Quantitative estimation of right ventricular hypertrophy using ECG criteria in patients with pulmonary hypertension: A comparison with cardiac MRI

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ABSTRACT

In patients with pulmonary arterial hypertension (PAH), right ventricular mass (RVM) correlates linearly with pulmonary artery pressure, and decreases with successful treatment. Accurate measurement of RVM currently requires cardiovascular magnetic resonance (CMR) imaging. We therefore tested the relationship between RVM and a simple, 12 lead ECG-derived value, the Butler-Leggett (BL) score. This has previously been validated in patients with RV hypertrophy (RVH) due to mitral stenosis. We also tested the diagnostic accuracy of the BL score in detecting RVH. The Scottish Pulmonary Vascular Unit database was reviewed retrospectively. Twenty-eight patients with PAH were identified, in whom CMR and ECG data had been recorded no more than 28 days apart. All had completed a comprehensive clinical assessment, including right heart catheterization. CMR-derived absolute RVM and RV mass index (RVMI=RV mass/LV mass) were correlated against BL score. The ability of this score to detect RVH was tested using 2 x 2 contingency tables. RVM and RVMI correlated with BL score (r=0.77, P<0.001 and r=0.78, P<0.001, respectively). A BL score >0.7 mV proved a highly specific but insensitive indicator of RVH, based on either absolute RVM (sensitivity 74%, specificity 100%) or a high RVMI (sensitivity 61%, specificity 100%). The BL score, which can be defined using a standard 12-lead ECG, correlates with RVM and RVMI in patients with PAH. A score >0.7 mV was a highly specific but insensitive indicator of RVH in these patients.

Key Words: ECG, magnetic resonance image, pulmonary hypertension, right ventricular hypertrophy

INTRODUCTION

In the normal adult heart, the right ventricle (RV) is a thin-walled, low-pressure pump that is poorly adapted to cope with a high afterload.[1] In patients with pulmonary arterial hypertension (PAH), elevated pulmonary vascular resistance (PVR) results in a rise in RV afterload. This typically occurs gradually, allowing a compensatory increase in RV mass (RVM), helping to maintain stroke volume and cardiac output. RVM is, therefore, an important measurement in PAH patients. Previous studies have shown that RVM decreases with successful treatment[2] and has a strong relationship with mean pulmonary artery pressure in PAH. This is true when RVM is recorded in

isolation,[3] but the correlation is more powerful when RVM is related to left ventricular (LV) mass in the same patient (known as RV mass index (RVMI)).[4]

The current "gold standard" method of directly measuring RVM is cardiovascular magnetic resonance (CMR) imaging. However, the high cost and limited availability of this technology restricts its clinical utility. We were interested in using the standard 12-lead ECG to describe RVM in PAH patients, given its clinical utility for this purpose in earlier

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studies. Al-Naamani et al.[5] used the ECG as a screening test for PAH; however, the criteria tested, including the dimensions of rightward and anterior QRS waveforms and QRS axis orientation, demonstrated insufficient levels of sensitivity and specificity. More recently, Henkens et al. used a vectorcardiographic (VCG) adaptation of the 12-lead ECG to more specifically study RVM in PAH patients.[6] Using a locally developed computer program for calculating ventricular gradient, which considered both the depolarization and the repolarization of the RV through analysis of the QRS complex and T wave, they were able to distinguish between normal RVM, mild RV hypertrophy (RVH), moderate RVH and severe RVH. However, this method requires a specific electronic program to analyze the ECG, which is not widely available.

We tested a simpler ECG method based on the previously described Butler-Leggett (BL) criteria derived from a standard 12-lead ECG. Butler et al. showed that this method could be used to identify RVH in patients with increased pulmonary resistance due to mitral stenosis and cor pulmonale.[7,8] The BL criteria are based on the principal that activation of the LV free wall produces forces directed posteriorly and leftward (PL). These forces are opposed by those generated by the RV free wall, which are directed anteriorly (A) and rightward (R).[9] This concept can be expressed by a formula $(A + R - PL)$, incorporating each of these forces, as measured on a standard 12-lead ECG. This results in a continuous variable (the BL score) for each ECG recording. In the normal situation, the LV forces dominate, but if the mass of the RV myocardium increases, as may occur in PAH, there is a net increase in rightward and anterior forces resulting in a higher BL score.

The current study was performed to test the hypothesis that the BL score would correlate closely with RVM in PAH patients. We suspected that any correlation would be stronger with RVMI than with absolute RVM, as this took into account the opposing contribution of the LV in any given patient. We also tested the diagnostic sensitivity of the BL score as a means of detecting RVH as a consequence of PAH.

MATERIALS AND METHODS

Case notes and clinical details from a prospectively recorded database were reviewed retrospectively. All patients who had attended the Scottish Pulmonary

Vascular Unit between August 2003 and May 2008 for diagnostic assessment were considered for inclusion. Only patients with a diagnosis of PAH, who had undergone both CMR imaging and 12-lead ECG within a 30-day period, were considered for inclusion. In addition, a copy of the ECG had to be available in the case notes, as ECGs were not recorded digitally at that time. Patients were excluded if they had a history of significant left heart disease or if their ECG showed complete right or left bundle branch block or ST depression (preventing accurate measurement of the S wave in leads I, V_1 or V_6). Twenty-eight patients met these criteria. All were subjected to rigorous diagnostic evaluation, including right heart catheterization, echocardiography, high-resolution computed tomography (CT) thorax, CT pulmonary angiography and pulmonary function testing.

Six control subjects were recruited and underwent CMR to establish a normal range for RVMI (normal have not previously been published). All gave informed written consent. None had any history of cardiorespiratory disease. The mean age of the control population was 37 (±10) years and all were male. Systemic blood pressure was normal in these individuals (systolic 114 [±8], diastolic 73 [±6], mean 87 [±6]).

ECG analysis

The QRS duration was measured using handheld calipers. Patients with QRS duration above 110 ms were reviewed by two observers (authors James Kinsella and Nina Hakacova, hereinafter JK and NH) for the presence of complete left or right bundle branch block. A modified version of the BL criteria was used as shown in Table 1. The terms "positive waveform" or "negative waveform" replaced designations of specific waveforms to remove the ambiguity of differentiation between the two QRS waveforms, which both indicate that the balance of forces is either toward (R and R' waves) or away from (Q and S wave) the positive pole of a particular ECG lead. JK and NH performed the waveform measurements using handheld calipers (to the nearest 0.1 mV). Disagreements in measurements were reviewed and consensus achieved. Anterior forces (A) were designated as the largest positive waveform in either lead V_1 or V_2. Rightward forces (R) were designated as the largest negative waveform in either lead I or V_6, and posterior–lateral forces (PL) as the negative waveform in V_1. These measurements were

	Anterior forces	Rightward forces	Posterolateral forces	Formula
Table 1: Original and modified methods of defining the Butler-Leggett score				
Original	Maximal R or R' in V_1 or V_2	Maximal S in I or V_6	Minimal S in V_1 or R in I or V_6	A+R-PL
Modified	Maximal positive waveform in V_1 or V_2	Maximal negative waveform in I or V_6	Maximal negative waveform in V_1	A+R-PL

The modified method was used in the current study; **A:** anterior forces; **R:** rightward forces; **PL:** posterolateral forces

combined into the BL formula through the equation: A + R − PL=BL score (mV).

Magnetic resonance image acquisition

Magnetic resonance image (MRI) scans were performed using a 1.5 Tesla scanner (Sonata Magnetom, Seimens, Germany). Fast imaging with steady-state precession sequences were used to generate the initial axial scout images required to localize the heart within the thoracic cavity and all subsequent cine images. Vertical and horizontal-long axis (VLA and HLA) cines were planned and acquired based on the scout images. The first of a series of short axis (SA) cines was then planned on image 1 of the HLA cine, intersecting the atrioventricular valve roots on this view. The SA imaging plane was then propagated apically, covering both ventricles with 8-mm SA imaging slices, separated by a 2 mm interslice gap. The traditional LV SA cine stack is used for the acquisition of both RV and LV images.

CMR image analysis

All CMR images were analyzed by a single operator (KGB) using the Argus analysis software (Siemens, Erlangen, Germany). The endocardial and epicardial borders of the image in end-diastolic and -systolic phases of the cycle at each slice position within the SA stack were defined by manual planimetry, including trabeculae and papillary muscles. These methods have been published previously.[10,11] RV and LV mass were determined as the product of the difference between the end-diastolic and end-systolic volume for each ventricle and the quoted density of cardiac muscle (1.05 g/cm^3). RVM was determined as RV free wall mass, with the interventricular septum considered part of the LV. RVMI was calculated by dividing RVM by LV mass.

Statistical analysis

For all variables, a normal distribution was verified using Kolmogorov-Smirnov tests. Pearson's correlation method was used to assess the relationship between BL score and both RVM and RVMI derived from MRI. Contingency tables (2×2) were used to calculate the sensitivity and specificity of the various BL scores as a means of detecting RVH. RVH was defined by two different methods to allow comparison. By method 1, RVH was defined as an RVM two standard deviations above the previously published normal mean RVM (35 [±8] g).[12] By this method, RVH was defined by a measured RVM >51 g. By method 2, RVH was defined by the upper 95% confidence interval of the mean RVMI (0.5002) of our control subjects. This defined RVH by an RVMI >0.582. The BL score with the greatest diagnostic accuracy (that which produced the lowest number of false-positive and false-negative results) was chosen. Negative and positive predictive values (PPV and NPV) for results either side of this threshold were

then calculated. The implications of an above-threshold result were quantified by likelihood ratios and Fisher's exact test. All data are presented as mean (±SD), unless otherwise stated.

RESULTS

Results of right heart catheterization in the 28 patients with PAH are shown in (Table 2). Twenty were female, and the mean age of the population was 51 (±17) years. Nine had connective tissue disease-associated PAH (CTD-PAH) and 19 had idiopathic PAH (IPAH); 26/28 had CMR imaging and ECG within 8 days, one had CMR imaging 18 days after ECG and one had CMR imaging 23 days after ECG.

ECG and CMR imaging results

The mean BL score among PH patients was 1.12±1.51. Mean RVM, LV mass and RVMI were 86.2 (±36.0) g, 92.1 (±31.3) g and 0.95±0.3, respectively.

Correlation between BL score and RVM and RVMI

The correlation between RVM and BL score was r=0.77, P<0.001 (Fig. 1a). The correlation between RVMI and BL score was r=0.78, P<0.0001 (Fig. 1b).

Detection of RVH

The BL score performed best at the 0.7 mV threshold for detecting RVH by either of the methods studied (elevated absolute RVM or elevated RVMI). Using a definition of RVH as an RVM >51 g (method 1), this threshold yielded no false-positives, but yielded six false-negatives. This produced a sensitivity of 74% (95% confidence interval 52–90%) and a specificity of 100% (95% confidence interval 48–100%). NPV and PPV were 45% and 100%, respectively.

Based on the definition of RVH as an RVMI>0.582 (method 2), a BL score >0.7 mV yielded no false-positives but 10 false-negatives. This resulted in a sensitivity of 61% (95% confidence interval 41–79%) and a specificity of 100% (95% confidence interval 81–100%). NPV and PPV were 9% and 100%, respectively.

Table 2: Right heart catheterization data	
	Mean±SD
Systolic PAP (mmHg)	83 (±26)
Diastolic PAP (mmHg)	29 (±14)
Mean PAP (mmHg)	50 (±17)
PA wedge pressure (mmHg)	8 (±4)

Results of right heart catheterization in 28 patients with pulmonary arterial hypertension; **PAP:** pulmonary artery pressure; **PA:** pulmonary artery
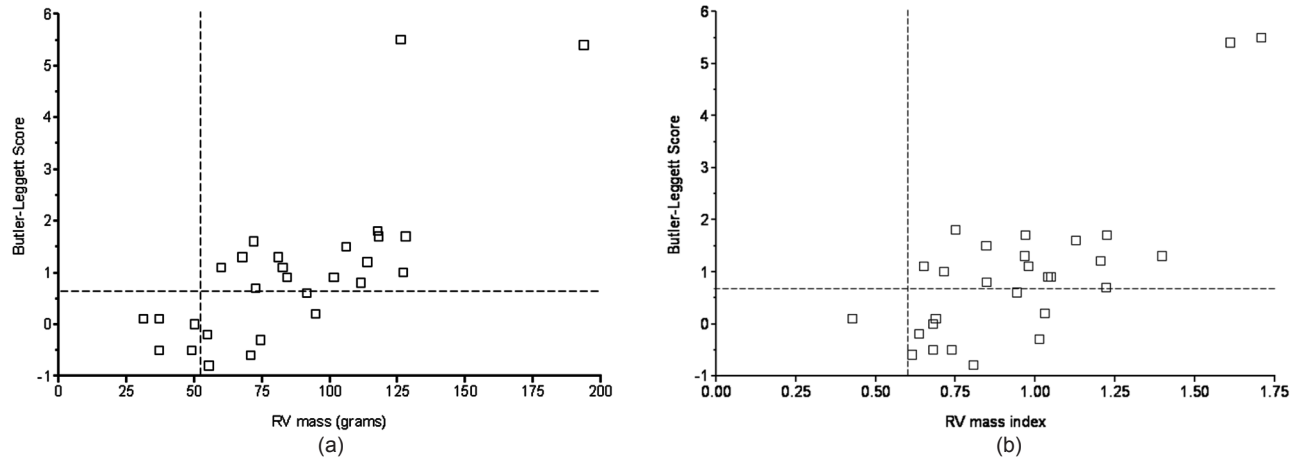
Figure 1: Right ventricular mass (RVM) and RV mass index (RVMI) were calculated from the cardiac magnetic resonance images acquired in 28 patients with pulmonary arterial hypertension. These data were correlated against Butler-Leggett (BL) scores derived from standard 12-lead ECG recordings. (a) Relationship between BL score and RVM (r=0.77, P<0.001). (b) Relationship between BL score and RVMI (r=0.78, P<0.001). On both scatter plots, the vertical lines indicate the upper limits of normal for RVM (51 g) and RVMI (0.6); values to the right of this line indicate RV hypertrophy (RVH). The horizontal lines on each figure indicate the threshold of BL score (0.7 mV) that proved most accurate in identifying RVH.

DISCUSSION

The primary result of this study is that a BL score ≥0.7 mV proved a highly specific indicator of RVH (as defined by either RVM or RVMI). However, this threshold was relatively insensitive (sensitivity 74% and 61% for RVM and RVMI, respectively). The BL score also correlated linearly with RVM and RVMI in PAH patients. Although the BL score is the electrical equivalent of RVMI, which reflects the relative mass of the ventricles, its relationship with RVMI was not any more powerful than that with absolute RVM.

Our findings are consistent with the results of an earlier PH screening study that demonstrated insufficient diagnostic sensitivity using different ECG criteria.[5] We used a slightly modified version of the original BL criteria (Table 1). This was necessary to avoid confusion when considering the two negative waveforms (Q and S) and the two positive waveforms (R and R'). This modification is in accordance with methods used in a recent study by Siddiqui et al., in which the BL criteria were used in patients with RV volume overload.[13] The exclusion of R wave amplitudes in leads I or V_6 is valid as analysis of the formation of the ECG has shown that these waveforms do not reflect postero–lateral forces; this revision of the original BL methodology has been included in subsequent reprints of the formula.[14]

The BL score used in the current study also differs from the VCG method used by Henkens et al.[6] That method incorporates information regarding both ventricular depolarization and repolarization by analyzing both QRS complexes and T waves. The authors were able to show that their VCG method is a highly accurate means of identifying increased RV afterload and differentiating

between subgroups of patients with mild-to-moderate and severe RV pressure overload. They showed a moderate inverse correlation between RVM and VCG projection on the x-axis, as determined by their method.[6] The strength of this correlation (r=−0.323, P=0.048) was lower than that detected in the current study using BL criteria (r=0.77, P<0.001). Clearly, these two methods are not directly comparable and we did not look for any relationship between RV afterload and BL score in the current study. Nevertheless, it would be interesting to directly compare the performance of the two methods in a future study. Although the VCG method is complicated by the requirement for a noncommercially available program to derive the ECG information, this could be overcome with appropriate software, and both approaches may have future clinical applications.

Most of the patients in the current study had IPAH (19/28); the remainder had CTD-PAH (9/28). Recent echocardiographic and CMR imaging studies have shown that RV diastolic and systolic function and RV pulmonary arterial coupling are adversely affected in CTD-PAH in comparison with IPAH patients, at equivalent levels of pulmonary hypertension.[15] Despite this, we found no difference in the extent of RVH on CMR imaging between these disease groups and no difference in their BL scores. Although it is possible that this reflects the relatively small sample size in our study, we do not believe that this factor significantly altered our conclusions.

Because the BL score correlates strongly with RVM, and a score ≥0.7 mV was a highly specific indicator of RVH, this method may be useful in referral centers with no access to CMR imaging, or in the outpatient PH clinic. Although a high BL score is a strong indicator that RVH

is present (PPV 100%), a normal score does not exclude RVH, given the low sensitivity (<70%) and NPV (<42%) of this method. As RVM has been shown to decrease with effective treatment,[2] the BL score may also decrease. This might prove useful in the noninvasive monitoring of treatment effect, but this hypothesis would need to be tested in a prospective study. Interestingly, a recent study has demonstrated that alterations in QRS axis, P wave amplitude in lead II and T wave axis correlate well with hemodynamic improvements on PAH therapies.[16]

The number of patients in the current study was relatively small. It would therefore be inappropriate to propose that the specific BL threshold (0.7 mV) for RVH that we report be applied more widely in PAH populations. CMR imaging does provide, however, an extremely accurate and reproducible gold standard for RVM, limiting the number of patients required for such studies. ECGs and CMR imaging studies were not acquired contemporaneously in all patients. This introduces a source of potential error in the results described, although the likelihood and magnitude of any change in RVM, even over the maximal interval between studies (23 days), are both likely to be small.

CONCLUSION

The BL score, which can be defined using a standard 12-lead ECG, correlates linearly with both RVM and RVMI in patients with PAH. A score of >0.7 mV was a highly specific but relatively insensitive indicator of RVH in these patients.

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