REVIEW

Echocardiographic RV-E/e′ for predicting right atrial pressure: a review

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Abstract

Right atrial pressure (RAP) is a key cardiac parameter of diagnostic and prognostic significance, yet current two-dimensional echocardiographic methods are inadequate for the accurate estimation of this haemodynamic marker. Right-heart trans-tricuspid Doppler and tissue Doppler echocardiographic techniques can be combined to calculate the right ventricular (RV) E/e′ ratio – a reflection of RV filling pressure which is a surrogate of RAP. A systematic search was undertaken which found seventeen articles that compared invasively measured RAP with RV-E/e′ estimated RAP. Results commonly concerned pulmonary hypertension or advanced heart failure/transplantation populations. Reported receiver operating characteristic analyses showed reasonable diagnostic ability of RV-E/e′ for estimating RAP in patients with coronary artery disease and RV systolic dysfunction. The diagnostic ability of RV-E/e′ was generally poor in studies of paediatrics, heart failure and mitral stenosis, whilst results were equivocal in other diseases. Bland–Altman analyses showed good accuracy but poor precision of RV-E/e′ for estimating RAP, but were limited by only being reported in seven out of seventeen articles. This suggests that RV-E/e′ may be useful at a population level but not at an individual level for clinical decision making. Very little evidence was found about how atrial fibrillation may affect the estimation of RAP from RV-E/e′, nor about the independent prognostic ability of RV-E/e′ . Recommended areas for future research concerning RV-E/e′ include; non-sinus rhythm, valvular heart disease, short and long term prognostic ability, and validation over a wide range of RAP.

Key Words

- echocardiography
- Doppler
- right atrial pressure
- right heart catheterisation
- diastolic function

Introduction

Right atrial pressure (RAP) is a haemodynamic variable that provides important diagnostic and prognostic information in both cardiovascular and pulmonary disease patients (1, 2, 3). Despite its usefulness in routine clinical assessment the gold-standard measurement technique remains invasive right-heart catheterisation (RHC), a procedure which requires radiation exposure, is associated with a degree of patient risk and is not available as a bedside test; RHC is, therefore, unsuitable for regular serial assessment. Thus, accurate non-invasive alternatives to determining RAP are advantageous both clinically and for patient safety/experience; transthoracic echocardiography (TTE) offers one such method. Estimation of RAP is required during echocardiography to combine with measurements of tricuspid and pulmonary regurgitation velocities to estimate pulmonary artery pressures (4). Existing estimation methods centre around inferior vena cava (IVC) size and its collapse upon inspiration

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but are prone to the technical limitations related to subcostal window imaging (poor acoustic quality and IVC movement out of the imaging plane during respiration). There is equivocal evidence for their accuracy in predicting RAP (5, 6, 7) and accordingly, alternative ways of assessing RAP are needed.

During normal sinus rhythm, right ventricular (RV) diastolic filling is a biphasic process. In early diastole, elastic recoil of myocardial fibres results in early rapid relaxation of the RV, leading to a sharp fall in pressure and early passive filling of the ventricle through a suction effect. In late diastole, filling occurs through the atrial contraction. The maximum pressure difference between the two chambers can be calculated via the Bernoulli equation from the peak blood velocity of the forward flow on continuous-wave Doppler, however, this does not provide us with an estimate of the absolute pressure in either chamber. RV filling in early diastole can be assessed using Doppler and tissue Doppler echocardiography by taking the ratio of trans-tricuspid valve early diastolic peak velocity (E) to early diastolic tricuspid annular tissue peak velocity (e′). This ratio (RV-E/e′) is an echocardiographic reflection of RV filling pressure and is based on the same principle as that of left ventricular E/e′ diastolic assessment. When RV relaxation, compliance and filling pressures are normal, normal myocardial function results in normal lateral e′ velocity while normal/low RAP results in low trans-tricuspid E velocity; the ratio between E and e′ is therefore low. However, when RV diastolic function is impaired and filling pressures are increased, e′ velocities are reduced due to impaired myocardial relaxation whilst elevated RAP drives a higher trans-tricuspid E velocity; the ratio between E and e′ is therefore increased. The component parameters of the ratio are obtained in the apical four-chamber view by pulse-wave Doppler at the tips of the tricuspid valve leaflets and by tissue pulse-wave Doppler at the tricuspid valve lateral annulus respectively (Fig. 1).

RV-E/e′ is simple to obtain and calculate yet is not widely used, despite being recommended in multiple American Society of Echocardiography guidelines as a parameter to consider when estimating RAP (8, 9). Additionally, RV-E/e′ is now included in the British Society of Echocardiography 2020 right-heart assessment guideline as a parameter for assessing RV diastolic function (10). There is neither advice nor consensus regarding clinical conditions and situations where this parameter is or isn't valid for the estimation of RAP, which may be limiting its adoption into routine practice. Furthermore,

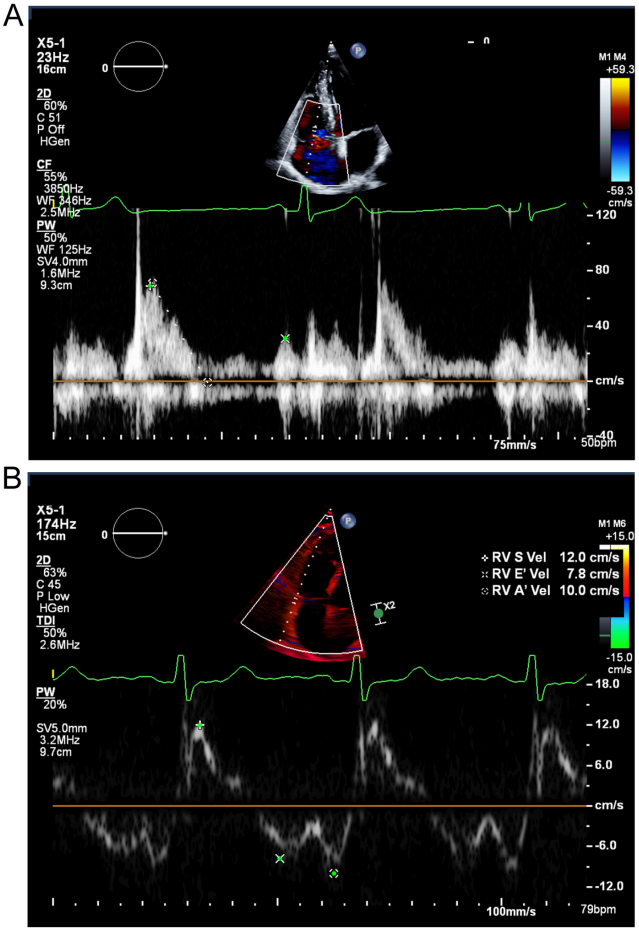

Figure 1
(A) Top pane shows the measurement of tricuspid valve E velocity by pulsed-wave Doppler in an apical four-chamber view where the inflow should be well aligned (parallel) with the Doppler beam, (B) bottom pane shows the measurement of tricuspid lateral annular e′ velocity using tissue Doppler imaging in the same view.

a perceived lack of published evidence concerning RV filling pressures (RV-E/e′) may contribute to low awareness in the echocardiography community.

Hence, the aims of this article are to systematically and critically review the currently available evidence regarding RV-E/e′ for predicting RAP, to advise the reader about pathologies or clinical situations where validity is supported, refuted or contentious and to make recommendations about further research which could improve applicability and adoption in clinical practice.

Systematic review methodology

Titles and abstracts in the EMBASE, MEDLINE, CINAHL and AMED databases were searched using the phrases;

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'e/e'', 'e:e'', 'e/e(a)', 'e:e(a)', 'e/ea', 'e/em', 'e:em', 'right', 'filling pressure*' and 'right atri* pressur*', plus appropriate medical thesaurus terms. In EMBASE, these terms were; 'Doppler echocardiography', 'Heart right atrium pressure', 'Heart catheterization' and 'Tricuspid valve'. In MEDLINE, terms were; 'Ultrasonography, Doppler', 'Ventricular function, right', 'Tricuspid valve', 'Atrial pressure', and 'Cardiac catheterization'. In CINAHL, terms were; 'Echocardiography', 'Atrium pressure', 'Ventricular pressure', 'Heart catheterization', and 'Tricuspid valve'. In AMED, terms were; 'Ultrasonography', 'Pressure', 'Catheterization', 'Heart valves' and 'Heart ventricle'.

The initial search was performed in September 2018 using the National Institute of Health and Care Excellence (NICE) Healthcare Databases Advanced Search (HDAS) platform. An overview of the search methodology and number of results is presented in Fig. 2; full strategy and initial results are available upon request. No filters were used. Initial inclusion criteria were reference to RV-E/e′ and performance of a RHC in the same subjects in the same article. Titles/abstracts of initial search results were manually filtered for inclusion (phase 1). Full versions of remaining articles were sought to confirm final eligibility for inclusion (phase 2) and to extract relevant data which may not have been in the abstract. Phase 2 inclusion criteria were measurement of RV-E/e′ by TTE, direct invasive measurement of RAP in the same subjects and assessment of the relationship between these two things. Articles which used surrogate markers of RAP such as central venous pressure or superior vena cava pressure, and conference abstracts, were excluded.

The subtle difference in phases 1 and 2 inclusion criteria was designed to prevent initial exclusion of relevant results where the relationship between RV-E/e′ and RAP was not the main focus of the paper and hence had not been explicitly mentioned in the title/abstract. References and citations of each remaining item were checked for any additional relevant articles.

A total of 1139 results were found which matched the initial search criteria. After deduplication, 791 unique results remained. After phase 1 filtering, 18 results remained. Full versions of all original articles were obtained and once assessed using phase 2 criteria, 11 original articles were deemed to have appropriately investigated the relationship between RV-E/e′ and RAP. Five additional items fulfilling the phase 2 inclusion criteria were found in citations or references of phase 2 results. Grey literature sources were searched by our institution's library staff with zero results. One further original article (11) was known about by the authors and

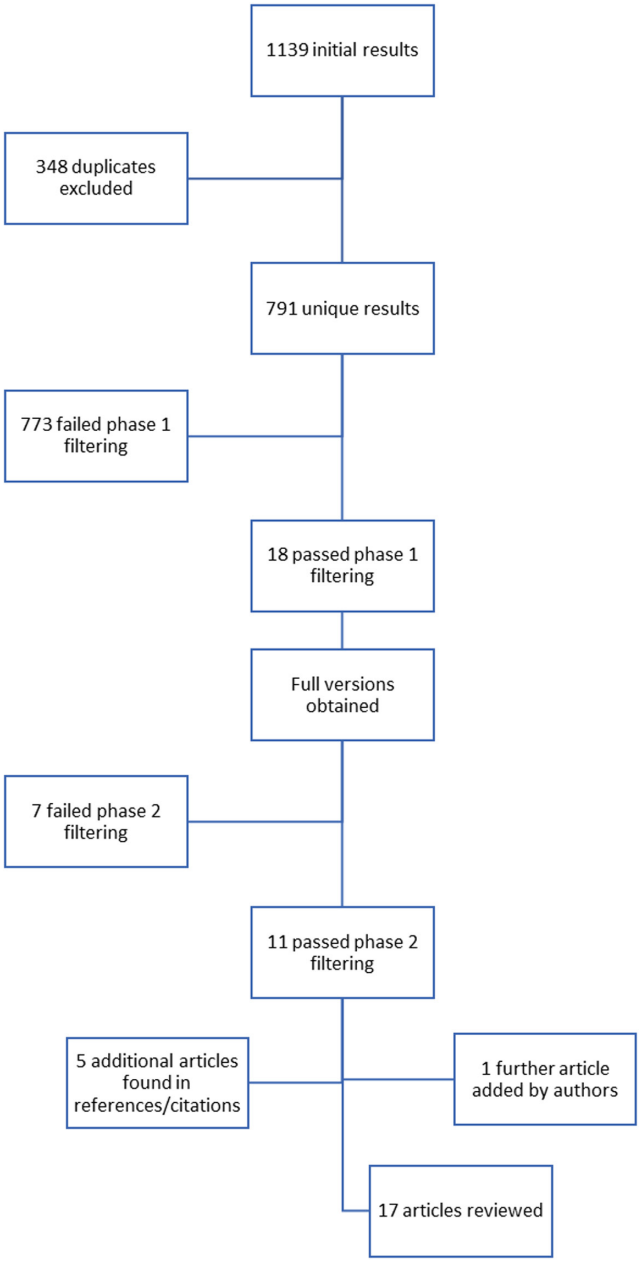

Figure 2
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) search methodology flow chart.

included. This produced a final total of 17 articles. Of these, zero studied animals and one was primarily written in Indonesian (12) but the abstract was in English and the remaining text was translated.

Results are discussed in groups by clinical theme to allow the reader to appreciate supporting/contradictory evidence. Emphasis is placed upon studies which report appropriate statistical tests (Table 1) such as receiver operating characteristic (ROC) and Bland–Altman

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Table 1 Summary of evidence concerning ability of RV-E/e′ to predict invasively measured right atrial pressure in humans in studies with appropriate statistical methodologies.

First author, year of publication	Number of data pairs	Population characteristics	RHC and echo timing	Bland–Altman analysis	Regression equation
Utsunomiya *et al.* 2009	50	IPAH = 23, chronic thromboembolic pulmonary hypertension = 14, Connective tissue disease = 11, other = 2	All <24 h	Bias ~0 mmHg. LofA ~5.6 to ~−5.6 mmHg (plot presented but values not given)	RAP = (1.44 × E/e′) − 1.54
Said *et al.* 2012	50	ACS = 21, Dilated cardiomyopathy = 15, CKD = 13, Ao-IE = 1	Simultaneous	Bias 0.21 mmHg. LofA 5.3 to −4.9 mmHg	RAP = (1.69 × E/e′) + 1.24
Nageh *et al.* 1999	62	CAD = 28, AoAnneur = 9, AVR = 6, CHF = 6, HTN = 1, PVD = 1, normal = 11	Simultaneous	Bias 0.3 mmHg. LofA 7.6 to −7.0 mmHg	RAP = (1.7 × E/e′) + 0.8
Sundereswaran *et al.* 1998	38	Heart transplant adults, mean age = 53 years, donor heart age = 30 years	Not given	Bias 0 mmHg. LofA 2.9 to −2.9 mmHg	RAP = (1.76 × E/e′) − 3.7
Hanifah *et al.* 2010	50 from 16 patients	12 Acute decompensated heart failure, 4 ACS. 6 on ventilation	Not given	Bias 0.01 mmHg. LofA 3.5 to −3.5 mmHg	RAP = (1.66 × E/e′) + 2.96
Sade *et al.* 2007	101 from 89 patients	On Cardio-thoracic intensive care unit. 55% had coronary artery disease	All Simultaneous	Not reported	RAP = (1.62 × E/e′) + 2.13
	Subgroup of 59	Without cardiac surgery		Bias 0.14 mmHg. LofA 6.0 to −5.7 mmHg	RAP = (1.84 × E/e′) + 1.26
	Subgroup of 42	Recent cardiac surgery (<5 days post)		Bias 2.0 mmHg. LofA 11.2 to −7.2 mmHg	RAP = (1.003 × E/e′) + 4.6
Tsutsui *et al.* 2014	123 from 71 patients	Acute decompensated heart failure	Immediately pre echo	Bias 0.89 mmHg. LofA 16.6 to −15.9 mmHg	Not given

ACS, acute coronary syndrome; AoAnneur, aortic aneurysm; Ao-I.E., aortic valve infective endocarditis; AVR, aortic valve replacement; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; Echo, echocardiogram; HTN, systemic hypertension; IPAH, idiopathic pulmonary arterial hypertension; LofA, limits of agreement; PVD, peripheral vascular disease; RAP, right atrial pressure; RHC, right heart catheterisation; RV-E/e′, right ventricular ratio of peak early diastolic blood velocity to peak early diastolic tissue velocity of tricuspid lateral annulus.

analyses. ROC analysis is a common way of assessing the diagnostic ability of a test to classify subjects into subgroups (13). A test parameter threshold (e.g. RV-E/e′ > 6) is found by the analysis, which is optimal for predicting result characteristics (e.g. raised RAP). The resulting sensitivity, specificity and area under the ROC curve are often reported, where a higher number indicates better diagnostic ability.

A highly informative statistical methodology for assessing a technique against an established or gold-standard technique (i.e. RV-E/e′ estimated RAP vs invasively measured RAP) is Bland–Altman analysis (14). This quantifies the accuracy (by calculation of bias, which is the mean of the differences between pairs of values) and precision (by calculation of the limits of agreement, between which the majority of the differences between techniques lay) of the technique.

Results

Results obtained by our systematic search pertained to a variety of clinical situations, pathologies and patient demographics; the relationship between RV-E/e′ and invasively measured RAP varied accordingly. Diseases where RHC are routinely performed clinically, such as in pulmonary hypertension (PH) and heart failure/transplantation, were prevalent amongst results (9 out of 17, 53%).

Valvular disease

Utsunomiya *et al.* (15) found that in 50 patients with a range of aetiologies of PH, RV-E/e′ was positively correlated with mean RAP (mRAP) ($r=0.80$, $P < 0.001$). Upon ROC analysis, an RV-E/e′ > 7.3 predicted mRAP > 10

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mmHg with 87% sensitivity, 97% specificity and area under the curve (AUC) of 0.92, suggesting good diagnostic utility for assessing RAP. Bland–Altman analysis showed trivial bias of almost zero between RV-E/e′ estimated RAP and invasively measured mRAP, indicating good accuracy. However, the precision was poor, evidenced by wide limits of agreement (~5.6 to ~−5.6 mmHg) relative to the absolute values of mRAP (mean 6 ± 5 mmHg). Of note, the positive correlation between RV-E/e′ and RAP remained regardless of; PH subtype, RV systolic function (normal or reduced) and severity of tricuspid regurgitation (TR) (severe TR was present in 50%).

Only two other results were found by our systematic search that investigated the validity of TTE estimates of RV filling pressure in the context of valvular heart disease. Hayabuchi *et al.* (16) found no significant correlation between RV-E/e′ and mRAP in 25 asymptomatic paediatric repaired Tetralogy of Fallot patients (r = 0.263, P = 0.11). No ROC or Bland–Altman analyses were presented.

Yildirimturk *et al.* (17) also reported no significant correlation between RV-E/e′ and RAP in a group of 39 patients with varying degrees of rheumatic mitral stenosis. Unfortunately, the statistical analysis values were not reported for this relationship which reduces the credibility of this piece of evidence.

Altered RV systolic function

As well as Utsunomiya *et al.* (15) who found a positive relationship between RV-E/e′ and RAP, two other papers also present data concerning this relationship in the context of normal and reduced RV systolic function. Nageh *et al.* (18) took a mixed cohort of 62 patients with common cardiac diseases (largest subgroup being coronary artery disease) and showed that the correlation between RV-E/e′ and mRAP was identical between the subgroup with normal RV function and the group as a whole (r = 0.75, P < 0.001). The relationship strengthened slightly in the subgroup with reduced RV systolic function (r = 0.80, P < 0.001). Upon ROC analysis, RV-E/e′ ≥ 6 predicted mRAP > 10 mmHg with 79% sensitivity and 73% specificity, although no AUC value was given. When the invasive and TTE methods were compared with Bland–Altman analysis, there was good accuracy of RV-E/e′ (bias = 0.3 mmHg) however poor precision (limits of agreement 7.6 to −7.0 mmHg) which reduces the clinical utility of RV-E/e′ in assessing individual patients.

In a slightly larger study of 101 pairs of data from 89 patients on a cardiothoracic intensive care unit (55% of whom had coronary artery disease), Sade *et al.* (19) demonstrated positive correlations between RV-E/e′ and mRAP in patients with normal RV systolic function (r = 0.59, P < 0.001), reduced RV systolic function (r = 0.83, P < 0.001), ventilated patients (r = 0.77, P < 0.001), those not ventilated (r = 0.68, P < 0.001) and those whom had not had recent (<5 days) cardiac surgery (r = 0.83, P < 0.001). Unfortunately, no ROC nor Bland–Altman analyses were performed for the normal/reduced RV systolic function groups.

Cardiac surgery

Perhaps not surprisingly, the subgroup of 36 patients who were recovering from recent cardiac surgery in the study by Sade *et al.* (19), exhibited an attenuated, but still significant, the relationship between RV-E/e′ and mRAP (r = 0.41, P = 0.007). In the non-surgical cohort, ROC analysis revealed that an E/e′ > 4.0 predicted a mRAP > 10 mmHg with 88% sensitivity, 85% specificity and AUC = 0.93. Upon Bland–Altman analysis in this subgroup, accuracy was good (bias = 0.14 mmHg) however precision was again poor (limits of agreement 6.0 to −5.7 mmHg) given that mRAP = 9 ± 5 mmHg. Accuracy and precision were worse in the recent cardiac surgery subgroup.

In contrast to the findings of Sade, Michaux *et al.* (20) found no significant association between the same two parameters in a group of 44 anaesthetised ventilated peri-operative coronary artery bypass graft patients (r = −0.11, P = 0.48). Unfortunately, no ROC or Bland–Altman analyses were presented by the authors, so the significance and strength of their finding is unclear.

Cardiac disease and heart failure

Hanifah *et al.* (12) discovered a positive correlation between RV-E/e′ and mRAP in patients on a cardiovascular care unit (r = 0.728, P < 0.001). In total, 50 pairs of RHC/TTE data were analysed from 16 patients (12 with acute decompensated heart failure and four with acute coronary syndromes). Six patients were on mechanical ventilation. Unfortunately, the time difference between RHC and TTE was not stated. RV-E/e′ > 3.95 predicted mRAP > 10 mmHg with 73% sensitivity, 71% specificity and AUC = 0.724. Bland–Altman analysis showed good accuracy of RV-E/e′ (bias = 0.01 mmHg) but moderate precision (limits of agreement 3.5 to −3.5 mmHg).

Patel *et al.* (11) presented data from 40 acutely decompensated heart failure patients where RV-E/e′ did not significantly correlate with mRAP (r = 0.09, P = 0.612).

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No ROC or Bland–Altman analyses were reported. This study had a good spread of RAP; mRAP = 11 ± 5 mmHg, range 2–22 mmHg, n = 18 (45%) had mRAP > 10 mmHg.

Further evidence from the setting of acute decompensated heart failure comes from Tsutsui *et al.* (21) who analysed 123 pairs of RHC/TTE data from 71 patients. The RHC was immediately before the TTE. A weak correlation was found between RV-E/e′ and RAP (r = 0.19, P = 0.04) but no ROC analyses were reported. Bland–Altman analysis showed modest accuracy (bias = 0.9 mmHg) but very poor precision (limits of agreement 16.6 to −15.9 mmHg).

Naderi *et al.* (22) presented data from 30 heart failure patients with reduced ejection fraction. A total of 22 had dilated cardiomyopathy, 8 ischaemic cardiomyopathy and all were in sinus rhythm. No relationship was found between RV-E/e′ and mRAP (r = 0.081, P = 0.676) and there were no ROC or Bland–Altman analyses.

A recent study of 30 patients with left ventricular assist devices by Frea *et al.* (23) found a positive correlation between RV-E/e′ and RAP acquired within 60 min of each other (r = 0.633, P < 0.001). ROC analysis showed RV-E/e′ predicted RAP > 10 mmHg with 75% sensitivity, 89% specificity and AUC = 0.77 suggesting potential utility in this clinical situation. A Bland–Altman analysis was not provided.

A study utilising simultaneous TTE and RHC data was published by Said *et al.* (24). In 50 patients with various diseases (largest subgroup being acute coronary syndrome), they demonstrated a positive correlation between RV-E/e′ and RAP (r = 0.84, P < 0.001). Upon ROC analysis, RV-E/e′ > 4.5 predicted RAP > 10 mmHg with 89% sensitivity, 100% specificity and AUC = 0.95. Upon Bland–Altman analysis, accuracy was good with a trivial bias of 0.21 mmHg but precision was again poor (limits of agreement 5.3 to −4.9 mmHg), given a median RAP = 14 mmHg in the cohort.

Patients with acute RV myocardial infarction were the focus of a study by Ivey-Miranda *et al.* (25). Their cohort of 45 patients had RHC immediately prior to TTE and they found that RV-E/e′ was not significantly elevated in the 21 patients with a RAP ≥ 13 mmHg compared to the 24 patients with a RAP < 13 mmHg (P = 0.052).

Heart transplantation

Three results found by our systematic search concerned patients post heart transplant. Sundereswaran *et al.* (26) studied 38 adult heart transplant recipients (mean age 53 years, mean age of donor heart 30 years). A positive correlation was observed between RV-E/e′ and RAP (r = 0.79, no P value reported). On ROC analysis a RV-E/e′ > 8.0 predicted RAP > 10 mmHg with 78% sensitivity and 85% specificity (no AUC given). Bland–Altman analysis revealed excellent accuracy (bias = 0.0 mmHg) but poor precision (limits of agreement 5.8 to −5.8 mmHg).

The remaining results investigating heart transplant patients were unsupportive of RV-E/e′ being useful in predicting RAP. Goldberg *et al.* (27) examined 52 paediatric heart transplant recipients with a mean age of 12 years and a mean time since transplant of 4 years. RHC was undertaken immediately post-TTE and showed no correlation between RV-E/e′ and RAP (r = 0.04, P = 0.79). The authors did note however that on dichotomous analysis, those with RV-E/e′ > 10 had higher RAP than those with RV-E/e′ < 10 (P = 0.04). No ROC nor Bland–Altman analyses were undertaken.

Savage *et al.* (28), investigated paediatric heart transplant recipients from whom 63 pairs of RV-E/e′ and RAP data were available. There was a weak relationship between RV-E/e′ and RAP (r = 0.31, P = 0.01) with an AUC of only 0.62, suggesting that RV-E/e′ was not so useful for predicting RAP in their patients. Sensitivity, specificity and Bland–Altman analysis were not presented. It was not clear from how many individual patients these 63 data pairs came from, but the whole paper examined 142 pairs from 24 patients, where the median patient age was 11 years and the median time since transplant was 4 months.

Pulmonary hypertension (PH)

In addition to the previously discussed findings of Utsunomiya *et al.* (15), evidence about the relationship between RAP and RV-E/e′ in the setting of PH also comes from the study by Tsutsui *et al.* (21), where the cohort had a mean pulmonary artery pressure of 36 ± 10 mmHg, presumably due to the acute decompensated heart failure which they were reported to have. Unsurprisingly given both left and right heart pathophysiology, and as described above, a weak correlation was found between RV-E/e′ and RAP, accuracy was modest and precision poor. In a study of paediatric PH, due to intracardiac shunt, Cevik *et al.* (29) reported no association between RV-E/e′ and RAP (r = −0.065, P = 0.737). TTE and RHC measurements were made simultaneously but no ROC or Bland–Altman analyses were performed. The mean RAP was 4.8 ± 2.2 mmHg suggesting that most patients had a non-elevated RAP.

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Atrial fibrillation

Atrial fibrillation (AF) is a condition which may alter RAP through structural, functional and electrical alterations in the atrial myocardium. Despite this, our systematic search produced very little evidence about the relationship between RV-E/e′ and RAP in the setting of AF. The paper already discussed by Patel *et al.* (11) included ten patients (25% of total) who were in AF, however, subgroup analysis was not performed upon these.

Whilst not presenting specific r/*P* values, the paper already discussed by Yildirimturk *et al.* (17) did mention that they could not find a significant relationship between RV-E/e′ and RAP in the AF subgroup (n = 17) from their study. Furthermore, the previously discussed study of Tsutsui *et al.* (21) did include nine patients with AF in their overall analyses (which found a significant weak association between RV-E/e′ and RAP), however, this only represented 13% of their total cohort and they did not perform subgroup analysis.

Prediction of adverse cardiac events

Only one of the studies found by our systematic search took their investigations a step further and assessed the ability of RV-E/e′ to predict cardiac events. In the study of 50 PH patients by Utsunomiya *et al.* (15), 19 patients (38%) had an adverse cardiac event (cardiac death or hospitalisation due to RV failure) during a mean 14 ± 1-month follow-up. In multivariate analysis, RV-E/e′ was predictive of cardiac events with a hazard ratio of 1.3. ROC analysis showed that RV-E/e′ > 6.8 had 42% sensitivity, 97% specificity and AUC=0.71 for predicting cardiac events. Kaplan–Meier analysis showed that those with RV-E/e′ > 6.8 at baseline had significantly worse outcomes than those with a lower ratio.

Discussion

Valve disease

There was a lack of evidence concerning the relationship between RAP and RV-E/e′ in valvular heart disease. The findings of Utsunomiya *et al.* (15) suggest that RV-E/e′ estimation of RAP is accurate in those with severe TR, a cohort where the estimation of right-sided pressures was previously considered inaccurate (30, 31). Although the statistical analyses suggest that RV-E/e′ is a useful predictor of RAP in this cohort, the significant time-frame of up to 24 h between invasive measurement and TTE estimate may be a limitation of these finding's reproducibility.

Significant weaknesses of the study by Hayabuchi *et al.* (16) were their small cohort size of 25 data pairs and the timeframe between RHC and TTE of up to 7 days. In the study of mitral stenosis patients by Yildirimturk *et al.* (17), 44% of patients were in atrial fibrillation which may have confounded matters. There was also a lack of rigorous statistical analysis in their paper. Given the overall weakness of evidence, and the wide spectrum of possible valvular heart diseases, RV-E/e′ remains unproven in these patients. Further investigation into the effects of valvular disease upon the ability of RV-E/e′ to predict RAP is warranted.

RV function

All three papers examining RAP and RV-E/e′ in altered RV systolic function found a positive association. A strength of the study by Sade *et al.* (19) over others reviewed is that all echo and RHC measurements were made simultaneously, thereby removing the potential error associated with variations in fluid status, cardiac haemodynamics and patient position (supine vs semi-supine). The two other studies in this area (Utsunomiya *et al.* (15) and Nageh *et al.* (18)) suffered from small sample sizes. Hence, there is a suggestion that the relationship between RV-E/e′ and RAP may be strengthened when RV systolic function is reduced, although the reason for this is unclear.

Cardiac surgery

Synthesising the findings concerning cardiac surgical patients of Sade *et al.* (19) and Michaux *et al.* (20), there appears to be no strong evidence to support the use of RV-E/e′ in the cardiac surgery (non-transplant) peri-operative or acutely post-operative setting to predict RAP. Reasons for a lack of relationship may include structural alterations caused by the pericardium being breached, haemodynamic alterations caused by altered fluid status and haemodynamic alterations due to pharmacological interventions. Further research into the individual and combined effects of anaesthesia, cardio-supportive drugs and mechanical ventilation would be helpful here.

Cardiac diseases and heart failure

Findings in the setting of common cardiac diseases and heart failure were equivocal, however, detailed appraisal of the articles revealed many possible reasons for this. Caution should be taken in the interpretation of the findings of Said *et al.* (24) as no subgroup analysis was presented,

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yet the underlying medical conditions were quite different (acute coronary syndrome, dilated cardiomyopathy, chronic kidney disease on haemofiltration and infective endocarditis).

Several studies, such as that of acute decompensated heart failure by Tsutsui *et al.* (21) found poor precision of RV-E/e′ to estimate RAP. For their particular study, that may be partly explained by the majority of patients ($n = 55$, 77%) having a pacemaker, implantable cardioverter defibrillator, cardiac resynchronisation therapy, or a combination of. It is interesting to note that 67 patients (94%) had PH and RAP was >10 mmHg in 71% of cases.

The study of acute RV infarction by Ivey-Miranda *et al.* (25) used a cut-off of 13 mmHg for defining raised RAP, whereas the other studies included in this review applied the widely used cut-off of 10 mmHg to distinguish normal from raised RAP. This is likely to have affected the correlation and statistical significance of the Ivey-Miranda *et al.* results. Data interpretation was further limited by the absence of correlation coefficient, ROC and Bland–Altman analyses within the report.

Therefore, the data reviewed does not strongly support the validity of RV-E/e′ for assessing RAP in patients with common cardiac diseases or heart failure. However, a commonality of the papers reviewed in this section was the lack of rigorous statistical analysis or inappropriate statistical interpretation. Future research must combine the assessment of agreement between invasive/TTE methods with an assessment of the ability of RV-E/e′ to predict RAP across a broad range of values. We advise against simply assessing the direct correlation between RV-E/e′ and invasive RAP, and instead advocate the analysis of dichotomous cut-offs of RV-E/e′ for predicting RAP > 10 mmHg, in a way which mirrors left ventricular filling pressure assessment.

Heart transplant

Post heart transplant studies reviewed in this article were heterogeneous in terms of subjects and methodologies. Limitations of the evidence presented by Sundereswaran *et al.* (26) were: a variable time since transplantation (8 within 1 week of surgery, 22 < 1 year, 28 > 1 year), the authors did not state the time interval between TTE and RHC, reported statistics were incomplete, and left-sided systolic function was highly variable (ejection fraction 23–70%). Despite these, they did report support for predicting RAP with RV-E/e′.

Potential confounding was introduced to the results of the Savage *et al.* (28), investigation into paediatric heart transplant recipients through the varied post-transplant period of 5 days to 10 years, and through the variation in patient age of less than 6 months to 21 years old. Over such a large time period, cardiac remodelling and patient growth would occur that may affect the relationship between RV-E/e′ and RAP. This evidence is further limited by the narrow range of pressures across the cohort; median RAP was 7 mmHg, 25th percentile 5 mmHg and 75th percentile 10 mmHg. This makes differentiation of the relationship between RAP and RV-E/e′ difficult as you need relatively higher statistical power to determine if variation in RV-E/e′ is due to error or a true relationship.

The Goldberg *et al.* (27) study of paediatric heart transplant recipients was strengthened by the short time frame in between RHC and TTE, however only seven of their patients had a RV-E/e′ > 10, so their findings must be interpreted with care due to small subgroup size. No ROC or Bland–Altman analyses were undertaken, which was a consistent feature of the results in this review that did not find a relationship between RV-E/e′ and RAP.

We advocate the use of Bland–Altman analysis for comparison of echocardiographic and invasive assessment of RAP. The overall poor precision but good accuracy of RV-E/e′ in the seven studies which performed Bland–Altman analysis leads us to conclude that RAP estimated by RV-E/e′ may be best suited to population studies rather than to calculating specific values of RAP in individual patients.

Overall, it is hard to draw firm conclusions from the published literature about the utility of RV-E/e′ for predicting RAP in the setting of heart transplant; there were incomplete statistical analyses and large variations in patient demographics, methodology and time since transplant. Well-powered studies utilising multiple statistical techniques in more homogeneous subgroups of the heart transplant population would be well placed to shed further light upon the relationship between RV-E/e′ and RAP.

Pulmonary hypertension

The three studies examining patients with PH all had very different cohort characteristics (pre-/post-capillary PH, adult/paediatric, etc.) which may partly explain their contradictory findings. It remains unclear if RV-E/e′ is helpful in predicting RAP in this group where accurate non-invasive estimation would massively help improve estimates of pulmonary artery pressures. Further research should examine RV-E/e′ across well-powered homogeneous subgroups of PH and across a wide range of RAP with thorough statistical analyses.

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Atrial fibrillation

Being the most common sustained atrial arrhythmia, atrial fibrillation is a frequently encountered complication in many of those for whom evaluation of RAP is warranted. Knowledge of whether RV-E/e′ is valid to predict RAP in AF, and evidence to suggest if it modulates the predictive ability of RV-E/e′ in those with other cardiovascular conditions, should form the basis of future work. This situation should be investigated further with large prospective studies of patients with isolated AF, using rigorous methodology such as obtaining measurements at held end-expiration and averaging a suitable number of cardiac cycles to create a high-quality evidence base.

Prediction of adverse cardiac events

Regarding the ability of RV-E/e′ to predict adverse cardiac events, and given that there was only one piece of evidence concerning this found by our search, future work should aim to investigate an optimal cut-off for event prediction, examine if RV-E/e′ remains prognostic in other disease states and query if RV-E/e′ is linked to outcomes over other time frames.

Conclusions

Numerous dual studies of invasive right-atrial haemodynamics and right-heart Doppler echocardiography exist. Some have shown the echocardiographic parameter RV-E/e′ to be useful for predicting raised or normal RAP in a dichotomous fashion across different pathophysiological states, however other pieces of evidence were found which do not support its clinical accuracy in individual patients. Some situations have been shown to maintain or augment the relationship (e.g. reduced RV systolic function and tricuspid regurgitation) whilst others suggest that RV-E/e′ is not valid to predict RAP in their presence (e.g. acute decompensated heart failure and rheumatic mitral stenosis).

Key features of the reviewed literature were heterogeneous subject groups/characteristics and limited statistical analyses, with a lack of ROC analysis for assessing the predictive ability of RV-E/e′ and a lack of Bland–Altman analysis for assessing the accuracy and precision of RV-E/e′ for estimating RAP being the main methodological shortcomings.

Recommendations for future research have been given: new evidence in this area may help to increase applicability, awareness and adoption of RV-E/e′ amongst those performing and reporting cardiac ultrasound.

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