows a cumulative incidence of all events (death, cardiac re-intervention, symptomatic arrhythmia, stroke, heart failure, endocarditis) continuing to worsen in the third decade, with event-free survival of only 25\% at 40 years, consistent with other series.\textsuperscript{2}

Although PI itself is not an independent predictor of functional status, decompensated
chronic volume load likely underlies the progression of ventricular dysfunction, associated late arrhythmia and mortality.\textsuperscript{5,11} In addition to fueling valve-sparing approaches at the front end, these findings also underlie a controversial examination of timing for pulmonary valve replacement (PVR) in the adult with chronic PI. Does an asymptomatic patient with 25-year freedom from PVR count as a success, or as a failure to intervene in time to forestall the decline that is already silently underway? In the absence of symptoms, heart failure, or arrhythmia, there is not clear consensus about PVR indications. Pulmonary valve replacement is a treatment that can both cause and prevent a cardiac event. Is preventive maintenance a justified risk? Are there any patients who will never need PVR?

The criteria justifying PVR are reasonably moving in the direction of earlier intervention. A QRS duration of \(>180\) msec. predicts ventricular tachycardia, and QRS duration stabilizes after PVR.\textsuperscript{11} Reasoned thresholds for PVR based on QRS prolongation have moved from \(180\) msec. toward \(140\) msec.\textsuperscript{12} Functional recovery of the right ventricle after PVR is less likely if the preoperative RV end diastolic volume is \(>170\) ml/M\(^2\), and that threshold is moving toward \(150\) ml/M\(^2\).\textsuperscript{12} Exercise criteria, RV mass-to-volume ratio, and other metrics support lowering the threshold.\textsuperscript{13}

The Rotterdam data reports results of a conservative strategy, with PVR reserved for those with symptoms.\textsuperscript{14} The threshold for asymptomatic patients with PI has moved earlier in recent years, but long-term data about the effect of proactive intervention remains incomplete. Competing risks of a more aggressive approach to PVR include an uncertain benefit and the higher risk of re-interventions after earlier PVR. Overall, the mortality for PVR is low and getting lower, durable improvement in symptoms and functional class after PVR has been shown, though a survival advantage has so far not.\textsuperscript{15,16} Further complicating the question are the
unknowns about the long-term fate of catheter-based PVR. Clarity awaits long-term results of the current more aggressive strategies and their effect on the tail of the Kaplan-Meier curve. Late overall data on chronic PI shows cause for concern that we may be intervening too late, and earlier PVR seems a reasonable direction to continue leaning. Patient-tailored, evidence-based strategies for determining the threshold for PVR are maturing in sophistication and point to earlier intervention.12

The Rotterdam group and others show self-perceived health status among TOF patients to be generally good, despite declining cardiac function.2,17 Self-assessment may be a misleading portrait of the disease state, and may delay their presentation for treatment. This points to the importance of improving the follow-up systems for adults with congenital heart disease, who commonly disappear from surveillance after they transition out of pediatric care, unless specific transition programs are developed.

The goal of healthcare is to optimize both quantity and quality of life for patients. Challenging evidence-based medicine is the fact that evidence commonly comes from groups, but medicine is applied to individuals. The challenge broadens when our evidence from yesterday’s groups is all we have to gauge what is best for today’s individual. As our experience with TOF repair enters a 5th decade, the steady progression of functional decline justifies earlier intervention at both ends of the treatment timeline, with encouraging early results that await the test of coming decades. Positive patient self-assessments in the face of declining physiologic status should alert us to the need to further refine the threshold for PVR, and to devise systematic surveillance systems to identify earlier progression of silent disease.

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References:


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