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EDITORIAL

Secondary tricuspid regurgitation in patients with left ventricular systolic dysfunction: cause for concern or innocent bystander?

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This editorial refers to 'Clinical presentation and outcome of tricuspid regurgitation in patients with systolic dysfunction', by Y. Topilsky *et al.*, doi:10.1093/eurheartj/ehy434.

Secondary (functional) tricuspid regurgitation (TR) has long been neglected and regarded not so much as a genuine problem, but as a surrogate of a more fundamental condition. TR was deemed clinically insignificant, a result of collateral damage from other underlying conditions, often left-sided valvular lesions, pulmonary hypertension, or atrial fibrillation.[1,2] This school of thought has influenced the management of secondary TR for a long time, which was largely conservative with diuretic therapy or with TR expected to improve following treatment of the culprit conditions.[2] Surgical intervention for TR was at best scarce, even for severe TR. If tricuspid valve surgeries were performed, they were often carried out during concomitant left-sided valve surgery or when other indications for open heart surgery were present.[1] In the USA, an estimated 1.5 million of the adult population were affected by moderate to severe TR.[3,4] However, according to data from the Society of Thoracic Surgeon (STS), ~5000 isolated tricuspid valve surgeries were performed each year in the USA,[5,6] reflecting the vast unmet clinical needs in the management of TR.

As our understanding of the natural history of TR has improved in recent years, the tricuspid valve has finally been receiving the attention that it deserves. Indeed, as the surgical techniques improve and the momentum of percutaneous tricuspid intervention gathers, the tricuspid valve has been garnering increasing interest from interventionists, cardiac imagers, heart failure specialists, and cardiac surgeons alike. Despite the attention from the cardiac community, long-term outcome studies on TR are still scarce. In addition, the prognostication of patients with TR is often muddled by the heterogeneity of TR aetiologies or confounded by the presence of left-sided valve diseases, most notably mitral regurgitation or stenosis.[7] These gaps in the literature form the major impetus for the study by Topilsky *et al.* in the current issue of the *European Heart Journal*, where the authors studied the specific risk attached to TR in the presence of left ventricular (LV) systolic dysfunction.[8] In order to separate the wheat from the chaff, the authors selected only patients with secondary TR and reduced LV ejection fraction (EF <50%). Importantly, the study patients had no other significant valvular heart disease, defined as organic valve lesions of moderate or higher severity, neither did they have organic or primary TR, congenital causes of TR, or any previous valve surgery. The stringent selection criteria positioned the authors' work well at isolating the impact of secondary TR on long-term outcome.

The authors studied a fair number, albeit a historical cohort, of consecutive patients enrolled in the Mayo Clinic prospective TR registry from 1995 to 2005. Clinical outcomes up to 5 years, which included all-cause death, new onset of atrial fibrillation (AF), or heart failure admission, were reported. Quantitative assessment of TR using the proximal isovelocity surface area (PISA) method to calculate effective regurgitant orifice area (EROA) was performed for all patients. Severe TR was defined as an EROA $\geq$0.4 cm^2. Right ventricular function was evaluated qualitatively and by indexes of myocardial performance (right ventricular index of myocardial performance or myocardial performance index). Based on the EROAs, the study population was divided into cases, denoted by patients with mild to severe TR and controls, which included patients with trivial TR. Clinical presentation and outcomes were compared between the case and control groups. To correct for potential confounders, the authors matched the groups by age, gender, EF, year of diagnosis, co-morbidity index, and TR peak velocity.

At least mild–moderate to severe isolated TR was independently associated with excess mortality and cardiac events, warranting heightened attention to TR grading (*Take home figure*). Patients with mild–moderate TR had higher NYHA class, signs of right heart failure, liver dysfunction, and right ventricular enlargement on

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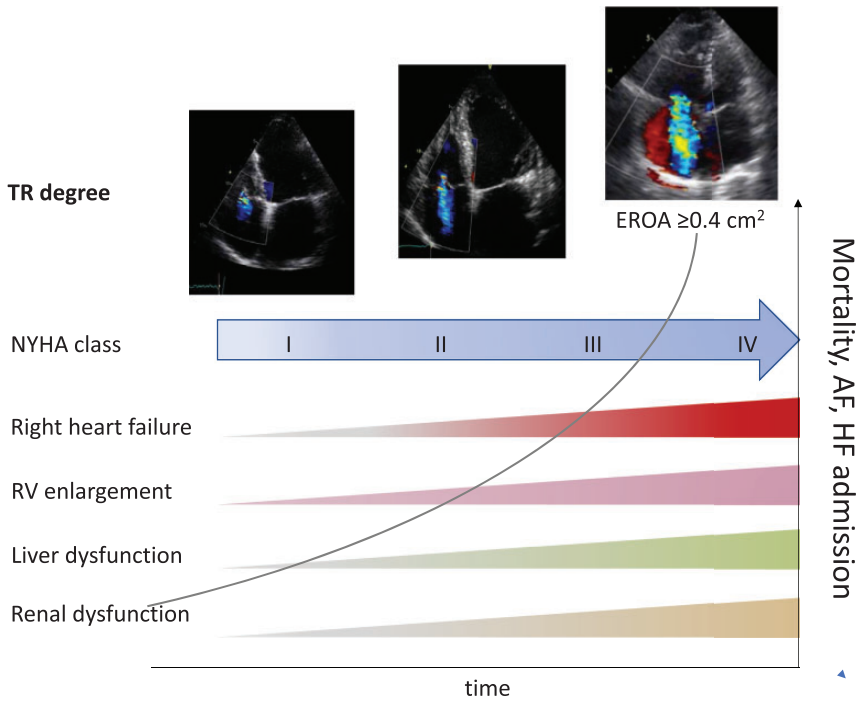

Take home figure Presentation and outcome of secondary tricuspid regurgitation (TR). AF, atrial fibrillation; HF, heart failure; RV, right ventricle.

echocardiogram compared with those with trivial TR. Those with severe TR (EROA ≥0.4 cm^2) had a 60% increased risk of death and a 90% increased risk of death or new-onset AF or heart failure admission compared with those with lesser TR (EROA <0.4 cm^2). Note that this is likely to be an underestimation given that a considerable number of patients, ranging from 22% among patients with trivial TR to 46% of patients with severe TR, already had AF at presentation. Despite the sobering morbidity and mortality figures, the vast majority of patients (97%), including those with severe TR, were treated conservatively with medical therapy. About 3% of patients underwent tricuspid valve surgery after a median wait of 1.9 years; by then all patients had developed symptoms of right heart failure. Arguably, this is a historical cohort and the surgical management of TR has since improved. However, according to the STS registry, which includes data as recent as 2010, only 14% of all tricuspid valve surgery was on the isolated tricuspid valve problem, despite the improvement in surgical mortality over the decade, from 10.6% in 2000 to 8.2% in 2010.[5]

Another aspect that sets this work apart from the published literature is the use of quantitative assessment of TR severity. The authors demonstrated outstanding ability to obtain quantitative TR measurement by EROA in not only most, but all, patients. This is indeed an extraordinary feat as the PISA quantification in secondary TR is often challenging due to the leaflet tethering angle and the non-circular shape of the regurgitant orifice. Other studies have shown that secondary TR usually has an elliptical or complex star-shaped geometry and only rarely is the orifice circular.[9] The authors have proven that the PISA method was not only feasible, but also reproducible, with excellent inter- and intraobserver variability. We should not lose sight of the fact that the enrolment was started in 1995 and continued until 2005, with only 2D greyscale and colour Doppler technology, making the achievement of the authors even more impressive.

Although current guidelines recommend an integrative valvular assessment using qualitative, semi-quantitative, and quantitative approaches,[10] only quantitative and semi-quantitative assessments of TR are routinely performed in most clinical practices. Apart from technical limitations that render quantitative assessment impossible, such as eccentric regurgitant jet and non-circular shape of the regurgitant orifice, quantitative TR assessment is also subjected to variations in respiration and right ventricular loading conditions.[11] Despite these technical difficulties, TR quantitation using EROA or regurgitant volume has many advantages. It is objective and allows serial comparisons within subjects or across the population. This is especially relevant in the era of percutaneous tricuspid valve intervention, where precise, reproducible quantification of TR reduction post-procedure is called for. Although not a focus in the current paper, the authors showcased an interesting observation, which is worth highlighting. In this study cohort, the mean EROA for patients with severe TR was 0.68 ± 0.2 cm^2. This is >0.28 cm^2, or a grade higher (assuming a grade difference of 0.20 cm^2) than the conventional cut-off for severe TR, which is set at 0.40 cm^2. An EROA of 0.68 cm^2 is high considering the study population were selected from the echocardiographic laboratory and not valve clinics or heart failure services, where the patients tend to be sicker and have more advanced stage valve problems. It was not apparent how the cut-off of 0.40 cm^2 came about or whether the authors studied higher thresholds for severe TR, between 0.40 and 0.68 cm^2. Studies on high-risk patients referred for percutaneous tricuspid valve intervention have shown that most patients had TR a grade or two higher than the current 0.40 cm^2

threshold.[12] As a result, expansion of TR severity grading to include massive and torrential TR, based on quantitative assessment, has been proposed.[13] According to the proposed grading, the study patients in fact had massive TR (ERO by PISA 0.60–0.79 cm^2), which further explains the high mortality rate.

Of note, the LV systolic function of the study population was moderately impaired, with a mean LVEF of 31% across all the TR severity groups. A previous study by Neuhold *et al.* has shown that TR predicted outcome in patients with mild to moderate congestive heart failure and not among those with advanced heart failure.[14] In the current study, Topilsky *et al.* did not find a significant interaction between TR and LVEF. This, as the authors pointed out, could be due to the sample size and possible underpowering.

All in all, the authors should be congratulated for the well thought out study design, patient selection, and matching processes, which enabled them to study the effect of secondary TR on outcome without the influence of other concomitant conditions. They have created a cohort of secondary TR with impaired LVEF, which is largely homogenous in terms of TR aetiology. This almost sufficiently addressed the recurring criticisms of many outcome studies on TR, i.e that the impact of TR was diluted, if not overshadowed, by the miscellany of accompanying conditions. However, it must be said that the potential impact of the severity of right ventricular dysfunction has not been satisfactorily assessed, given the lack of use of modern methods of analysis (e.g. tricuspid annular plane systolic excursion, lateral annular systolic velocity, and strain and strain rate).

In conclusion, whether this study strengthens the case for early tricuspid valve intervention still awaits to be seen. Further, ideally larger studies are needed to investigate whether patients with secondary TR and depressed LVEF will benefit from early tricuspid interventions.

Conflict of interest: none declared.

References

1. Cohen SR, Sell JE, McIntosh CL, Clark RE. Tricuspid regurgitation in patients with acquired, chronic, pure mitral regurgitation. II. Nonoperative management, tricuspid valve annuloplasty, and tricuspid valve replacement. *J Thorac Cardiovasc Surg* 1987;**94**:488–497.
2. Braunwald NS, Ross J, Morrow AG. Conservative management of tricuspid regurgitation in patients undergoing mitral valve replacement. *Circulation* 1967;**35**: I63–I69.
3. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;**368**: 1005–1011.
4. Singh JP, Evans JC, Levy D, , Larson MG, Freed LA, Fuller DL, Lehman B, Benjamin EJ. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation. *Am J Cardiol* 1999;**83**:897–902.
5. Kilic A, Saha-Chaudhuri P, Rankin JS, Conte JV. Trends and outcomes of tricuspid valve surgery in North America: an analysis of more than 50,000 patients from the society of thoracic surgeons database. *Ann Thorac Surg* 2013; **96**:1546–1552.
6. Zack CJ, Fender EA, Chandrashekar P, Reddy YNV, Bennett CE, Stulak JM, Miller VM, Nishimura RA. National trends and outcomes in isolated tricuspid valve surgery. *J Am Coll Cardiol* 2017;**70**:2953–2960.
7. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol* 2004;**43**:405–409.
8. Topilsky Y, Inojosa JL, Benfari G, Vaturi O, Maltais S, Michelena H, Mankad S, Enriquez-Sarano M. Clinical presentation and outcome of tricuspid regurgitation in patients with systolic dysfunction. *Eur Heart J* 2018;doi:10.1093/eurheartj/ehy434.
9. Badano LP, Muraru D, Enriquez-Sarano M. Assessment of functional tricuspid regurgitation. *Eur Hear J* 2013;**34**:1875–1885.
10. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, Badano L, Zamorano JL; Scientific Document Committee of the European Association of Cardiovascular Imaging. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2013;**14**:611–644.
11. Topilsky Y, Tribouilloy C, Michelena HI, Pislaru S, Mahoney DW, Enriquez-Sarano M. Pathophysiology of tricuspid regurgitation: quantitative Doppler echocardiographic assessment of respiratory dependence. *Circulation* 2010;**122**: 1505–1513.
12. Hahn RT, Meduri CU, Davidson CJ, Lim S, Nazif TM, Ricciardi MJ, Rajagopal V, Ailawadi G, Vannan MA, Thomas JD, Fowler D, Rich S, Martin R, Ong G, Groothuis A, Kodali S. Early feasibility study of a transcatheter tricuspid valve annuloplasty: SCOUT trial 30-day results. *J Am Coll Cardiol* 2017;**69**: 1795–1806.
13. Hahn RT, Zamorano JL. The need for a new tricuspid regurgitation grading scheme. *Eur Heart J Cardiovasc Imaging* 2017;**18**:1342–1343.
14. Neuhold S, Huelsmann M, Pernicka E, Graf A, Bonderman D, Adlbrecht C, Binder T, Maurer G, Pacher R, Mascherbauer J. Impact of tricuspid regurgitation on survival in patients with chronic heart failure: unexpected findings of a long-term observational study. *Eur Heart J* 2013;**34**:844–852.