Ventricular mass index correlates with pulmonary artery pressure and predicts survival in suspected systemic sclerosis-associated pulmonary arterial hypertension

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Objective. The ventricular mass index (VMI) has been proposed as a diagnostic tool for the assessment of patients with suspected pulmonary hypertension (PH). We hypothesized that in patients with SSc it may predict the presence or absence of PH.

Methods. Details of all consecutive SSC patients undergoing MRI and right heart catheterization were collected prospectively. Subsequently, the VMI for all patients was calculated, and further baseline data were collected.

Results. Data for 40 patients, 28 of whom were diagnosed with PH at rest (PHREST), were analysed. VMI correlated strongly with mean pulmonary artery pressure (mPAP; r = 0.79). Using a VMI threshold of 0.56, positive predictive value (PPV) for PHREST was 88% and negative predictive value (NPV) was 100%. Using a threshold of 0.7, PPV was found to be 100% and NPV 53%. Echocardiographically obtained tricuspid gradient (TG) also demonstrated a strong correlation with mPAP. Two-year survival in patients with VMI <0.7 and ≥0.7 was 91 and 43%, respectively (P < 0.001).

Conclusion. VMI correlates well with mPAP in patients with SSC and may have a role in non-invasively excluding clinically significant PH in breathless SSc patients in whom echocardiographic screening has failed. Further study in larger groups of patients is justified.

Key words: Pulmonary hypertension, Systemic sclerosis, Magnetic resonance, Ventricular mass index, Prognosis.

Introduction

Pulmonary arterial hypertension (PAH) is a frequent complication of SSc, occurring in between 7.85 and 12% of the patients with limited cutaneous disease [1, 2]. Survival in historical studies was exceedingly poor, with a 1-year survival of 45% [3]. Several classes of medical therapy have been introduced into clinical practice over the last decade [4]. In spite of improvement in survival over recent years, the disease still has a relatively poor prognosis, with a survival after 3 years of ~50% being observed in recent observational studies [5, 6]. The early identification of patients with SSc-associated PH (SSc-PAH) is important to allow the prompt and appropriate introduction of targeted therapies. Screening programmes utilizing echocardiography and lung function testing have been adopted in some areas, although their impact on outcome remains unstudied [7]. In a large series, the tricuspid gradient (TG) measured using echocardiography was found to correlate only moderately, and the gas transfer (TGCO) weakly, with invasively measured pulmonary haemodynamics [8]. An additional reliable form of non-invasive assessment of pulmonary haemodynamics in patients with suspected SSc-PAH would be clinically useful.

MRI has been used extensively in patients with pulmonary hypertension (PH). It is non-invasive, involves no radiation and allows measurement of cardiac chamber volumes without the need for complex geometric assumptions. The ventricular mass index (VMI), being the ratio of the right and left ventricular end diastolic mass, was found to correlate strongly with the mean pulmonary artery pressure (mPAP) in a study involving 26 patients referred for investigation of suspected PH [9]. We therefore hypothesized that VMI may be helpful in the assessment of patients with suspected SSc-PAH.

Patients and methods

Haemodynamic and demographic details of all patients assessed at our unit for suspected SSc-PAH between January 2002 and January 2007 were prospectively recorded on a database. Patients were referred on the basis of echocardiography and/or gas transfer abnormalities suggestive of possible PH or on the basis of symptoms compatible with PH [10]. SSc had been diagnosed by the referring rheumatologist. If a new diagnosis of SSc was made in our unit, this was confirmed by a rheumatologist according to standard criteria [11, 12]. Hospital records of all patients who had undergone MRI were subsequently reviewed by R.C. to confirm the diagnosis and collect clinical data. Vital status on the censor date of 1 January 2008 was assessed using the hospital patient administration system. Date of diagnosis was taken as the date of the diagnostic right heart catheter. PH at rest (PHREST) was defined as an mPAP ≥25 mmHg at rest. PAH was diagnosed if the pulmonary capillary wedge pressure (PCWP) was ≤15 mmHg. If the mPAP was normal at rest but ≥30 mmHg on exercise, then exercise-induced PH (PHEX) was diagnosed. Right heart catheterization was performed using a balloon-tipped 7.5 Fr thermodilution catheter (Becton-Dickinson, USA).

MRI was performed on a 1.5 Tesla Eclipse scanner (Philips, The Netherlands) using a four channel-phased array chest receiver coil. A segmented spoiled gradient echo sequence was used with a phase encode view-sharing technique. Short axis cine images from the apex to the base of the ventricles were obtained (flip angle, 35°; slice thickness, 6 mm; field of view, 350 mm; and echo time, 3.8 ms). Echocardiography was performed by experienced echocardiographers using Powervision 6000 and 8000 machines (Toshiba, Japan). Multiple windows were used to obtain the best Doppler estimation of tricuspid regurgitant velocity (V). The TG was calculated using the modified Bernoulli equation (TG = 4V^2). Approval for the retrospective analysis of imaging techniques had been granted by the North Sheffield ethics committee.

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VMI calculation

One investigator (D.H.), who was blinded to the pulmonary haemodynamics, calculated left and right ventricular end diastolic masses using the method described by Katz et al. [13]. The ventricular epicardial and endocardial borders on each end diastolic short axis slice image were outlined (Fig. 1) using MASS MR analytical software V4.2 (Medis, The Netherlands). The interventricular septum was classified as part of the left ventricle. The myocardial volume for each slice was calculated by multiplying the area between these outlines by the slice thickness. The product of the sum total of the myocardial slice volumes for each ventricle and the density of myocardium (1.05 g/cm³) thus gave an estimate of right end diastolic ventricular mass (RVEDM) and left end diastolic ventricular mass (LVEDM). The VMI was calculated by dividing RVEDM by LVEDM [9]. In 10 patients, measurements were repeated by the same investigator to assess intra-observer variability and by a second investigator (N.W.) to assess inter-observer variability.

Statistical analysis

Analysis was performed by R.C. using the SPSS software package. Continuous data were expressed as mean ± s.d., and were compared using the independent t-test. Discrete data were compared using the χ² test. The relationship between ventricular mass measurements and pulmonary haemodynamics were assessed using Pearson’s test. Survival from date of investigation was assessed using the Cox regression and Kaplan–Meier methods. To ensure maximal reliability, correlations and calculation of predictive values for VMI were performed only on those patients whose MRI was performed ≤ 30 days before or after the diagnostic right heart catheterization. As the majority of patients underwent echocardiography over 1 month before right heart catheterization, correlation coefficients and predictive values of TG were analysed if echocardiography had been performed within 90 days of right heart catheterization, in keeping with previous studies [8]. Optimal diagnostic thresholds for VMI and TG were assessed using receiver operated characteristic (ROC) curves.

Results

Forty-two patients who were assessed for suspected SSc-PAH underwent MRI and right heart catheterization during the study period. In two patients, imaging (including echocardiography) strongly suggested an elevated left ventricular end diastolic pressure, with significant left ventricular hypertrophy and left-sided chamber enlargement. In these patients, VMI would have been an unsuitable method for non-invasively excluding PAH, as abnormalities in left ventricular mass and function would significantly affect its value. These two patients were therefore excluded from further analysis. Of the remaining 40 patients, 28 had PHREST whereas 12 patients had no evidence of PHREST; 7 of these did, however, have evidence of PHEx. A single patient with PHREST had an elevated PCWP. This patient did not have imaging suggestive of elevated left-sided pressures and was therefore included in the further analysis. The baseline characteristics of the analysed patients are shown in Table 1. There was no significant difference in the LVEDM of those patients with or without PH (119 ± 33 vs 139 ± 39 g, P = 0.10). Both the RVEDM (102 ± 34 vs 76 ± 27 g, P = 0.03) and VMI (0.89 ± 0.3 vs 0.55 ± 0.1, P < 0.001) were significantly elevated in those patients with PH.

In total, 180 SSc patients had been admitted for investigation of suspected SSc-PH during the study period. Initially, access to MR scanning was limited and so a significant number of investigated patients did not undergo MRI and thus could not be included in the present study. A decision to perform MRI was not influenced by the results of right heart catheterization as all patients were routinely booked, where possible, for both investigations. There was no statistically significant difference in age or pulmonary haemodynamics between those who did or did not undergo MRI.

Haemodynamic correlations of VMI

MRI had been performed within 30 days of right heart catheterization in 31 patients. VMI correlated strongly with both mPAP (r = 0.79, P < 0.001) and pulmonary vascular resistance (PVR; r = 0.80, P < 0.001), and moderately strongly with cardiac index (CI; r = −0.65, P < 0.001; Fig. 2A–C). The correlations between RVEDM and mPAP (r = 0.60, P < 0.001) and PVR (r = 0.44, P = 0.01) were weaker and there was no significant correlation of RVEDM with CI (r = −0.34, P = 0.06).

Diagnostic strength of VMI

VMI performed strongly as a diagnostic test for SSc-PH in the population under study. The area under the ROC curve for diagnosing patients with PHREST was 0.92 (Fig. 3A). The strongest VMI threshold determined using ROC analysis, balancing a high sensitivity with low false positive rate, was 0.56. This threshold had a sensitivity of 100%, specificity of 70%, positive predictive value (PPV) of 88% and a negative predictive value (NPV) of

FIG. 2. Correlation between VMI and (A) mPAP ($r = 0.79$, $P < 0.001$), (B) PVR ($r = 0.80$, $P < 0.001$) and (C) CI ($r = -0.65$, $P < 0.001$).

FIG. 3. ROC curve demonstrating strength of (A) VMI and (B) TG in diagnosing patients with PH$_{\text{REST}}$. 

\[ \text{AUC} = 0.92 \]

\[ \text{AUC} = 0.96 \]
100% for diagnosing PH\textsubscript{REST}. The diagnostic strengths of four thresholds of VMI (0.5, 0.56, 0.6 and 0.7) are shown in Table 2.

**Discussion**

This is the first study to assess the diagnostic utility of VMI in patients with suspected SSc-PAH. We found that in referred patients, on the basis of echocardiography and/or gas transfer abnormalities or symptoms suggesting a possible diagnosis of SSc-PAH, and who did not have imaging suggestive of significant left ventricular abnormalities, the VMI correlated strongly with both mPAP and PVR.

Our findings of a correlation between VMI and mPAP of $r = 0.79$ concur with those of Saba \textit{et al.} \[9\], who studied 26 patients undergoing investigation of possible PH and found a correlation of VMI and mPAP of $r = 0.81$ \[9\]. A subsequent study involving 44 heterogeneous patients with PH, however, found a weaker correlation between VMI and mPAP of 0.56 \[14\]. The reason for the differences in correlations observed between these two previous studies is not clear. Roeleveld \textit{et al.} \[14\] suggested that analysing two subgroups of patients (those with and without PH) may produce a good correlation, whereas the correlation within each subgroup may be far less. However, if only those patients with a final diagnosis of PH\textsubscript{REST} or PH\textsubscript{REST+EX} were analysed, the correlation between VMI and mPAP ($r = 0.66$, $P = 0.001$ and $r = 0.76$, $P < 0.001$) was still better than the one observed by Roeleveld \textit{et al.} Furthermore, the primary aim of the present article was to investigate whether VMI could be used to assess patients with suspected PH, and so correlations over the whole group of PH and non-PH patients were calculated. The distribution of mPAP within a group of patients is likely to have an impact on observed correlations. It is possible that the distribution of mPAP within the patients in the present study was different to that which would be seen in an unselected cohort of SSc patients.

In both the present study and the study by Saba \textit{et al.} \[9\], stronger correlation coefficients were observed between pulmonary haemodynamics and VMI than with RVEDM. VMI may correlate better with the degree of RV overload than RV measures in isolation, as relatively small variations in RV and LV masses within the population are partially corrected for.

We have also examined the potential of VMI as a diagnostic tool. We observed that in this study population, a VMI of $< 0.56$ excluded PH\textsubscript{REST} in 100% of cases, whereas a VMI of $\geq 0.7$ had 100% PPV for the diagnosis of PH\textsubscript{REST}. However, it must be acknowledged that the number of patients in the present study was relatively small, making firm conclusions on the predictive value of VMI difficult. In addition, these results pertain to a population where SSc-PAH is already suspected. It is interesting

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**Prognostic value**

When all patients ($n = 40$) with suspected SSc-PAH were analysed, 1- and 2-year survival was 91% for patients with a VMI $< 0.7$ compared with 65 and 43% in patients with a VMI $\geq 0.7$ (Fig. 4A; $P < 0.001$). The 1- and 2-year survival was 100% in patients with a VMI $< 0.56$ (the previously identified strongest diagnostic threshold), compared with 75 and 64% in patients with a VMI $\geq 0.56$ (Fig. 4B; $P = 0.017$).

**Table 2. Sensitivity, specificity, PPV and NPV of VMI and TG in diagnosing PH\textsubscript{REST}**

<table>
<thead>
<tr>
<th>VMI</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
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<td>$&lt; 0.5$ vs $\geq 0.5$</td>
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<td>50</td>
<td>81</td>
<td>100</td>
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<td>70</td>
<td>88</td>
<td>100</td>
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<tr>
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<td>70</td>
<td>87</td>
<td>88</td>
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<td>$&lt; 0.7$ vs $0.7$</td>
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<td>100</td>
<td>100</td>
<td>53</td>
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<tr>
<th>TG, mmHg</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
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<tr>
<td>$&lt; 30$ vs $\geq 30$</td>
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<td>40</td>
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**Fig. 4.** Survival from the date of MRI in patients with (A) VMI $> 0.7$ or $< 0.7$, (B) VMI $\geq 0.56$ or $< 0.56$. 
to note that 3-year survival of those patients with a VMI of <0.56 was 100%, with none of these patients receiving advanced therapies. This suggests that a practice whereby right heart catheterization is deferred in mildly symptomatic patients with a VMI of <0.56 and with a standardized clinical follow-up monitoring for symptomatic, functional or echocardiographic deterioration may be reasonable. Again, due to the number of patients studied, this conclusion must be interpreted with caution.

The role of echocardiography in the assessment of suspected SSc-PH has been investigated previously. Denton et al. [15] performed right heart catheterization to diagnose PH in 21 out of 33 patients with suspected SSc-PH, and found that TG correlated strongly with values obtained at right heart catheterization (r = 0.83). In a subsequent study of 137 patients with suspected SSc-PH, Mukerjee et al. [8] observed that the TG had only a moderate correlation with mPAP obtained at right heart catheterization (r² = 0.44). In the present study, we have reproduced the strong correlation between TG and invasively measured pulmonary pressures that was observed by Denton et al., and have found that this correlation was similar to that seen between VMI and mPAP.

Mukerjee et al. reported that whereas a TG >45 mmHg had a high PPV for diagnosing PH at rest or exercise (PHREST&EX), no lower threshold could be identified that could exclude PHREST&EX. Hsu et al. [16] recently compared non-invasive tests, including echocardiography and pulmonary artery diameter and maximal velocity, as assessed by MRI, with pulmonary haemodynamics. They observed that, using a TG threshold of >37 mmHg, false negatives for PHREST&EX were noted in 10/24 (42%) of the cases. The false negative rate for PHREST was lower, occurring in 4/24 (16%) of the cases. The MRI parameters measured by Hsu et al. performed poor as diagnostic tests than did TG, which may be due to the specific parameters chosen. In the paper by Roeleveld et al. [14] previously referred to, neither pulmonary artery area nor velocity correlated with mPAP, whereas the strongest predictor of pulmonary pressure was VMI.

As echocardiography is cheaper and more widely available than MRI, VMI cannot be recommended as a first-line screening tool for SSc-PAH for the majority of the patients. There are, however, certain situations where VMI may be especially indicated as a diagnostic tool. In a proportion of patients poor echo views are obtained, most commonly as a consequence of body habitus. In a review of 53 patients assessed at a local rheumatology institution for possible referral to our own unit, 34% of the patients could not have a TG measured at echocardiography [17]. In these cases, VMI may be helpful in assessing further the likelihood of SSc-PAH. MRI has a superior reproducibility to echocardiography [18], and so MRI parameters such as VMI may have more promise as surrogate markers of disease progression and response to therapy in both the clinical and research setting. MRI performed to assess VMI also provides an opportunity to assess other features such as intra-cardiac shunts, which may be of prognostic value, and myocardial enhancement abnormalities suggestive of possible myocardial fibrosis [19].

Wolferen et al. [20] have recently demonstrated that other parameters, such as end diastolic volumes, have superior prognostic value to ventricular mass in patients with PH. However, in their paper the prognostic strength of RVEDM and LVEDM (corrected for body mass index) but not the VMI, as defined in the present article, were analysed. Furthermore, to our knowledge, correlations of end diastolic volumes with invasively measured haemodynamics have not been reported. As we were primarily interested in the use of an MRI parameter in the assessment of patients with suspected SSc-PH, we therefore chose to investigate VMI.

There are several limitations to this study. The number of patients was relatively small and our data should therefore be viewed as preliminary. A single patient with pulmonary venous hypertension was included in the analysis. We were interested to find whether VMI could have a role in excluding PH, and so analysis was performed using an ‘intention to investigate further’ method. Excluding a single patient with an elevated wedge pressure least affected the sensitivity, specificity, PPV and NPV for a VMI of <0.56 (100, 70, 86 and 100%) or a TG of <40 mmHg (100, 70, 87 and 100%). As discussed earlier, patients with imaging suggestive of significant left-sided cardiac problems were therefore not analysed. Fast low-angle shot (FLASH) imaging was used to obtain the MRIs. If balanced steady state-free precession had been used instead, then a greater contrast between the myocardium and blood pool could have been demonstrated, which may have affected the calculated VMI [21].

Conclusion
We have demonstrated that in patients with suspected SSc-PAH, VMI correlates strongly with mPAP. Although superiority of VMI over TG as a diagnostic tool has not been demonstrated, it may have a role in non-invasively excluding clinically significant PAH in breathless SSc patients in whom echocardiographic screening has failed. Further study, involving larger numbers of patients in a screened population, to confirm this is warranted.

Rheumatology key messages
- VMI correlates well with pulmonary pressure in SSc patients.
- VMI may be useful for patients with suspected SSc-PAH in whom echocardiography is suboptimal.
- It may be appropriate to defer invasive investigations in such patients when VMI < 0.56.

Disclosure statement: The authors have declared no conflicts of interest.

References