European Heart Journal - Cardiovascular Imaging (2021) **22**, 886–887
doi:10.1093/ehjci/jeab109

INVITED EDITORIAL

The value of cardiac output measurement in tricuspid regurgitation

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Received 4 May 2021; editorial decision 6 May 2021; accepted 13 May 2021; online publish-ahead-of-print 21 June 2021

This editorial refers to 'Natural history of functional tricuspid regurgitation: impact of cardiac output' by E. Chen *et al.*, pp. 878–885.

> 'Everything should be made as simple as possible, but not simpler'.—Albert Einstein

Functional or secondary tricuspid regurgitation (STR) is the predominant form of TR, accounting for 85% of TR cases in adults. STR is a consequence of right ventricular (RV) remodelling with annular dilatation and leaflet tethering, often in the presence of pulmonary hypertension, left-sided heart diseases, or RV cardiomyopathy. In ∼10% of STR cases, no aetiological cause can be identified, which is termed idiopathic or isolated TR.[1] Little is known about isolated STR although the study has shown that it is often present in older patients and those with atrial fibrillation.[1] Isolated STR is associated with increased morbidity and mortality even in the absence of significant comorbidities, overt cardiac or pulmonary causes. Topilsky *et al.*[2] have demonstrated that isolated severe STR independently predicts 10-year risk of heart failure (HF) and cardiac death in patients with no intrinsic tricuspid disease, pulmonary hypertension, pacemaker/defibrillator wire across the tricuspid valve or other significant valve diseases, and preserved left ventricular (LV) function.

Cardiac output (CO, L/min) measures the antegrade LV pump function. CO is often indexed to the body surface area and expressed as cardiac index (CI, L/min/m^2). Traditionally, CI is used to define low- and high-CO states instead of CO as CI, being a more stable parameter, is not influenced by gender, obesity, and age.[3] A recent study of 4040 normal subjects proposed a definition of low output as CI <1.9 L/min/m^2, while high output was defined as CI >4.3 L/min/m^2 for both genders. The study also showed that the normal reference values for CO are lower in women (3.3–7.3 L/min) compared to men (3.5–8.2 L/min) and obese patients had higher CO compared to non-obese subjects.[3]

Doppler echocardiographic assessment of CO has been shown to closely correlate with invasive methods using Swan-Ganz catheterization. Study in advanced HF patients has shown excellent correlation between Doppler-derived central haemodynamics (pulmonary artery systolic pressure, pulmonary capillary wedge pressure, CO, and pulmonary vascular resistance) and simultaneous invasive haemodynamic assessment. The correlation remains strong even after unloading manipulations, with low interobserver variability.[4] Traditionally, echocardiographic-derived CO is calculated from stroke volume (SV), which is a product of LV outflow tract cross-sectional area and velocity-time integral. Calculation of SV using the difference between LV end-diastolic and end-systolic volumes is also feasible. Doppler-derived CO has been shown to predict clinical outcomes, although the definition of low output varies in the literature. Low output state, defined by SV index between <22 and 35 mL/m^2 has been shown to predict cardiac events.[5–7] While there is a paucity of outcome data on Doppler-derived high-CO state, cardiac catheterization study has shown that high-CO HF, defined by CI ≥4 L/min/m^2 was associated with increased mortality rate.[8] Obesity was the most common aetiology of high-output HF, followed by liver disease, arterio-venous shunts, lung disease, and myeloproliferative disorders.[8] The idea of using Doppler-derived CO to further risk stratify patients with significant STR is attractive. Identifying highest-risk patients who are most likely to benefit from tricuspid intervention has become an important imperative with the increasing awareness that symptoms and signs are often unreliable in the setting significant TR. This would also be of interest during transcatheter tricuspid valve interventions for TR. The lack of change in CO is easily measurable during the procedure using echocardiography. And, decisions regarding further intervention can be made notwithstanding the

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dynamic changes in the loading conditions and haemodynamics associated with general anaesthesia.[9]

In this issue of the Journal, Chen *et al.*[10] aimed to investigate the impact of CO on mortality in patients with ≥moderate isolated STR. While the conventional definition of isolated STR excludes patients with LV dysfunction, the current study allowed inclusion of patients with mildly impaired systolic function, with Left Ventricular Ejection Fraction (LVEF) ≥40%. In this study, CO subgroup stratification was based on the mean CO ± 1 standard deviation. Normal CO was defined as 3.28–6.22 L/min, with no distinction between gender, body size, and age. There is also a slight departure in the definition of high CO (>6.22 L/min) compared to a large normative reference value study (>7.3 L/min in women and >8.2 L/min in men) published recently.[3] This study showed that the patients with significant isolated STR had a mortality rate of 19%. As the study only included patients with at least moderate TR, i.e., patients with no/trivial/mild TR were excluded, it was unable to show if increasing TR severity confers higher mortality since there was no reference group for comparison. A novel finding in this study was the U-shaped relationship between CO and mortality, i.e., mortality increased in low- and high-CO groups compared to patients with normal CO. The authors presented the Kaplan–Meier curve that showed good separation in survival probabilities of those with abnormal vs. normal CO (log-rank $P = 0.034$). But, the current study did not include the severity of TR severity in the multivariable analysis, which has previously been shown to predict mortality in the literature,[2] Therefore, it is unclear if there is incremental benefit of adding CO during the assessment of TR, above and beyond the prognostic value of TR severity.

Furthermore, the authors have presented statistics for both the unadjusted and adjusted hazard ratios (HRs) in the overall group. In order to support the authors' statement that the low- and high-CO groups were statistically different from the normal CO group, statistics for the low- and high-CO subgroup should have been presented. Also, of note, the 95% confidence interval (95% CI) of the adjusted HR for the low-CO group crosses the line of unity (95% CI 0.62–8.08) and the small number ($N = 12$) in the high-CO group. Thus, based on the data from this study, the U-shaped relationship between CO and mortality is an interesting finding. It is notable that although both low- and high-CO states have been shown to predict mortality separately, the current study is the first that showed increased mortality at both ends of the CO spectrum in the same patient cohort, i.e., those with significant TR.

Despite the low patient number and a lower cut-off value for high-CO in this study, it is intriguing that the high-CO group had worse outcome compared to those with low CO. It would have been instructive if more is known about the characteristics of patients with high CO in this study. The current understanding of the mechanisms of high-CO HF is that it is related to lower arterial afterload and higher metabolic demand. Whether the same mechanisms are at work in TR patients remains unanswered, warranting further study. Also worth studying is the relationship between CO and TR, if significant TR can be further phenotyped according to CO. Building on the foundation of this study, the follow-up research question could be if CO modifies the relationship between TR and mortality, e.g., comparing the outcomes of patients with moderate TR but abnormal CO vs. those with severe TR but normal CO, which might clarify the incremental value of CO at risk stratification of significant TR patients. In the present study, there were no statistically significant differences in the distribution of TR patients of various severity in all CO strata. Whether this was due to the low number in each category, thus lacking statistical power or there was indeed no relationship between TR severity and CO subtypes remains to be seen.

This study marries a readily available Doppler parameter, the CO, with the need for a simpler, reliable marker of risk stratification in patients with significant TR, and to assess the effectiveness of newer catheter-based therapies. CO may be one such promising marker. However, for the ease of comparison, perhaps conventional cut-off values for low/normal/high CO or CI should be considered in further studies. Until then, the additive value of CO measurement in the routine assessment, risk stratification, and evaluation of effectiveness of therapy in significant functional TR remains unresolved.

Conflict of interest: None.

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