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RESEARCH ARTICLE

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Non-invasive surrogates for right Ventricular-Pulmonary arterial coupling: a systematic review and Meta-Analysis

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Abstract

Right ventricle-pulmonary artery (RV-PA) coupling describes the energetic relationship between RV contractility and its afterload. The gold standard for assessment of this relationship requires invasive pressure-volume (PV) loop measurements. Non-invasive surrogates of RV-PA coupling have been developed, such as the echocardiographic tricuspid annular plane systolic excursion to pulmonary artery systolic pressure ratio (TAPSE/PASP), but their performance has not been systematically assessed. We sought to assess performance of TAPSE/PASP ratio compared to PV loop-defined RV-PA coupling. A systematic search was conducted. Studies were included if PV loop derived RV-PA coupling metrics were compared to echocardiographic or magnetic resonance imaging surrogates. We conducted a meta-analysis of TAPSE/PASP correlation to PV loop-defined RV-PA coupling. 1452 studies were identified in the initial search, of which ten met inclusion criteria. Five studies allowed for pooled analysis of TAPSE/PASP to Ees/Ea correlation ($r = 0.52$, 95% confidence interval 0.36–0.65). There was moderate heterogeneity across the pooled studies. Despite the common use of Non-invasive surrogates of RV-PA coupling, there is only moderate correlation with gold standard measurements. These metrics do not inform on the individual components of RV-PA coupling, limiting their use in the management of patients with RV dysfunction.

KEYWORDS

meta-analysis, pulmonary circulation, pulmonary hypertension, right ventricle, ventricular-vascular coupling

Abbreviations: Ea, effective arterial elastance; EDV, end diastolic volume; Ees, elastance at end systole; EF, ejection fraction; ESA, end systolic area; ESV, end systolic volume; FAC, fractional area change; FWS, free wall strain; GLS, global longitudinal strain; HFrEF, heart failure with reduced ejection fraction; MPAP, mean pulmonary artery pressure; MRI, magnetic resonance imaging; PASP, pulmonary arterial systolic pressure; PH, pulmonary hypertension; PRIMSA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; PV, pressure-volume; RCT, randomized controlled trial; RHC, right heart catheterization; RV, right ventricle; RV-PA, right ventricle-pulmonary artery; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion.

Jem M. Golbin and Neehal Shukla contributed equally to this study.

INTRODUCTION

There is growing recognition of the pivotal role of the right ventricle (RV) in various disease states. Despite inconsistent definitions across studies, RV dysfunction increases mortality risk in heart failure,[1,2] pulmonary hypertension (PH),[2] acute respiratory distress syndrome,[3] and sepsis.[4] Heightened appreciation of the mortality burden conferred by RV dysfunction underscores the necessity for a comprehensive understanding of RV function.

Ventricular-arterial coupling describes the relationship between a ventricle and its downstream vasculature. Right ventricle-pulmonary artery (RV-PA) coupling describes the energetic relationship between the RV and its afterload. RV-PA coupling can be mathematically defined as the ratio of the RV elastance at end systole (Ees) to the effective arterial elastance (Ea) of the pulmonary circulation.[5] The gold standard methodology for assessment of RV-PA coupling requires invasive pressure-volume (PV) loop measurements, which are not widely available and require expertise for adequate acquisition and interpretation. Noninvasive surrogates derived from both echocardiography and magnetic resonance imaging have demonstrated prognostic value.[6–9] The most common example is the tricuspid annular plane systolic excursion (TAPSE) to pulmonary arterial systolic pressure (PASP) ratio (TAPSE/PASP).

Despite the growing use of noninvasive surrogates, their accuracy compared to gold standard PV loops have never been systematically assessed. The purpose of this systematic review and meta-analysis is to quantify the performance of non-invasive surrogates of RV-PA coupling (and its individual components, Ees and Ea) to gold standard values obtained using PV loop measurements.

METHODS

Data eligibility, sources, search, and study selection approach

We searched Medline, Embase, and Cochrane Library from inception to June 28, 2024. We included studies that compared invasive PV loop measurements via conductance catheters to RV-PA coupling estimations by echocardiographic or magnetic resonance imaging in adult patients with any disease. Cohort studies and randomized control trials were included; conference abstracts were excluded due to limited reporting and high risk of bias. The comprehensive search strategy was developed by an information specialist (NN) and is included in the **Online Supplement** and was registered online, before analysis, at https://osf.io/ysn5x. The original search was performed on May 18, 2023 and updated as more than 1 year had passed, and to make the search terms more inclusive of all possible studies. Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia; www.covidence.org) was used for information management. Title and abstract screening, full text review, and extraction were independently completed by two authors, with conflicts resolved by a third. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[10] for reporting this work.

Data items

We included RV-PA coupling data obtained from PV loops measured by conductance catheterization, specifically Ees, Ea, and the ratio Ees/Ea. The method used to construct the PV loops (single beat vs multi-beat method) was also collected. Echocardiographic and magnetic resonance imaging variables used as potential RV-PA coupling surrogates were also collected if a direct comparison (i.e. correlation) to the invasive measurements was also reported. We collected pertinent information about disease states of the included cohorts.

Risk of bias assessment

Two reviewers independently and in duplicate assessed the risk of bias using the QUADAS-2 tool for quality assessment of diagnostic accuracy studies.[11] Results were compared, and disagreements were resolved through discussion.

Outcomes

The primary analysis was the correlation of noninvasive TAPSE/PASP ratio to invasive Ees/Ea. This outcome was chosen as it was expected to be most commonly available based on a priori knowledge of the literature. Secondary analyses included correlation of all additional available Noninvasive variables (echocardiographic and magnetic resonance imaging) to Ees/Ea or its individual components.

Data synthesis and evidence certainty

For the primary analysis, studies were analyzed with a random-effects model (DerSimonian and Laird inverse variance method) due to anticipated between-study

variation in correlation coefficients. Heterogeneity was quantified with the I^2 statistic, reflecting the percentage of total variability in outcome estimates due to between-study heterogeneity rather than chance.[12] Based on the small number of pooled studies, analysis for publication bias was not performed. No certainty assessment was performed. All analyses were performed using R Statistical Software (v4.1.2; R Core Team 2021) and the metafor package.[13]

RESULTS

Study selection and characteristics

A total of 1452 studies were identified in the initial electronic search, of which 31 were assessed in full text review. Of these, ten studies met inclusion criteria (Figure 1, Table 1). The collective studies included 424 patients in total, predominantly with precapillary pulmonary hypertension (PH). Eight studies included echocardiographic parameters,[14,16,17,19–23] and four reported cardiac MRI data[14–16,18] Three studies employed the multibeat method for PV loop acquisition[16,17,22]; the remainder used the single-beat method. Two studies derived some of their parameters (namely PASP and mean pulmonary artery pressure from right heart catheterization (RHC) and combined these with TAPSE from echocardiography,[14,19] though most studies did not specific the source of PASP measurement. Six of the ten studies reported the correlation of TAPSE/PASP to Ees/Ea. Two studies[18,19] reported on substantially overlapping cohorts, hence duplicate echocardiographic data was not included in the meta-analysis.

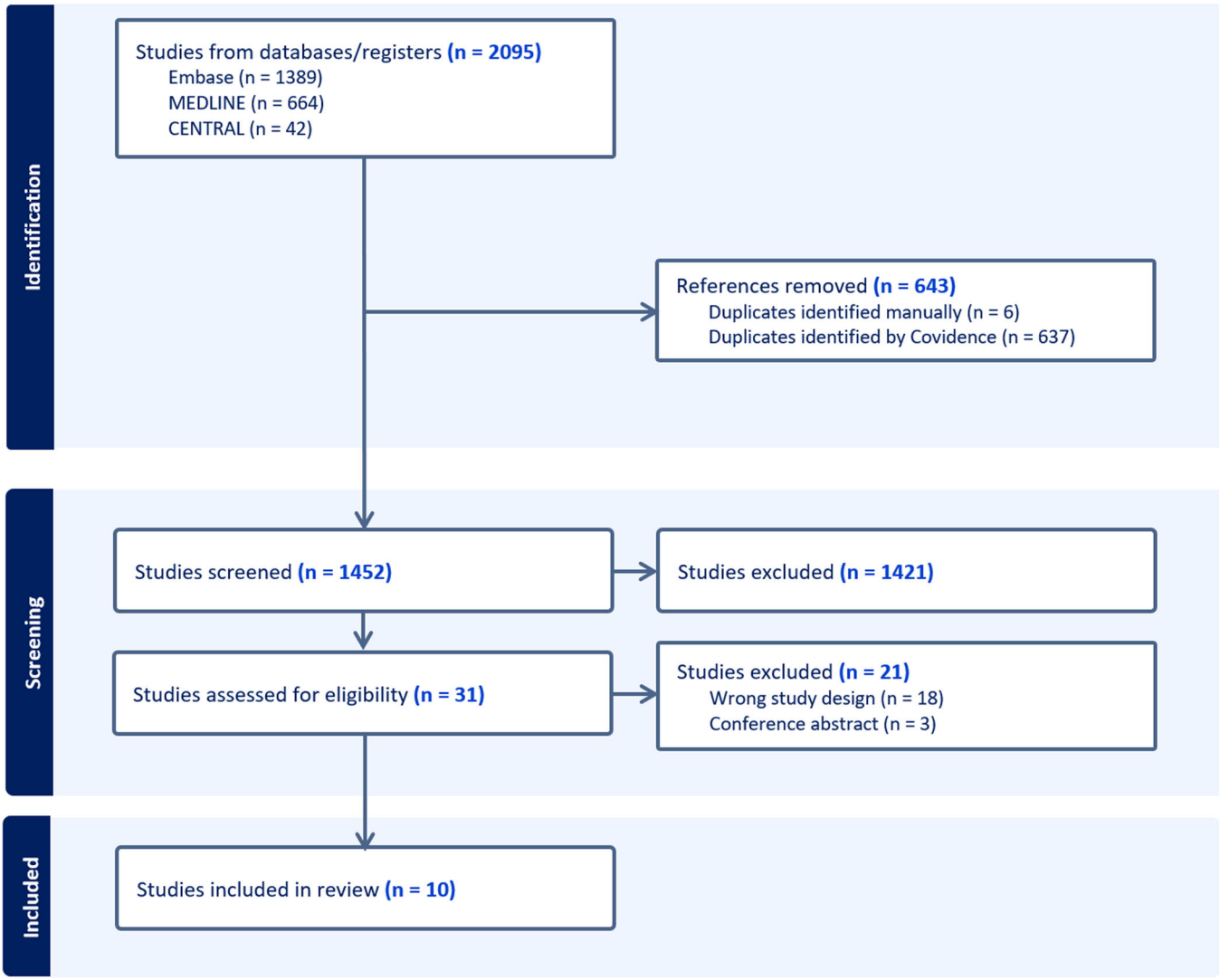

FIGURE 1 PRISMA diagram.

TABLE 1 Characteristics of included studies.

Study	Study Design and PV loop method	Population	Number of participants	Modality	Measure	Comparator	Correlation
Tello et al.[14]	Post-hoc analysis of prospective cohort, SB	Precapillary PH	52	Echo	TAPSE/PASP	Ees/Ea	0.44
						Ea	−0.49
					FAC/mPAP[a]	Ees/Ea	0.58
						Ea	−0.71
				MRI	RV Area change/ESA	Ees/Ea	0.51
						Ea	−0.54
					SV/ESA	Ees/Ea	0.52
						Ea	−0.67
Tello et al.[15]	Post-hoc analysis of prospective cohort, SB	Precapillary PH	38	MRI	GLS	Ees/Ea	−0.59
						Ea	0.43
Richter et al.[16]	Unspecified cohort, MB	Precapillary PH	38	Echo	TAPSE/PASP	Ees/Ea	0.50
				MRI	SV/ESV	Ees/Ea	0.68
Ireland et al.[17]	Prospective Cohort, MB	Confirmed or suspected PH (any type) during exercise	35	Echo	TAPSE/PASP	Ees/Ea	0.38
					TAPSE	Ees/Ea	0.36
Schmeisser et al.[18]	Post-hoc analysis of prospective cohort, SB	Advanced HFrEF, majority postcapillary PH	50	MRI	RV EDV	Ees/Ea	−0.79
					SV/ESV	Ees/Ea	0.93
					RV EF	Ees/Ea	0.93
Schmeisser et al.[19]	Post-hoc analysis of prospective cohort, SB	Advanced HFrEF, majority postcapillary PH	74	Echo	TAPSE/PASP[a]	Ees/Ea	0.71
						Ees	0.089
						Ea	−0.63
					TAPSE	Ees/Ea	0.77
						Ees	0.36
						Ea	−0.51
					FAC	Ees/Ea	0.90
						Ees	0.40
						Ea	−0.60
					FAC/PASP	Ees/Ea	0.79
						Ees	0.12
						Ea	0.68
Richter et al.[20]	Prospective cohort, SB	Precapillary pH	35	Echo	TAPSE/PASP	Ees/Ea	0.42
					SV/ESV	Ees/Ea	0.87
Richter et al.[21]	Retrospective cohort, SB	Precapillary PH	29	Echo	FWS/PASP	Ees/Ea	−0.43
					GLS/PASP	Ees/Ea	−0.53
Lakatos et al.[22]	Post-hoc analysis of prospective cohort, MB	Confirmed or suspected PH	60	Echo	RVEF	Ees/Ea	0.55
						Ees	−0.14
					GLS	Ees/Ea	0.40

TABLE 1 (Continued)

Study	Study Design and PV loop method	Population	Number of participants	Modality	Measure	Comparator	Correlation
						Ees	−0.067
					Global myocardial work index	Ees/Ea	−0.44
						Ees	0.67
Scheel et al.[23]	Prospective Cohort, SB	LVAD and reference patients	13 with echo comparison (7 LVAD, 5 reference)	Echo	FWS (all)	Ees	−0.08
					FWS (LVAD)	Ees	−0.45
					Septal strain (all)	Ees	0.63
					Septal strain (LVAD)	Ees	0.78

Abbreviations: ESA, end-systolic area; ESV, end-systolic volume; FAC, fractional area change; FWS, free wall strain; GLS, global longitudinal strain; LVAD, left ventricular assist device; MB, multibeat method; mPAP, mean pulmonary arterial pressure; MRI, magnetic resonance imaging; PASP, pulmonary artery systolic pressure; RVEF, right ventricular ejection fraction; SB, single-beat method; TAPSE, tricuspid annular plane systolic excursion; 3D, three-dimensional,
[a]Measured via RHC

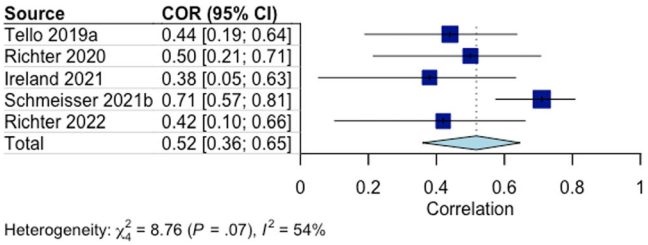

FIGURE 2 Pooled analyses of TAPSE/PASP to Ees/Ea correlation.

Risk of bias

Risk of bias tabulation is included in the **Online Supplement,** eTable 1. All ten studies were deemed low risk of bias by index test (echocardiography and magnetic resonance imaging) and reference standard (conductance catheter-based PV loop measurements). All studies have unclear risk of bias regarding patient selection, flow, and timing of study, due to incomplete reporting of these data.

Primary outcome

Five studies were available for the pooled analysis of TAPSE/PASP to Ees/Ea correlation. In meta-analysis, TAPSE/PASP ratio had moderately strong correlation with Ees/Ea ($r = 0.52$, 95% confidence interval [CI] 0.36, 0.65) as seen in Figure 2. Notably one study that included patients with postcapillary PH showed a stronger correlation ($r = 0.71$) when compared to the others measured PASP invasively by RHC. Overall, there was moderate-to-high heterogeneity among studies ($I^2 = 54\%$), likely due to the small, heterogenous patient cohorts as well as minor differences in acquisition and measurement techniques.

Secondary outcomes

Other echocardiographic parameters

Schmeisser[19] demonstrated moderately strong correlations between the ratio of fractional area change (FAC)/PASP ($r = 0.79$), FAC alone ($r = 0.90$), and TAPSE alone ($r = 0.77$) compared to Ees/Ea. The correlation of TAPSE to Ees/Ea was weaker ($r = 0.36$) in the Ireland study.[17] Richter[21] used RV free wall strain (FWS)/PASP and global longitudinal strain (GLS)/PASP as their comparators to Ees/Ea and found that the correlations were moderately strong ($r = -0.43$ and $r = -0.53$, respectively). Lakatos demonstrated correlations of RV ejection fraction (EF), GLS, and global myocardial work index to Ees/Ea ($r = 0.55$, 0.40, and −0.44, respectively).

Only four studies[14,19,22,23] compared echocardiographic parameters to individual Ea and Ees measurements. In the Schmeisser study,[19] TAPSE demonstrated weak direct correlation with Ees ($r = 0.36$) and moderate inverse correlation with Ea ($r = -0.51$). FAC showed stronger inverse correlation with Ea ($r = -0.60$) compared to Ees ($r = 0.19$). Similarly, Tello[14] identified only a moderate inverse correlation between TAPSE/PASP and Ea ($r = -0.49$). FAC/mPAP had the strongest inverse correlation with Ea ($r = -0.71$) closely followed by stroke volume (SV)/end

systolic area (ESA) ($r = -0.67$). Lakatos[22] demonstrated weak non-significant correlations of RV EF and GLS with Ees, though global myocardial work index correlated with Ees moderately ($r = 0.67$). Scheel[23] similarly showed moderate correlation of FWS with Ees in left ventricular assist recipients ($r = -0.45$), and even strong correlation of septal strain to Ees ($r = 0.78$) in the same population. Detailed results of all relevant echocardiographic parameters are shown in Table 1.

Cardiac MRI parameters

Tello[15] demonstrated moderate correlation of MRI-derived GLS with both Ees/Ea and Ea (−0.59 and 0.43, respectively). The Schmeisser[18] study exhibited a strong inverse correlation between Ees/Ea and RV end diastolic volume (EDV) ($r = -0.79$), and direct correlation between Ees/Ea and SV/end systolic volume (ESV) ($r = 0.93$) and RV EF ($r = 0.93$). This aligns with the study by Richter[16] which found a direct correlation between Ees/Ea and SV/ESV ($r = 0.68$). Detailed results of all relevant MRI parameters are shown in Table 1.

DISCUSSION

In this systematic review and meta-analysis, across a small number of studies with moderately high heterogeneity, we found only moderate correlation between TAPSE/PASP and invasively derived RV-PA coupling (Ees/Ea). Several other individual metrics, whether derived from echocardiography or cardiac MRI, had moderate to strong correlation with Ees/Ea, but poorer correlation with the individual components, i.e. Ees and Ea. The included studies overwhelmingly evaluated patients with pre- or post-capillary PH, limiting the generalizability to other diseases.

To our knowledge, this is the first systematic review to evaluate the correlation of non-invasive surrogates of RV-PA coupling to the gold standard conductance catheter-based measurements. Despite the insufficient validation of these non-invasive measurements of RV-PA coupling, particularly in diseases other than PH, there is a proliferation of studies using TAPSE/PASP across various conditions, including diseases of the critically ill.[24–26] In addition, most of these studies evaluating surrogates of RV-PA coupling tested TAPSE/PASP as a prognostic factor rather than a diagnostic assessment or treatment target.

Importantly, we found insufficient evidence to support the use of Non-invasive surrogates to assess the individual components of RV-PA coupling, i.e. Ees and Ea. This lack of validation has both diagnostic and therapeutic implications. Without understanding these components (ventricular elastance and pulmonary arterial elastance) individually, it is difficult to appropriately diagnose and treat RV dysfunction. For instance, an abnormal TAPSE/PASP ratio could result from either impaired RV contractility or high afterload—two pathologic conditions which require very different treatment strategies.

This study has limitations. We employed a broad search strategy, but it is possible some eligible studies were not captured. The studies included in pooled analyses come from a relatively small group of authors with expertise in PV loop evaluation, as well as overlap in patient cohorts, which also limits generalizability of test performance. The overall small sample size of individual studies also diminishes the ability to draw strong conclusions from this analysis.

Our work does highlight, however, that further investigation is needed to better define parameters of RV-PA coupling which can be used for research and clinical care. While invasive PV loop measurement is the gold standard for assessing RV-PA coupling, the cost, invasiveness, and required expertise make it impractical for routine use. One potential solution is to use invasive right ventricular pressure-derived approximations of Ees/Ea as previously described[27] and recently implemented in several clinical investigations,[28,29] as this data can be obtained from routine RHC. This method may also be used as a reference to define other Non-invasive methods of PV loop construction.[20] Non-invasive surrogates are needed to diagnose and treat RV dysfunction across a spectrum of diseases. The mediocre performance of existing non-invasive indices may represent an opportunity to leverage advanced echocardiographic tools such as strain measurements and three-dimensional echocardiography to assess the individual components of RV function.

CONCLUSION

Despite the proliferation of publications using non-invasive surrogates of RV-PA coupling, there is only moderate correlation with gold standard PV loop measurements. Furthermore, these surrogate metrics do not permit a clear understanding the individual components of RV-PA coupling, which limits their use in the management of patients with RV dysfunction.

AUTHOR CONTRIBUTIONS

Jem M. Golbin, and Neehal Shukla participated in the data curation, original drafting of and critical revision of the manuscript. Neil Nero conceived the search strategy and critically revised the manuscript. Maxwell A.

Hockstein and Adriano R. Tonelli participated in the data analysis, drafting, and revision of the manuscript. Matthew T. Siuba conceived of the study, completed the data analysis, drafted and revised the manuscript, and is the guarantor of the work.

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CONFLICT OF INTEREST STATEMENT

ART has participated in advisory boards for Janssen and Merck. All other authors have no relevant financial conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

All data is publicly available via prior published articles.

ETHICS STATEMENT

This study is exempt from ethical approval as it only incorporates information from previously published work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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