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Title: Right ventricular-pulmonary artery coupling: a simple marker to guide complex clinical decisions?

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Identifying the patients most at risk, and even predicting the individual benefit of any therapeutic strategy, remains a challenge when deciding to apply costly and/or invasive therapeutic strategies. Right ventricular-pulmonary artery (RV-PA) coupling is an interesting and simple emerging echographic marker that deserves attention.

The RV-PA coupling is deemed to reflect the matching between the RV systolic function, represented by the tricuspid annular plane systolic excursion (TAPSE), and its afterload, represented by the pulmonary artery systolic pressure (PASP)(1). As a ratio of two simple echographic parameters, this non-invasive, readily available index seems to be a promising parameter in the evaluation of complex patients, since a low RV-PA coupling (“RV-PA uncoupling”) has recently been found to be associated with poor prognosis in various cardiac conditions (table 1). More, its correlation with the invasive gold standard of pressure-volume loop analysis has been assessed in the field of severe pulmonary hypertension (6).

In this issue of *JACC: Cardiovascular Interventions*, Cahill TJ et al. studied the incidence and prognostic significance of RV-PA uncoupling in 570 low surgical risk patients with severe aortic stenosis included in the PARTNER 3 trial (5). The 222 (38.9%) patients with RV-PA uncoupling (defined here by a TAPSE/PASP ratio ≤ 0.55 mmHg at inclusion) had an increased incidence of the primary endpoint (the composite of all-cause mortality, stroke and rehospitalization: 19.1% vs 9.9%, $p = 0.002$), all-cause mortality (5.9% vs 0.6%, $p < 0.001$), cardiovascular mortality (4.1% vs 0.6%, $p = 0.003$) and rehospitalization (13.5% vs 7.3%, $p = 0.018$) at 2 years. Baseline RV-PA uncoupling remained an independent predictor of the primary endpoint at two years on multivariable analysis. After aortic valve replacement, echographic parameters usually associated with a poor prognosis (such as tricuspid regurgitation, low left ventricle stroke volume, or estimated pulmonary hypertension) are more frequent in patients with RV-PA uncoupling. In addition, evolution of RV-PA differed according to the management of the aortic stenosis since (contrary to TAVR) SAVR was associated with marked early (and persistent) impairment of the RV-PA coupling.

This interesting work is a further demonstration of the potential value of the RV-PA coupling analysis. Considering the exponential growth of TAVR during the last two decades, a better assessment of patients’ prognosis before aortic valve replacement is more than welcomed. RV-PA coupling analysis may play a key role. Authors should be congratulated for highlighting the potential value of this simple marker. More, RV-PA uncoupling assessment improved the prediction of all-cause mortality and heart failure hospitalization in 50 and 33% of patients, respectively, compared to a simple predictive model including age, STS score and left ventricular ejection fraction.

Nevertheless, authors also hit some snags, which illustrated some of the remaining weakness of the RV-PA coupling analysis, and may prevent its widespread implementation in current clinical practice:

The choice of the parameters. The 2 parameters entering the RV-PA ratio were collected at rest and non-invasively, by transthoracic echocardiography. The incremental value of stress (either by exercise or pharmacologic testing) for evaluation of the RV-PA coupling, the RV contractile reserve, or the pulmonary resistance is well-reported. However, stress evaluation is usually not recommended in patients with symptomatic severe aortic stenosis. More, although strongly correlated with invasive measure of PASP, the echographic assessment of pulmonary pressure, based on tricuspid valve regurgitation peak velocity, may lack accuracy, especially in patients with severe RV tricuspid regurgitation. Wisely, authors checked that RV-PA uncoupling kept its predictive value in a sensitivity analysis excluding patient with severe tricuspid regurgitation. Still, the standard assumed right atrial pressure of 8 mmHg used for all patients raises question, since it obviously does not correspond to reality in all patients.

Besides, assessment of RV systolic function is still a subject for debate. As a well-recognized load-dependent measure, TAPSE may be the most obvious parameter to choose, because of its availability, reproducibility and prognostic value. However, because it only reflects part of RV longitudinal function, TAPSE should not be used alone, but combined with other RV function measurements, such as RV fractional area change, strain characteristics or 3-D ejection fraction (7).

RV afterload results actually from the interaction of RV wall tension and PA compliance, resistance and wave reflection, better resumed by the pulmonary vascular resistance (PVR). Pulmonary pressures derive from the interaction between this PVR and the pulmonary blood flow, which depend on RV systolic function. Thus, using PASP as a surrogate for RV afterload has the advantage of simplicity but does not quite correspond to the complexity of the physiology of the cardiopulmonary unit. New non-invasive alternatives, such as RV myocardial work, recently applied in a heart transplant population, exist (8).

Last, while analyzing data from a well-conducted randomized clinical trial, authors had to exclude 40% (380/950) of the PARTNER-3 initial population due to missing or uninterpretable measurement of TAPSE, PASP or both. Thus, the availability of these 2 parameters is questionable in usual practice.

The cutoff value for RV-PA coupling. Any dichotomous cutoffs of continuous value should be very carefully determined. The relation between this parameter and prognosis is supposed to be linear and the objective in proposing a cut-off is to facilitate its clinical applicability. In Cahill's work, the optimal cut-off for TAPSE/PASP was determined by Cox proportional hazards, in order to get sensitivity and specificity for predicting the primary outcome. Worth of note, this ratio was however predictive for the primary outcome for a very wide range of values, from 0.42 to 0.70. As presented in table 1, most of the published work about RV-PA analysis adopted a similar strategy, whilst some considered the median TAPSE/PASP ratio value of the overall population as the cutoff. According to the studied population, these different methodologies led to a highly variable proportion of RV-PA uncoupled patients and, more troublesome, to a large range of cutoff values for RV-PA coupling. However, since each author

report a different cutoff for RV-PA coupling according to the studied population, its clinical application remains unclear: in the very specific field of aortic stenosis, is this cutoff value of 0.55 mm/mmHg reliable for the all-comer population?

Last, *the therapeutic impact of RV-PA coupling*. One should keep in mind that a low RV-PA ratio should not lead by itself to disqualify a patient for an aortic valve replacement. Indeed, patients with RV-PA uncoupling experienced here equivalent improvement in symptoms after aortic valve replacement compared to those with normal RV-PA coupling. Besides, a 4 stages classification currently allows an objective characterization of the extent of cardiac damage associated with aortic stenosis, where stage 4, corresponding to RV damage, is associated with the poorer outcome after aortic valve replacement (9). Thus, the prognostic added value of RV-PA coupling compared to the usual cardiac damage stages still needs to be demonstrated.

In conclusion, Cahill TJ et al. report here a very interesting and worthy analysis about the impact of RV-PA coupling on clinical outcomes in a large population of low surgical risk patients with severe aortic stenosis. This work is one more evidence of the informative prognostic value of this marker. However, because complex issues rarely have simple solution, there is still room for improvement in characterizing the value of the impact of the afterload on the left ventricle, the left atrium, and the ventricle-pulmonary artery coupling.

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Table 1: non-exhaustive resume of some recent studies about RV-PA uncoupling, using the TAPSE/PASP ratio.

Table 1 abbreviations: *TAPSE: Tricuspid annular plane systolic excursion; PASP: pulmonary arterial systolic pressure; RV-PA: Right Ventricular-Pulmonary Artery; ROC: receiver-operating curve; CRT: cardiac resynchronization therapy; TR: tricuspid regurgitation; TTVR: transcatheter tricuspid valve repair; SMR: secondary mitral regurgitation; TMVR: transcatheter mitral valve repair; NYHA: New York Heart Association; TAVR: trans aortic valve repair; SAVR: surgical aortic valve repair*

FIGURE 1 Nonexhaustive Resume of Some Recent Studies About RV-PA Uncoupling, Using the TAPSE/PASP Ratio

	Studied population	Number of patients	TAPSE/PASP cut-off for RV-PA uncoupling (Method for determining this cut-off)	Population with RV-PA uncoupling	Main outcome independently associated with basal RV-PA uncoupling	Main finding at follow-up
Guazzi M. et al. ¹	Heart failure population	293	0.36 mm/mmHg (derived from ROC curve analysis)	26.6%	21-month cardiac-related mortality	
Stassen J. et al. ²	CRT recipients	807	0.45 mm/mmHg (derived from spline curve analysis)	44.6%	120-month all-cause mortality	Worse survival in patients without TAPSE/PASP improvement after CRT implantation
Brener M. et al. ³	GlobalTriValve registry: TR patients undergoing TTVR or replacement	444	0.406 mm/mmHg (median value of the overall population)	50.0%	12-month all cause mortality	-Independent association between a decline in RV-PA coupling after TTVR or replacement and odds reduction of all-cause mortality -Independent association between a greater decline in TR severity after TTVR or replacement and a reduction in the RV-PA coupling ratio
Karam N. et al. ⁴	EuroSMR registry: SMR patients undergoing TMVR	817	0.274 mm/mmHg (derived from ROC curve analysis)	25.8%	24-month all cause mortality	Trend toward a lower rate of NYHA functional class I or II among patients with RV-PA uncoupling
Cahill TJ. et al. ⁵	PARTNER 3 trial: low-risk patients with symptomatic severe aortic stenosis undergoing TAVR or SAVR	570	0.55 mm/mmHg (Cox proportional hazards)	38.9%	24-month composite outcome (all-cause mortality, stroke and rehospitalization)	- Equivalent improvement in symptoms after aortic valve replacement in patients, regardless of RV-PA coupling - Improvement in RV-PA coupling after TAVR - Deterioration of RV-PA coupling after SAVR

CRT = cardiac resynchronization therapy; EuroSMR = European Registry on Outcomes in Secondary Mitral Regurgitation; TriValve = Transcatheter Tricuspid Valve Therapies; PARTNER 3 = Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients With Aortic Stenosis; PASP = pulmonary arterial systolic pressure; ROC = receiver-operating curve; RV-PA = right ventricular-pulmonary artery; SAVR = surgical aortic valve repair; SMR = secondary mitral regurgitation; TAPSE = tricuspid annular plane systolic excursion; TAVR = trans aortic valve repair; TMVR = transcatheter mitral valve repair; TR = tricuspid regurgitation; TTVR = transcatheter tricuspid valve repair.