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EDITORIAL

Terrible TR: A Marker or Maker of Cardiac Dysfunction?

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In medical school many of us learned the first rule of surgery: "Eat when you can, sleep when you can, and don't mess with the pancreas." In cardiology we've learned a similar axiom — "don't mess with the tricuspid valve". As clinical experience and new evidence accumulates, this axiom is becoming harder to accept.

In 1967, an early report on the natural history of tricuspid regurgitation (TR) following mitral valve replacement famously concluded, "tricuspid regurgitation will improve or disappear after mitral replacement and that tricuspid valve replacement is seldom necessary."[1] For decades to follow there was a common perception that the function of the tricuspid valve was relatively less important (certainly less important than the left heart valves), and that severe TR could be well tolerated and medically managed almost indefinitely. Overtime that thinking has clearly changed. In 2004, Nath et al.[2] examined a large Veterans Affairs hospital echocardiography database and reported that increasing TR severity was associated with worse survival in men regardless of left ventricular ejection fraction or pulmonary artery pressure. Indeed, severe TR was associated with poor prognosis that was independent of age, biventricular systolic function, or RV size. These findings and others since have established that at a minimum, significant TR is a marker of cardiac dysfunction and poor prognosis. The principle that severe TR creates cardiac dysfunction has been more difficult to establish.

In this issue of *Structural Heart*, Montalto and colleagues[3] report a retrospective observational study of TR prevalence and clinical outcomes in consecutive patients referred for echocardiography at a single tertiary referral center. In a cohort of 6309 patients, mild TR was noted in 26.1%, moderate TR in 6.6%, and severe TR in 4.3%. The etiology of TR was functional in 75% which included patients with pulmonary hypertension, left side valve disease, and tricuspid annular dilation due to atrial fibrillation. Clinical endpoints that occurred within 1 year of the index echocardiogram were reviewed. These included cardiovascular mortality, major adverse cardiac and cerebrovascular events (MACCE), and net adverse clinical events (NACE) including rehospitalization.

For the patient group with moderate or greater TR (11% of the total study cohort), they noted that severe TR is associated with worse NHYA functional class, higher doses of loop diuretics, and greater surgical risk scores. At 1 year, patients with severe TR had relatively high rates of mortality (15%), MACCE (20%), and NACE (52%). Renal and liver function were independent predictors of 1-year CV mortality. Among this patient group with at least moderate TR, only a small minority (5%) underwent surgical correction of any valve defect.

Is this observational data sufficient to now refer patients for surgical TR correction earlier in the disease natural history? To answer that question we should first address several more fundamental questions.

Why is the presence of TR so deadly?

Acknowledging that there must be some referral bias within an echocardiographic clinical database, there remains a clear message that having moderate TR is bad, and having severe TR is worse. In explaining this association, it is important to note that roughly three-quarters of significant TR is secondary to RV or annular dysfunction and remodeling. Although typical causes of secondary TR such as pulmonary artery hypertension, myocardial ischemia, or atrial fibrillation are themselves prognostically important, the data presented by Montalto et al. indicates that only renal function (blood urea nitrogen concentration) and liver function were independent predictors of cardiovascular mortality.

Although multiple forms of cardiac dysfunction will negatively impact forward flow and cardiac output, TR is somewhat unique in its additional impact on venous congestion of the visceral organs. Renal dysfunction in particular is often simplistically associated with pre-renal azotemia secondary to reduced perfusion volume. However, organ prefusion (and performance) depends not only on the delivery of blood, but also on the trans-renal pressure gradient. Several years ago, Mullens and colleagues[4] reported that venous congestion was the most important hemodynamic factor for worsening renal function in patients with advanced decompensated heart failure. While the recognition is not new that renal (and hepatic) venous congestion contribute to excess morbidity and mortality, it is now appropriate to more fully consider the role of significant TR in this cascade of additional organ dysfunction.

Why don't we fix TR more often?

It is estimated that more than 1.5 million Americans have moderate or greater TR severity yet fewer than 8000 tricuspid repair or replacement operations are performed annually.[5] Of the tricuspid valve repair procedures that are performed, the vast majority are done in conjunction with left-sided surgery.

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Several factors contribute to this chronic and unique undertreatment of a structural heart condition: (1) there is currently no data to support the notion that survival is improved by surgery (or emerging catheter-based interventions) to repair or replace the tricuspid valve. Case reports and individual provider experience support the expectation that morbidity does improve after surgery; but data on any mortality benefit are still lacking; (2) for many years the nationally reported *in-hospital* mortality for isolated TV repair has remained remarkably high at 9%.[6] It is widely acknowledged that this high mortality is related to patients being referred for surgery relatively late in the course of illness (when severe TR is accompanied by RV dilation and severe systolic dysfunction; and liver dysfunction on the basis of chronic venous congestion contributes to excess bleeding); and (3) The current ACC/AHA guidelines for the management of valvular heart disease provide class I and class 2a recommendations for secondary TR *only* at the time of left heart surgery; or a weaker 2B recommendation to consider repair or replacement if the patient has had prior left heart surgery and does not have severe RV systolic dysfunction or severe pulmonary hypertension.[7] These appropriately restrictive guidelines reflect the absence of data to support stronger recommendations for the surgical treatment of isolated secondary TR.

When faced with a patient with severe symptomatic TR, a medical provider must consider the following: There is a high mortality associated with repair or replacement, and there is currently no data to suggest that patients will live longer following the surgical procedure.

What do we need to learn?

The work by Montalto et al. has provided us with an estimate of the prevalence of significant TR (~11%) within a large tertiary center echo data base. It has also provided a stark reminder of the high 1-year cardiovascular mortality (~15%) associated with severe TR. However, by itself, this study cannot answer the questions of; which patients were dying irrespective of their severe TR; which patients were dying because of their TR; and which patients may have benefited from surgical or catheter-based valve intervention.

In the discussion of what we still don't know, we should acknowledge that the key concept of early versus late intervention is actually very difficult to define. Although severe pulmonary hypertension is a solid maker of "too late"; the use of RV systolic function is more challenging. Severe RV systolic dysfunction is very unlikely to improve after tricuspid valve intervention (and thus is a reasonable marker for "too late"). But apparently normal RV function may be grossly overestimated using imaging methods such as fractional area change, or visual estimates of RV systolic function. At the heart of this limitation is the current lack of methods to accurately define RV functional reserve—critical to a prediction of how the RV will respond to a new contractile environment with a competent tricuspid valve. Perhaps, with greater study, the echo quantification of RV lateral wall strain, or cardiac MRI strain methods will provide much needed guidance. Conceivably, measurement of RV contractile reserve in response to intravenous inotropes could be useful, but data are lacking.

Multiple transcatheter devices for treating functional TR are in early feasibility trials. Such devices offer the potential to reduce TR severity safely and appear to improve symptoms and quality of life over short-term followup.[8,9] However, whether transcatheter devices (or minimally invasive surgery) provide durable TR reduction and quality-of-life benefits or whether they improve mortality will not be available until pivotal trials are completed.

Today we are left with the notion that significant TR remains both a cause and a consequence of cardiac dysfunction. Thoughtful approaches to treatment options including earlier intervention, and clinical data reporting will undoubtedly continue to improve our understanding of the valve that is no longer forgotten.

Disclosure statement

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