The utility of eccentricity index as a measure of the right ventricular function in a lung resection cohort

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Context: Right ventricular (RV) dysfunction occurs after lung resection and is associated with postoperative morbidity. Noninvasive evaluation of the RV is challenging, particularly in the postoperative period. A reliable measure of RV function would have value in this population. Aims: This study compares eccentricity index (EI) obtained by transthoracic echocardiography (TTE) with cardiovascular magnetic resonance (CMR) determined measures of RV function in a lung resection cohort. CMR is the reference method for noninvasive assessment of RV function. Design and Setting: Prospective observational cohort study at a single tertiary hospital. Materials and Methods: Twenty-eight patients scheduled for elective lung resection underwent contemporaneous TTE and CMR imaging preoperatively, on postoperative day (POD) 2 and at 2-month. Systolic and diastolic EI was measured offline from anonymized and randomized TTE and CMR images. Statistical Analysis: Bland-Altman analysis was performed to determine agreement between EITTE and EICMR. Changes over time and comparison with CMR determined RV ejection fraction (RVEFCMR) was assessed. Results: Bland-Altman analysis showed a negligible mean difference between EITTE and EICMR, but limits of agreement were wide (SD 0.24 and 0.28). There were no significant changes in EITTE and EICMR over time (P > 0.35). We found no association between EITTE with RVEFCMR at all-time points (P > 0.22). Systolic and diastolic EICMR on POD 2 demonstrated moderate association with RVEFCMR (r = −0.54 and r = −0.59, P ≤ 0.01). At 2-month, only diastolic EICMR correlated with RVEFCMR (r = −0.43, P = 0.03). There were no meaningful associations between EITTE and EICMR with TTE-derived RV systolic pressure (P > 0.31). Conclusions: TTE determined EI is not useful as a noninvasive method of assessing RV function following lung resection.

Introduction

Lung cancer is the leading cause of cancer death worldwide,[1],[2] and in suitable cases, the best chance of cure is surgical resection. Lung resection, however, is associated with high rates of perioperative complications and significant long-term morbidity,[3] such as reduced cardiopulmonary function and exercise capacity.[4],[5],[6] These changes are poorly associated with postoperative lung function,[6],[7],[8] and the role of cardiac limitation, particularly right ventricular (RV) dysfunction, is increasingly recognized.[9],[10] Several studies have reported a deterioration in RV function following lung resection,[11],[12],[13] with peri-operative changes being associated with postoperative morbidity.[12],[13],[14],[15],[16] The previous work using cardiovascular magnetic resonance (CMR) has demonstrated a median relative decrease in RV ejection fraction (RVEF CMR) of 10.9% from baseline by postoperative day (POD) 2.[17] CMR is a reference method for noninvasive assessment of RV function, but unfortunately, the requirement for breath holds and transfer to an isolated CMR scanner mean its use in the immediate postoperative thoracic surgery patient is limited. A validated bedside alternative could be of significant clinical value.

Transthoracic echocardiographic (TTE) assessment of the RV, however, is challenging in this population; the difficulties of the RV's complex geometry, retrosternal position, and marked load dependence are compounded following thoracic surgery.[18],[19] Many of the conventional TTE parameters for assessing RV function are not valid in this population.[20] In comparison, the assessment of the left ventricular (LV) cavity is easier and more reliable; and therefore, a method of assessing RV function 'indirectly' from the LV (as with eccentricity index [EI]) may have value in this setting.

Excess RV volume and increased RV afterload result in deviation of the interventricular septum, deforming the circular cross-section of the LV.[21],[22],[23] EI, which can be measured using TTE or CMR, quantifies this septal shift occurring as a result of abnormal ventricular interactions. EI is defined as the ratio of two short-axis diameters, where one is parallel and the other perpendicular to the interventricular septum. This surrogate measure was first described on TTE images by Ryan et al . to distinguish between RV pressure and volume overload,[24] and has been further used for RV hemodynamic assessment in many other clinical settings,[25],[26],[27],[28],[29] though it has never been reported following lung resection.

This study compares TTE measured EI (EI TTE) against CMR-derived parameters in a lung resection population. If associated, we hypothesized that EI TTE might have utility as an easily derived measure of RV function in this population. Changes in CMR-derived EI (EI CMR) and the association between EI, RVEF CMR, and RV systolic pressure (RVSP) over the same period were also explored.

Materials and Methods

This study was approved by the West of Scotland Research Ethics Committee (13/WS/0055), April 16, 2013.

This was an a priori secondary endpoint of an observational cohort study using CMR and TTE to assess RV function after lung cancer resection. Patients attending for elective lung resection by thoracotomy and lobectomy were screened and approached for inclusion. Informed written consent was obtained from each patient following a full explanation about the purpose and nature of all procedures. Individuals with pregnancy, on-going participation in any investigational research which could undermine the scientific basis of the study, contraindications to CMR imaging, wedge/segmental/sublobar lung resection, pneumonectomy, isolated middle lobectomy, and thoracoscopic lung resection were excluded. Surgical technique was standardized to a single surgeon performing a posterolateral muscle-sparing thoracotomy with anatomically appropriate lymph node clearance. Anesthetic technique was standardized and included the use of thoracic epidural blockade for postoperative analgesia and a volatile agent for anesthetic maintenance.

Contemporaneous TTE and CMR imaging were performed preoperatively, on POD 2 and at 2-month follow-up. TTE image acquisition was performed on a Vivid E9 cardiovascular ultrasound (GE Healthcare, Chicago, United States) by band 7, the British Society of Echocardiography accredited cardiac physiologists, none of whom were involved in data analysis. The image acquisition was performed according to a standardized protocol incorporating all aspects required for a comprehensive standard echocardiogram.[30] CMR imaging (1.5 Tesla, Siemens Avanto, B17 Software, Siemens, Germany) was performed using ECG-gated fast imaging steady-state free precession cines (TrueFISP, Siemens) throughout. Methodological details of particular importance include standardized imaging parameters of repetition time, echo time, flip angle, voxel size, field of view = 4.3 ms, 1.2 ms, 60[degrees], 1.4 mm x 1.4 mm x 6 mm, 340 mm, respectively; 6 mm imaging slices were used with a 4 mm interslice gap. Short-axis imaging was performed during breath holds and initiated at the atrioventricular valve plane, identified from a horizontal long-axis view of the heart, and propagated sequentially to the cardiac apex to provide complete coverage of both ventricles.

All TTE and CMR images were anonymized and randomized prior to reporting. For each modality, all images were dually reported by the same author for the assessment of intraobserver variability. A subset of randomly selected images were reported separately by an additional coinvestigator for the assessment of interobserver variability.

EI TTE was determined from offline images using EchoPAC (GE Healthcare, Chicago, United States) software according to the method described by Ryan et al. [24] End-systole and end-diastole were identified by the smallest short-axis area and the peak of R wave, respectively [Figure 1]. Tricuspid regurgitant jet (TRJ) velocity was obtained by continuous wave Doppler from all available TTE views and measurements taken from the signal with the highest velocity. Care was taken not to overestimate the spectral envelope.[31] The pressure gradient across the tricuspid valve was estimated with the simplified Bernoulli equation. The right atrial pressure (RAP) was estimated from inferior vena cava (IVC) diameter; an IVC diameter ≤2.1 cm that collapses >50% with a sniff was given a value of 3 mmHg. An IVC diameter of ≥2.1 cm that collapses >50% with a sniff, or an IVC diameter of ≤2.1 cm that collapses <50% with a sniff, was given a value of 8 mmHg. An IVC diameter of >2.1 cm that collapses <50% with a sniff was given a value of 15 mmHg.[32] RVSP was determined as 4(TRJ velocity)2 + RAP.{Figure 1}

EI CMR was determined offline using the Argus analysis software (Siemens, Berlin, Germany). The original method described by Ryan et al .[24] was adapted for use in CMR images. The most basal short-axis image plane that showed full ventricular myocardial walls, no outflow tracts and no valves were identified.[27] End-systole and end-diastole were determined as planes with the smallest and largest short axis areas, respectively [Figure 2]. Papillary muscles were ignored, and a hypothetical line of the endocardial border was used. Care was taken to ensure the intersection of both short-axis diameters were perpendicular at the center of the LV cavity. EI has a normal value of 1, and any measurement >1 indicates a flattened interventricular septum. RVEF was determined by manual planimetry of short-axis images according to previously described methods.[33]{Figure 2}

Statistical analysis

Data were analyzed using SPSS Statistics version 22 (IBM, New York, United States). Reproducibility of EI measurements was assessed using the single measures intraclass correlation coefficient (ICC) for absolute agreement. All data were visually inspected and tested for normality using the Shapiro-Wilk test. Bland-Altman analysis was performed to assess the agreement between EI TTE and EI CMR. As CMR is the gold standard for the assessment of ventricular volumes, EI CMR was used as a reference instead of the mean of the two measurements.[34] Changes over time were assessed using one-way repeated measures analysis of variance or Friedman's test as appropriate to data distribution. The association between RVEF and RVSP was determined using Pearson's or Spearman's rank correlation coefficient as appropriate. A $P < 0.05$ was considered statistically significant.

Results

From September 2013 to August 2014, 28 patients were recruited. One patient was excluded from further participation in the study due to the unexpected discovery of an embedded piece of ferromagnetic material in the chest wall during preoperative scanning, meaning no usable images of the heart could be determined. There was no clinical sequela, but as the patient was unable to take any part in the main study, the patient was removed from all further analyses. The patient demographics are displayed in [Table 1]. Twenty-six patients underwent lobectomy or bilobectomy (incorporating the right middle lobe), and one patient required unplanned intraoperative conversion to pneumonectomy but is included in all analyses. Mean (standard deviation [SD]) time to 2-month follow-up was 55.9 (13.1) days.{Table 1}

Echocardiography was well tolerated with all 27 patients (100%) completing the preoperative protocol. Twenty-six patients (96.3%) completed the protocol on day 2 and 24 (88.9%) at 2 months. The one patient not scanned on POD 2 declined TTE imaging. Of the patients not completing the protocol at 2-month, two declined imaging and one was unwell at another hospital with a bronchopleural fistula. Six patients (one preoperative, four on POD 2 and one at 2-month) had inadequate images for assessment of EI due to inability to obtain mid-LV short-axis images or indiscernible endocardial borders.

CMR was well tolerated with all 27 patients (100%) completing the scan protocol preoperatively. Due to an administration error, one patient did not have short-axis images obtained, so it was not possible to calculate EI in this patient. Twenty-two (81.5%) patients completed the scan protocol on POD 2, with 24 (88.9%) completing the protocol at 2 months. Of the five patients unable to be scanned on POD 2, three declined, one was unwell with persistent air-leak requiring additional intercostal catheter drainage and MRI transfer was deemed unsafe, a final patient had an epidural catheter in situ that was not MRI compatible.[35] Of the three patients unable to complete the protocol at 2-month; one declined, one was an inpatient at another hospital with a bronchopleural fistula, and the third had a contraindication to MRI as a result of recent cataract surgery.

EI was calculated in all patients who completed the scanning protocol. There were good intraobserver and interobserver reliability for systolic EI TTE (ICC for absolute agreement; 0.88 and 0.82, respectively) and diastolic EI TTE (ICC; 0.97 and 0.96). Similarly, CMR measurements showed good intraobserver and interobserver reliability; systolic EI CMR (ICC; 0.89 and 0.84) and diastolic EI CMR (ICC; 0.98 and 0.83), respectively [Table 2].{Table 2}

Sixty-five paired (contemporaneously obtained CMR and TTE) measures of systolic EI and 66 paired measures of diastolic EI were available for analysis. There were no changes over time in systolic or diastolic EI measured by TTE and CMR [P > 0.35, Friedman's test, [Table 3]. Bland-Altman analysis using CMR as a gold standard [Figure 3] demonstrated a mean difference in systole of 0.07 with 95% limits of agreement of 0.54 and -0.40. In diastole, the mean difference was 0.00, and 95% limits of agreement were 0.54 and -0.54.{Table 3}{Figure 3}

Association between eccentricity index and right ventricular ejection fraction

There was no association between EI TTE, both during systole and diastole, and RVEF CMR at any time point [P > 0.22 for all, [Table 4]. On POD 2, there was moderate association between systolic and diastolic EI CMR and RVEF CMR [r = −0.54, P = 0.01 and r = −0.59, P = 0.004, respectively, [Figure 4]. At 2-month, there was moderate association between diastolic EI CMR and RVEF (r = −0.43, P = 0.03). There was no association between EI CMR and RVEF CMR preoperatively.{Table 4}{Figure 4}

Association between eccentricity index and right ventricular systolic pressure

Only systolic EI TTE on POD 2 demonstrated an association with RVSP (r = −0.55, P = 0.04). There was no association between EI TTE and RVSP preoperatively and at 2 months [Table 4]. There was no significant association between EI CMR and RVSP at any time point [P > 0.31 for all, [Table 4].

Discussion

This is the first study to describe the use of EI to assess RV function following lung resection. TTE derived EI showed no association with RVEF and hence is not suitable for routine perioperative assessment in this patient group. We hypothesize that this is partly due to the difficulty of obtaining clear acoustic window; local inflammatory response secondary to intraoperative manipulation of pulmonary ventilation and circulation can significantly reduce imaging quality by TTE. Furthermore, off-axis views can produce a falsely flattened septum, giving inaccurate measurements. With CMR, where image quality is better, and one can be confident in obtaining 'true' short-axis images, CMR determined EI was associated with RV function, on POD 2 and at 2-month. Although the mean bias between EI TTE and EI CMR was negligible, the limits of agreement were unacceptably large (SDs of 0.24 and 0.28, respectively), meaning no useful conclusions could be drawn. A validated noninvasive method of quantifying RV function in this population is yet to be elucidated.

The assessment of RV structure and function is an important aspect of the clinical management of patients with cardiopulmonary disease. The quantitative evaluation of the RV is challenging due to its complex geometry; it is roughly triangular, bounded by a thin free wall only one-sixth the mass of the LV. Its crescentic short-axis area, in addition to ill-defined heavily trabecularized endocardial surfaces, complicate the calculation of RV volume, and ejection fraction.

TTE is the main method for assessing RV function in clinical practice and offers the advantages of high availability, portability, low expense, and safety. The assessment of RV function by TTE is challenging; however, the lack of a reliable acoustic window means it is often difficult to visualize the full free wall of the RV myocardium. Consequently, there is a reliance on subjective assessment and the use of regional quantitative parameters to represent the function of the entire RV. The example include tricuspid annular plane systolic excursion (TAPSE), tissue Doppler-derived velocity, isovolumic myocardial acceleration, and speckle tracking RV strain/strain rate; many of these measures are useful in particular disease states and clinical settings but lack widespread validation.[19],[32],[36],[37],[38],[39] No echocardiographic measure of RV function has been validated in a lung resection population.[20]

Echocardiographic imaging of the LV is more reliable,[19] where the circular shape, thicker myocardium, and well-defined endocardial borders serve to overcome many of the challenges of RV echocardiography. The ability to reliably assess RV function indirectly by measuring the LV cavity would, therefore, have utility in all patient groups. This would be particularly true in the post lung resection population where postoperative changes including pneumothorax, intercostal catheters, lung collapse, surgical incisions, and pain, mean it is difficult to obtain high-quality TTE images. Of the six patients, where we were unable to obtain EI, four were on POD 2. In those patients, where imaging was possible, EI TTE showed excellent reproducibility with a high ICC for both inter- and intra-observer variability.

By assessing patients with RV dysfunction, in a cohort of 35 patients with 'RV overload' undergoing right heart catheterization, Ryan et al . demonstrated that systolic EI TTE was associated with RV pressure indices and diastolic EI TTE was associated with RV volumetric parameters.[24] Subsequent studies demonstrated that RV assessment with EI TTE is useful in patients with pulmonary arterial hypertension, in whom systolic EI TTE is significantly elevated.[40],[41] D'Alto et al . further described the ability of EI TTE to distinguish between precapillary and postcapillary pulmonary hypertension.[42] Our study found association between RVSP and EI TTE on POD2 only. The direction of this association, however, was in contrast to what we had hypothesized, revealing a negative association between RVSP and EI. This is also in contrast to previously described work where RV pressure overload was associated with higher EI.[24] We have no hypotheses offering biological plausibility for this finding; given this is a single finding which was inconsistent across time-point and obtained in a subset of just 14 patients, the potential for a-error is high. Thus, we feel this result must be treated with caution.

CMR overcomes some of the difficulties associated with the assessment of RV function and is the reference standard for noninvasive assessment of RV structure and function. It produces high-resolution images, unaffected by concomitant pulmonary disease and chest wall deformity, allowing accurate and reproducible quantification of RV volume, mass, and function.[19],[43] In patients with congenital heart disease, Yamasaki et al . demonstrated that systolic EI CMR was significantly associated with mean pulmonary artery pressure whereas diastolic EI CMR was associated with RV volumetric parameters (RVEF and RV end-diastolic volume).[29] Our study demonstrated similar association in patients undergoing lung resection; both systolic and diastolic EI CMR on POD 2 were associated with RVEF. The relationship of diastolic EI and RVEF persisted at 2 months but was not evident preoperatively. We hypothesize this relationship only exists postoperatively as a result of increased RV afterload occurring following lung resection.[12],[44]

Despite CMR being well tolerated in this cohort, its widespread use in this patient group is limited; first by availability and secondly by suitability in the immediate postoperative patient. CMR scanning requires transfer to isolated sites and the prolonged image acquisition time with breath holds in clinically unwell patients mean a validated bedside alternative would be desirable. TTE was well tolerated in this population with imaging being possible on all willing participants in the immediate post-operative period. Unfortunately, image quality was reduced on POD 2, and EI was unable to be calculated in some patients.

There are a number of limitations to our study. Despite being a priori analysis, this was a secondary endpoint of a larger study (using CMR to measure RVEF following lung resection [NCT01892800]) meaning statistical power could not be calculated. This study included a specific cohort of patients where perioperative cardiac imaging is inherently challenging; thus, we cannot comment from this study on the validity of EI on nonthoracic patients where image quality may be better. In addition, our study only included patients undergoing lung resection by open thoracotomy. There is a movement toward video-assisted thoracoscopic (VATS) surgery in the UK meaning the results may not be relevant for the wider lung resection population; though many of the challenges of postoperative mediastinal displacement, pneumothoraces, and intercostal catheters would also be applicable to a VATS cohort.

Conclusions

TTE determined EI is not a suitable method for noninvasive assessment of the RV following lung resection. CMR determined EI is a simple and reproducible measure of RV function, correlating with RVEF following lung resection. The difficulties of routine CMR use in this population mean this lacks clinical use in this population.

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Conflicts of interest

There are no conflicts of interest.

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