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Detection and Evaluation of Pulmonary Hypertension by a Synthesized Right-Sided Chest Electrocardiogram

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Background: Current standard 12-lead electrocardiogram (ECG) criteria for diagnosing pulmonary hypertension (PH) have a low sensitivity. Although the right-sided chest ECG (V3R–V5R) increases the diagnostic accuracy, these additional leads are not routinely recorded. The aim of the present study was to assess the usefulness of the synthesized right-sided chest ECG (Syn-ECG), generated from 12-lead ECG information, in the detection and evaluation of PH.

Patients and Methods: The Syn-ECG waveforms in 30 patients with PH, defined as an estimated pulmonary arterial systolic pressure (PASP) >35 mmHg, were compared to those in 30 age- and gender-matched normal subjects.

Results: The R wave amplitude and R/S ratio in the Syn-ECGs were significantly (P<0.01) greater in patients with PH than in the controls. The R wave amplitude in the Syn-ECGs exhibited a significant and better correlation (correlation coefficient 0.513–0.596, P<0.001) with the PASP than lead V1 (correlation coefficient 0.375, P=0.02). A receiver-operating characteristic curve analysis showed that the R wave amplitude (AUC 0.802, P<0.001) and R/S ratio (AUC 0.823, P<0.001) in the synthesized V5R was a good predictor of PH. New criteria, including 1) an R in V5R>0.12 mV, and 2) R/S ratio in V5R>0.42, had an improved sensitivity (0.63 and 0.73, respectively) and comparable specificity (0.93 and 0.87, respectively) to the conventional criteria (sensitivity 0.10–0.43, specificity 0.90–1.00).

Conclusion: The diagnostic criteria derived from the Syn-ECG provided better diagnostic accuracy than the known conventional criteria from the standard 12-lead ECG. This technique described in the present study may be useful for diagnosing and evaluating PH. (J Nippon Med Sch 2015; 82: 136–145)

Key words: vectorcardiography, synthesized electrocardiogram, right ventricular hypertrophy, criteria, diagnostic accuracy

Introduction

Pulmonary hypertension (PH) is a disease of the pulmonary vasculatures resulting in a progressive increase in the pulmonary arterial pressure, ultimately leading to right ventricular failure and death. For the diagnosis of PH, assessment of the pulmonary arterial systolic pressure (PASP) by right-heart catheterization or transthoracic Doppler echocardiography is necessary. However, these modalities may not be performed unless the diagnosis is specifically sought. The 12-lead electrocardiogram (ECG) is easily performed, inexpensive, and widely available. The ECG provides suggestive evidence of PH by demonstrating right ventricular hypertrophy (RVH). The current ECG criteria[1] for RVH is based largely on the criteria established by Myers[2] and Sokolow[3]. Those criteria depend primarily on changes in the right precordial leads: namely, an increase in the height of the R waves, decrease in the depth of the S waves, with an increase in the R/S ratio. Although the proposed criteria have a good specificity between 90 and 100 percent, the sensitivity is inadequately low, ranging from 0.5 to 40 percent[4,5]. Myers et al. suggested the use of leads from positions

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further to the right of the sternum to increase the sensitivity, and mentioned two instances in which a diagnosis of right ventricular hypertrophy was made from the appearance in V3R[6]. Rosenman et al. found that V4R was essential for the diagnosis of RVH in 5 of 25 cases[7]. Camerini et al. also reported that the accuracy of the diagnosis of RVH was improved by the use of V4R, which showed a R>S pattern in 27 percent compared with 12 percent in V1[8]. However, these additional ECGs are not routinely recorded because of the time-consuming procedure involved. Recently, a new system that synthesizes the waveforms of these right-sided chest leads from the standard 12-lead ECG information[9,10] has been developed. The accordance of these synthesized right-sided ECGs with the actual ECGs has been validated[9,11], and the synthesized right-sided ECGs have been utilized in the diagnosis of right ventricular myocardial infarctions[11] and the non-invasive localization of the focus of ventricular arrhythmias[12]. Currently, the role of the synthesized right-sided ECGs in the diagnosis of PH has not been established. Thus we sought to determine the usefulness of the synthesized right-sided ECGs for the detection of PH. Furthermore, we hypothesized that the degree of abnormality in the synthesized right-sided ECGs may be predictive of the degree of the PH.

Methods

Patients

We reviewed the findings of the transthoracic echocardiography (TTE) in 22,739 consecutive patients who underwent TTE at Nippon Medical School Hospital between January 2011 and June 2013. Among them, a total of 380 patients with suspected PH, defined as an estimated systolic pulmonary arterial pressure (PASP) >35 mmHg[13], were extracted. Since the PASP is equivalent to the right ventricular systolic pressure in the absence of a pulmonary outflow obstruction, the PASP is approximated by the measurement of the systolic regurgitate tricuspid flow velocity (v) and estimate of the right atrial pressure (RAP) in the formula: PASP = $4v^2$ + RAP. For the RAP, a standard value of 5 mmHg was applied. Then, patients with significant left heart disease, primary pulmonary disease (i.e. pulmonary emphysema or pneumonitis), or PH due to transient conditions (i.e. acute phase of pulmonary thromboembolism) were excluded by reviewing the medical records. Patients without available digitally stored ECGs recorded within 30 days of the transthoracic echocardiography, and those with complete right bundle branch block[14], or significant rhythm disturbances were also excluded. Finally, a total of 30 patients with PH due to idiopathic pulmonary arterial hypertension (N=5), chronic pulmonary thromboembolism (N=14) or an atrial septal defect (N=11) were included for the analysis (**Fig. 1**). Thirty age- and gender-matched control patients without any abnormal echocardiographic findings were chosen as the control.

Electrocardiographic Recording

Standard 10-s 12-lead ECGs were recorded in the supine position with an electrocardiographic recorder (ECG-1550, Nihon Kohden, Inc., Tokyo, Japan). All digital data from the standard 12-lead ECG signals were instantaneously processed at a sampling rate of 1 kHz. Electrocardiographic data were subsequently transferred to an ECG diagnostic information system (PRM-3000, Nihon Kohden) for analysis.

Generation of Waveforms in the Synthetized Right-sided Precordial Leads and Analysis

The synthetized V3R (Syn-V3R), V4R (Syn-V4R), and V5R (Syn-V5R) ECG waveforms were automatically generated using an automated ECG analysis system (ECAPS18, Nihon Kohden)[9,10]. In brief, the Syn-V3R, Syn-V4R, and Syn-V5R ECG waveforms were derived by substituting the waveforms of from limb leads I and II and those from the standard chest leads as vectors (Vs) into the following specific equations that included the coefficients representing the relationships between the standard leads and these extended leads: $V(\text{Syn-V3R}) = \alpha_{3RI}V_I + \alpha_{3RII}V_{II} + \alpha_{3RV1}V_{V1} + \alpha_{3RV2}V_{V2} + \alpha_{3RV3}V_{V3} + \alpha_{3RV4}V_{V4} + \alpha_{3RV5}V_{V5} + \alpha_{3RV6}V_{V6}$, $V(\text{Syn-V4R}) = \alpha_{4RI}V_I + \alpha_{4RII}V_{II} + \alpha_{4RV1}V_{V1} + \alpha_{4RV2}V_{V2} + \alpha_{4RV3}V_{V3} + \alpha_{4RV4}V_{V4} + \alpha_{4RV5}V_{V5} + \alpha_{4RV6}V_{V6}$, $V(\text{Syn-V5R}) = \alpha_{5RI}V_I + \alpha_{5RII}V_{II} + \alpha_{5RV1}V_{V1} + \alpha_{5RV2}V_{V2} + \alpha_{5RV3}V_{V3} + \alpha_{5RV4}V_{V4} + \alpha_{5RV5}V_{V5} + \alpha_{5RV6}V_{V6}$. The relationships used for deriving the synthesized right-sided chest lead ECGs were calculated from the QRS samples recorded by the actual right-sided leads and standard leads[9,10]. The amplitude of the R and S waves in the standard 12-lead ECG and those in the synthesized right-sided ECG were automatically measured.

Statistical Analysis

Continuous variables are expressed as the mean±SD, and 2-group comparisons were performed with either the parametric 2-sample Student's *t*-test or Mann-Whitney test according to the results of the Shapiro-Wilk normality test. Categorical variables were compared using the Fisher's exact test. A receiver-operating characteristic (ROC) curve was generated and the area under the curve (AUC) was calculated to determine the significance of ECG criteria for PH. The Pearson product-moment corre-

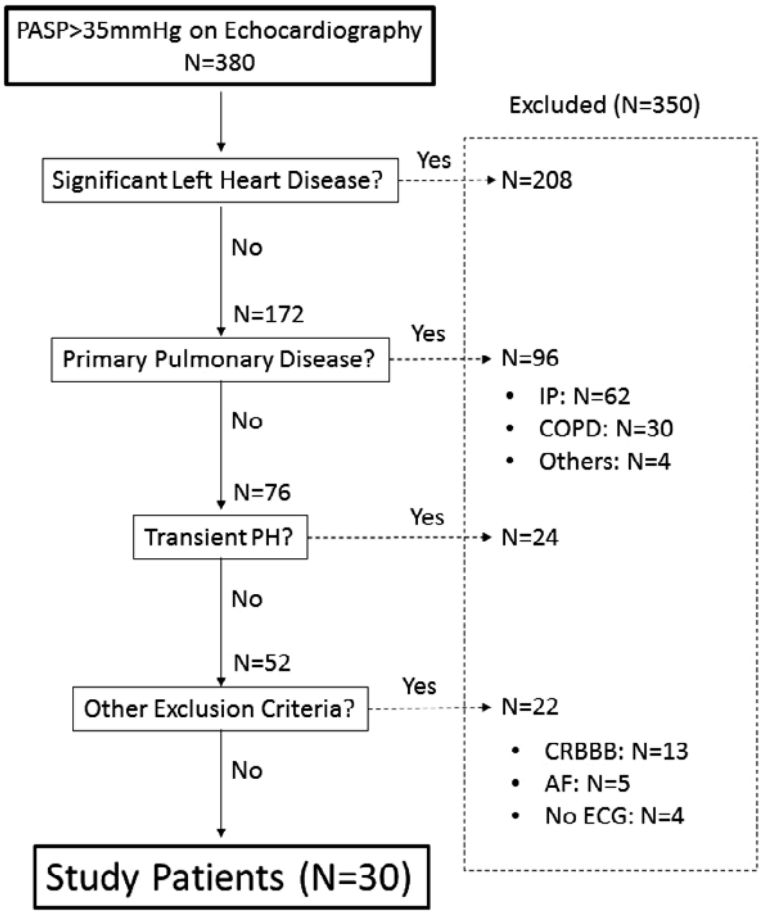

Fig. 1 Flow chart showing the process of selecting study patients with pulmonary hypertension (PH).
Patients with significant left heart disease, primary pulmonary disease, PH due to transient conditions, complete right bundle branch block (CRBBB), atrial fibrillation (AF) were excluded. Patients without available digitally stored ECGs recorded within 30 days of the transthoracic echocardiography were also excluded. IP, interstitial pneumonitis; COPD, chronic obstructive pulmonary disease

lation coefficient was used to determine the relationship between the ECG parameters and the degree of PH. All tests were two-tailed and statistical significance was established at a $P<0.05$. All analyses were performed with SPSS version 21 software (IBM Inc., Chicago, Illinois, USA).

Results

Patient Characteristics

The patient characteristics are presented in **Table 1**. There were no significant differences in the age (64±13 vs. 64±13 years, $P=1.00$) or gender (male 23% vs. 23%, $P=1.00$) between the PH patients and controls. The mean heart rate was 76±13 beats/min in the PH patients vs. 65±12 beats/min in the controls ($P=0.001$). The interventricular septal thickness (8±1 mm) and diastolic dimension of the left ventricle (40±6 mm) in the PH patients were normal and did not differ from those in the controls. Estimated PASP in PH patients and the controls were 69±29 and 25±3 mmHg, respectively ($P<0.001$).

Comparison of the ECG Waveforms

The typical waveforms of the standard 12-lead ECG, actual right-sided chest ECG, and synthetized right-sided chest ECG in a PH patient are presented in **Figure 2A**. The waveforms of the synthesized right-sided chest ECG were equivalent to those of the actual right-sided ECG, and demonstrated an increased R wave amplitude compared to that in a control patient (**Fig. 2B**). Box plots of the R wave amplitudes in the PH and control groups are demonstrated in **Figure 3A**. The R wave amplitude in the syn-V5R, syn-V4R, and syn-V3R was significantly ($P<0.01$) greater in the patients with PH than in the control patients, whereas no such difference was noted for the standard chest ECGs (V1, V2 and V3). The R/S ratio in

Table 1 General characteristics of the study population

	PH (N=30)	Control (N=30)	*P*-value
Age (years)	64±13	64±13	1.00
Male sex (%)	7 (23%)	7 (23%)	1.00
HR (beats per minute)	76±13	65±12	0.001
LVEF (%)	70±9	73±6	0.099
IVST (mm)	8±1	8±2	0.405
LVDd (mm)	40±6	43±5	0.057
TR (%)	30 (100%)	22 (73.3%)	<0.01
PASP (mmHg)	69±29	25±3	<0.001

PH: pulmonary arterial hypertension, HR: heart rate, LVEF: left ventricular ejection fraction, IVST: interventricular septal thickness, LVDd: diastolic dimension of the left ventricle, TR: tricuspid regurgitation, PASP: estimated pulmonary arterial systolic pressure

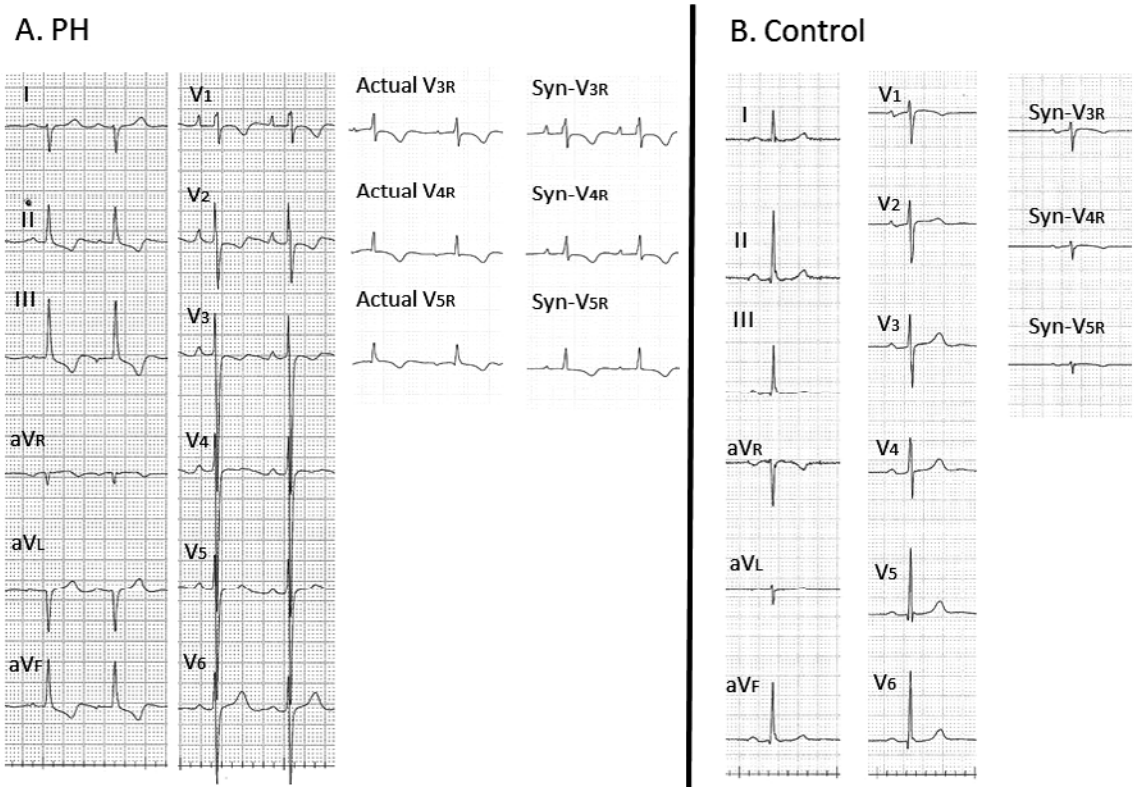

Fig. 2 Standard 12-lead and actual and synthesized right-sided chest ECGs

A: Representative ECG in a patient with pulmonary hypertension (PH). Note that the waveforms of the synthesized right-sided chest leads are equivalent to the actual waveforms.

B: Representative ECG in a control patient.

the synthesized right-sided chest ECGs and that of the standard chest ECG (V1, V2, and V3) are shown in **Figure 3B**. Since S waves were not present in leads V4, V5, and V6 in a significant number of control patients (V4: n=2, V5: n=6, V6: n=11), the R/S ratio in those leads was excluded from the analysis. The R/S ratio in syn-V5R, syn-V4R, syn-V3R, and V1 was significantly greater in the PH patients than in the control patients. The R wave amplitude and the R/S ratio in these four leads in the PH patients were not significantly different among the three conditions that caused PH (p=0.36–0.71).

Correlation between the PASP and ECG Parameters

Scattergrams demonstrating the relationship between the PASP and R wave amplitude in the right-sided chest ECGs are shown in **Figure 4**. The R wave amplitude in lead V1 had a significant but modest (correlation coeffi-

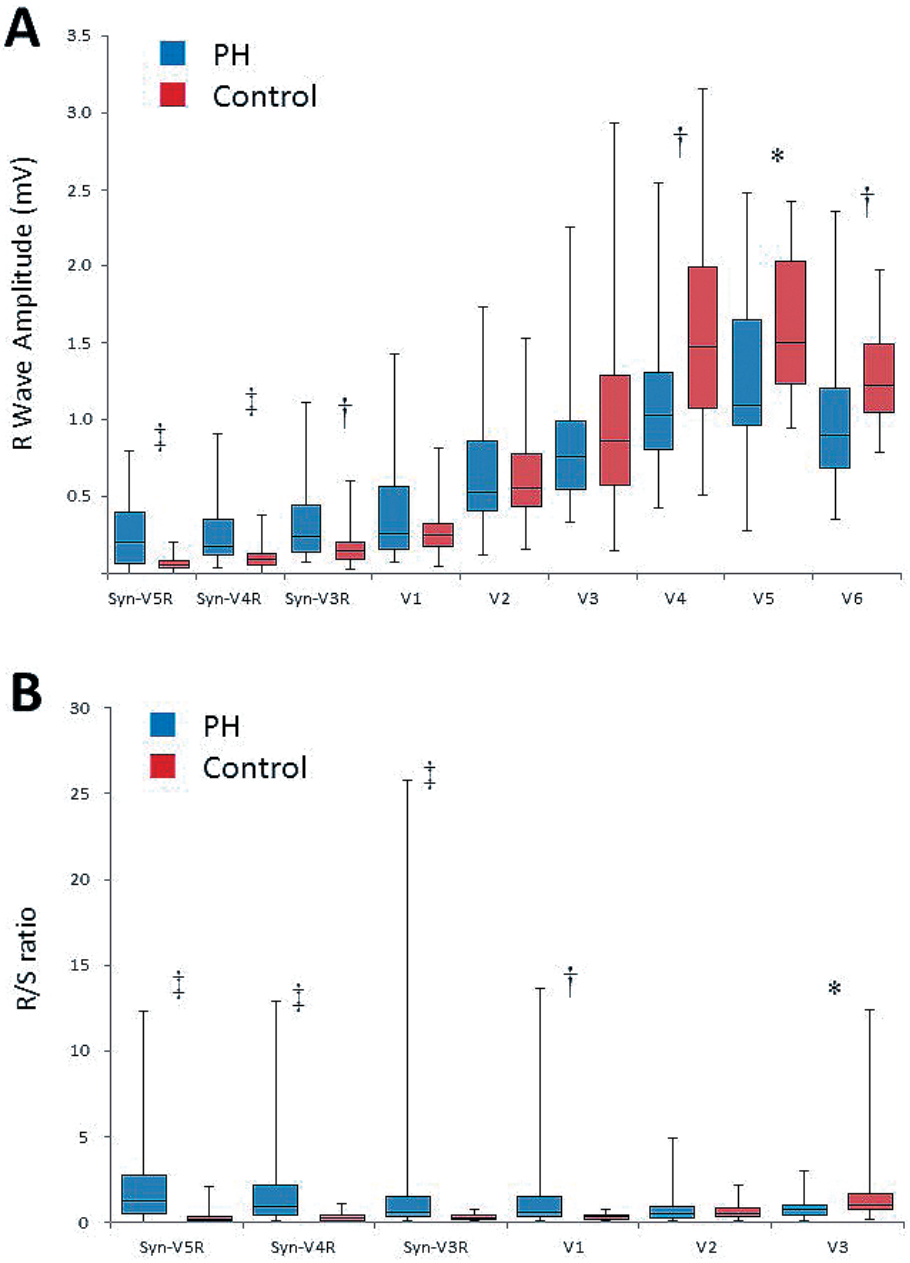

Fig. 3 Box plots of the R wave amplitude (A) and R/S ratio (B) in pulmonary hypertension (PH) and control patients. *P<0.05, †P<0.01, and ‡P<0.001 vs. control.

cient 0.375, P=0.02) positive correlation to the PASP, while that in the synthesized right-sided chest ECGs had a better correlation (correlation coefficient 0.513–0.596, P< 0.001) to the PASP.

Parameters of the Synthesized Right-sided Chest ECGs as a Predictor of PH

The ROC analysis for the R wave amplitude as a predictor of PH revealed that the best lead was Syn-V5R (AUC 0.802, 95% CI 0.687–0.917, P<0.001). The R wave amplitude in Syn-V4R (AUC 0.792, 95% CI 0.678–0.907, P<0.001) and Syn-V3R (AUC 0.701, 95% CI 0.568–0.834, P<0.01) was also a significant predictor, while that of V1 (AUC 0.558, 95% CI 0.409–0.707, P=0.442) was not a significant predictor (**Fig. 5**). Further, the R/S ratio in the synthesized right-sided chest ECGs was also good predictor (Syn-V5R: AUC 0.823, 95% CI 0.712–0.934, P<0.001, Syn-V4R: AUC 0.837, 95% CI 0.725–0.9313 P<0.001, Syn-V3R: AUC 0.822, 95% CI 0.715–0.929, P<0.001).

The sensitivity, specificity, positive and negative predictive values of the new criteria derived from parameters of the synthesized right-sided chest ECGs and those of the conventional criteria recommended in the current guidelines[1] for right ventricular hypertrophy are summarized in **Table 2**. Overall, the conventional criteria had a high specificity (0.90–1.00) and high positive predictive value (0.50–1.00), but a low sensitivity (0.10–0.46). In con-

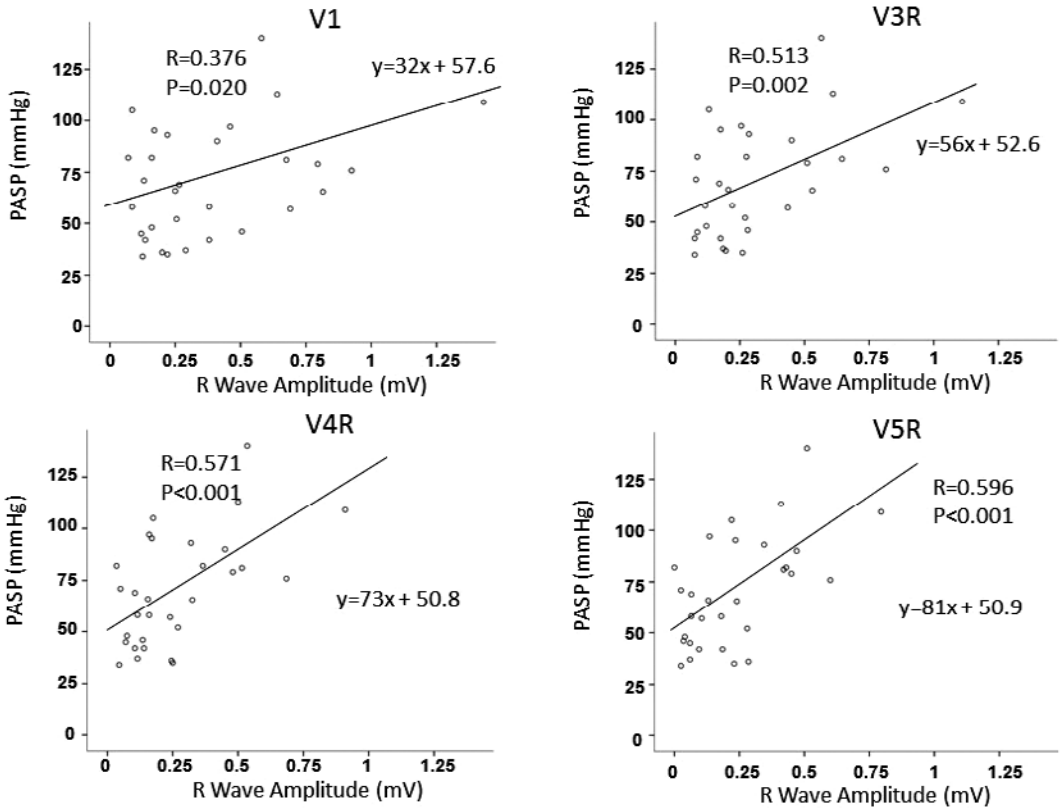

Fig. 4 Correlation between the estimated pulmonary arterial systolic pressure (PASP) and R wave amplitude in the right-sided chest ECGs in 30 patients with pulmonary hypertension (PH). The R wave amplitude in V1 had a modest (correlation coefficient 0.375, P=0.03) positive correlation with the PASP, while that in the synthesized leads had a better correlation (correlation coefficient 0.513–0.596, P<0.001).

trast, the new criteria derived from the synthesized right-sided ECG had an improved sensitivity without compromising the specificity; the criterion, R/S ratio for Syn-V5R >0.42, had a sensitivity of 0.73 and a specificity of 0.87 (P<0.001), and the criterion, an R wave amplitude in Syn-V5R>0.12 mV, had a sensitivity of 0.63 and specificity of 0.93 (P<0.001).

Discussion

Major Findings

To the best of our knowledge, this is the first study to evaluate the synthesized right-sided ECGs in the diagnosis of PH. The diagnostic criteria derived from the synthesized right-sided ECGs had a better sensitivity than the conventional criteria using the standard 12-lead ECG without compromising the specificity. The R wave amplitude in the synthesized right-sided ECGs was significantly correlated with the PASP. These findings suggested that the synthesized right-sided ECG was useful for diagnosing and evaluating PH.

Limitations of Conventional Criteria

The ECG is a component of the general practice for the detection and evaluation of PH. The presence of PH is suspected when the ECG demonstrates suggestive findings of RVH. Although the current American Heart Association ECG criteria[1] for RVH have had a good specificity in studies that included patients with previously diagnosed clinically advanced cardiopulmonary disease, the sensitivity is low, ranging from 10 to 40 percent[4,15–17,23]. In fact, the present study included patients with idiopathic pulmonary arterial hypertension, PH due to chronic pulmonary thromboembolism, and PH secondary to congenital heart disease, and the conventional criteria yielded a high specificity between 90 and 100%, but the sensitivity was insufficiently low, ranging between 15 and 47%. Further, when these conventional criteria were validated in the general population without clinical cardiovascular disease including only 6% of the subjects with mild RVH, the sensitivity became considerably low ranging from 0.5 to 12.5%[5]. Therefore, the current criteria for RVH are not sufficient for screening RVH and PH, not only in the general population but also in patients at high-risk for PH, such as patients with known genetic-mutations associated with PH, a scleroderma spectrum of

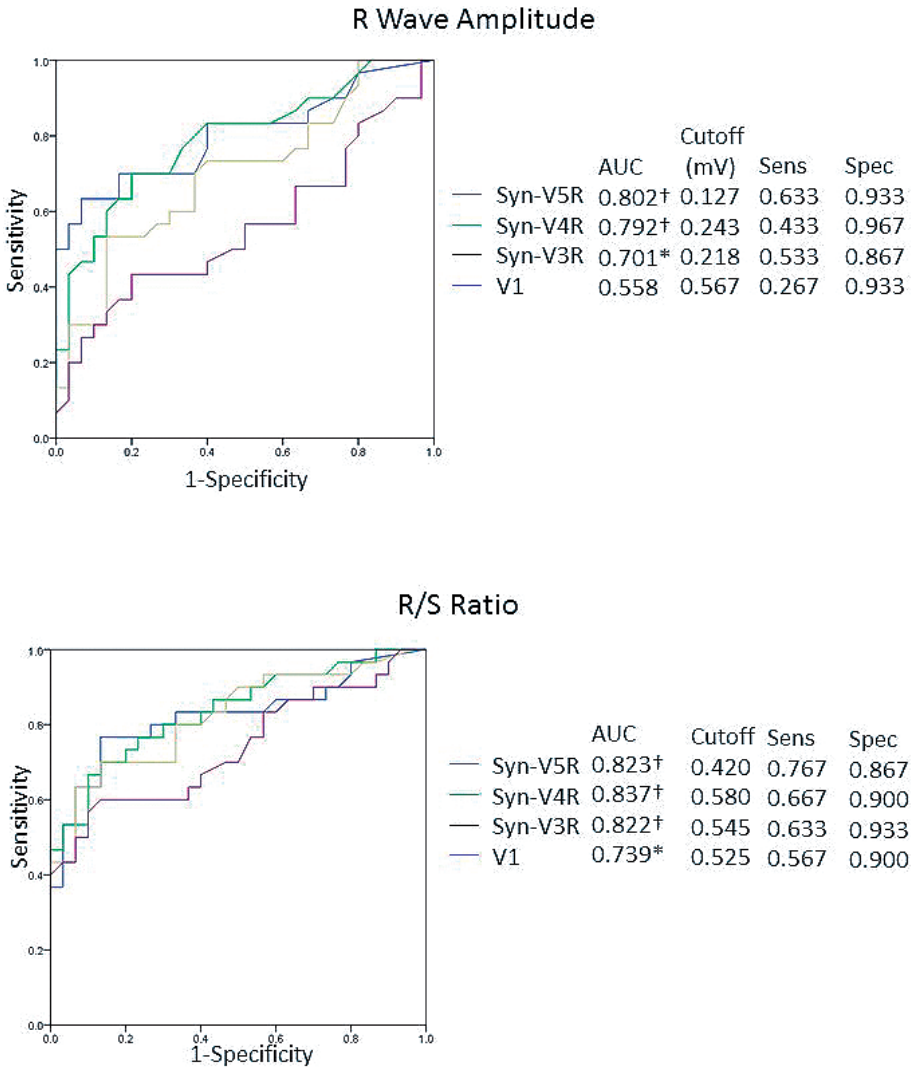

Fig. 5 Receiver-operating characteristics curves for the R wave amplitude (upper panel) and R/S ratio (lower panel) of the right-sided chest leads for the prediction of pulmonary hypertension. The area under the curve (AUC), cut off level, and sensitivity (Sens) and specificity (Spec) of each parameter are shown. *P<0.05 vs. AUC=0.5, †P<0.01 vs. AUC=0.5

disease, congenital heart disease, systemic-to-pulmonary shunts, or portal hypertension.

Usefulness of the Synthesized Right-sided Chest ECG

Vectorcardiography, a projection of the time course of the instantaneous electrical axis of the heart, has been recognized as a supplement to the conventional electrocardiogram in the diagnosis of RVH[18]. Generally, the vector loop in patients with severe RVH shows a rightward and anterior deviation of the horizontal plane loop[18] (**Fig. 6**).

Cowdery et al. developed a vectorcardiographic criteria for detecting RVH based on the voltage of the loop in the anterior (A), rightward (R), and posterolateral (PL) direction (**Fig. 6**), and provided a 60% sensitivity and 96% specificity in patients with RVH due to mitral stenosis[19]. Chou et al. developed criteria based on the duration of the vector in the rightward and posterior direction, and provided an 83% sensitivity for RVH due to mitral stenosis, atrial septal defects, or chronic obstructive lung disease. Chou's criteria were tested in the study population by Cowdery et al. and had a 52% sensitivity and 78% specificity[19]. Despite such better diagnostic accuracy, the vectorcardiography has several limitations. First, vectorcardiography is not readily available since it needs specific instruments and an extra lead between the middle of the back and the sternum that is called the Frank lead. Second, complex measurements are necessary for the analysis.

Vectorcardiography can be transformed to the standard

Table 2 The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the new and conventional criteria for the diagnosis of pulmonary hypertension or right ventricular hypertrophy

	Sensitivity	Specificity	PPV	NPV	*P*-value
New Criteria					
R/S ratio in V5R>0.42	0.73	0.87	0.85	0.76	<0.001
R in V5R>0.12 mV	0.63	0.93	0.86	0.71	<0.001
Conventional Criteria					
R in V1>0.6 mV	0.15	0.93	0.78	0.55	0.073
R/S in V1>1	0.37	1.00	1.00	0.61	<0.001
S in V5>1 mV	0.20	1.00	1.00	0.55	0.052
S in V6>0.3 mV	0.53	1.00	1.00	0.68	<0.001
R in aVR>0.4 mV	0.00	1.00	1.00	NA	NA
S in V1<0.2 mV	0.26	1.00	1.00	0.58	0.005
R/S ratio in V5<0.75	0.20	1.00	1.00	0.56	0.024
R/S ratio in V6<0.4	0.10	0.90	0.40	0.49	1.00
Butler index>0.7	0.43	0.90	0.81	0.61	0.007
R V1+S V5,6>1.05 mV*	0.47	1.00	1.00	0.47	<0.001

Butler index = (maximum R wave amplitude in V1 or V2) + (maximum S wave amplitude in lead I or aVL) – (maximum S wave amplitude in V1)
*R wave amplitude in V1+S wave amplitude in V5 or S wave amplitude in V6>1.05 mV[3].

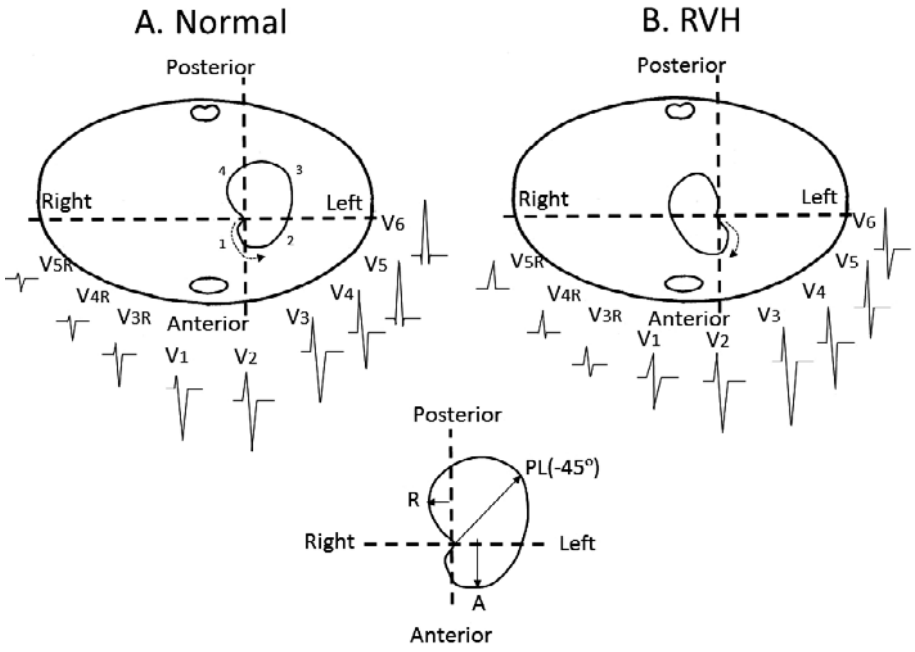

Fig. 6 Upper: Typical horizontal plane loop of the vectorcardiography in normal subjects (panel A) and in patients with right ventricular hypertrophy (RVH) (panel B) in relation to the thorax, location, and waveforms of the chest leads. In normal subjects, the vector is initially directed rightward and anteriorly (1), and then turns leftward (2), posterior (3), and then turns rightward (4) and comes back to the origin. In RVH, the horizontal loop exhibits a rightward and anterior deviation. Note that the standard chest leads are located leftward and anterior to the origin of the vector, while those of the additional right chest leads (V3R, V4R, and V5R) are located rightward and anterior.
Lower: An analysis by Cowdery et al.[19] based on the voltage of the horizontal loop in the anterior (A), rightward (R), and posterolateral (PL) directions.

chest lead ECG. The general relationship between the vectorcardiography and standard chest lead ECG is as follows: when the vector is coming toward the position of a chest lead, the signal of the lead exhibits a positive deflection (=R wave), and when it goes in a direction away from the chest lead, the signal exhibits a negative deflection (=Q or S wave).

Butler et al. translated the vectorcardiographic criteria by Cowdery et al.[19] into the conventional 12-lead ECG[16]. The maximal anterior (A), rightward (R), and posterolateral (PL) voltages of the horizontal vector loop were substituted with the voltage of the R wave in V1 or V2, S wave in I or V6, and S wave in V1, respectively. The derived criterion, A+R−PL≥0.7 mV, yielded a 34% sensitivity and 96.6% specificity for a diagnosis of RVH due to mitral stenosis.

From an anatomical viewpoint, it is noted that the standard chest leads (V1−V6) reflect a vector with an anterior and leftward direction better than that with a rightward and anterior direction, since the latter vector is directed mostly perpendicular to the vector of the standard chest leads, as illustrated in **Figure 6**. That may be the reason why any criteria for the standard ECG, regardless of being single or combined, are not sufficient for the diagnosis of RVH.

On the other hand, the additional right-sided chest leads (V3R−V5R) reflect a vector in the rightward and anterior direction. The usefulness of these additional leads has been reported in the past[6–8]. In the present study, the R wave amplitude and the R/S ratio in the synthesized right-sided chest ECGs were significantly greater in patients with PH than in the control patients, and the criteria, an R/S ratio in Syn-V5R>0.42, provided the best diagnostic accuracy with a 73% sensitivity and 87% specificity. Further, the amplitude of the synthesized right-sided chest ECGs exhibited a good and significant correlation to the PASP in the patients with PH.

It may be assumed that precordial lead patterns are derived predominantly from the muscle underlying the electrode. The magnitude of the potential variations recorded by a remote electrode varies inversely with the cube of its distance from the electrical source. It follows that the more remotely an electrode is placed from the heart, the more equally it is influenced by the potential variations of the two ventricles.

In normal subjects, the tricuspid valve is a mid-line structure and the position of V1, the fourth intercostal space at the right sternal border, overlies the right atrium, not the right ventricle[20]. The position for V3R, V4R and V5R is further away from the right ventricle. Therefore, the signals of the right-sided chest leads are likely to be influenced fairly equally by the potential variations of all parts of the heart. That may be the reason why V5R, which reflects rightward vector better than V3R, was the best lead for predicting PH. On the other hand, since the position for V5 and V6 is close to the left ventricle, the signals from V5 and V6 are likely to be predominantly influenced by the potential variations of the left ventricle. That may be another reason why the criteria derived from V5R were better than those derived from V6, although the vectors to these two leads are almost parallel to each other.

Study Limitations

The present study has several limitations. First, we did not perform a right heart catheterization for the measurement of the PASP. However, most studies report a high correlation between the echocardiographic and direct measurements of the PASP[21]. Second, we did not evaluate the PASP in the 8 control patients because they did not have tricuspid regurgitation. However, the absence of tricuspid regurgitation is quite rare (<5%) in patients with PH[22], and the absence of any abnormal findings in the echocardiography suggest the absence of PH. Third, cases with posterolateral myocardial infarctions that may have exhibited a dominant R wave in V1 and V4R[23] were not included in the control patients. Posterolateral infarctions should be excluded when the synthesized right-sided ECG exhibits suggestive findings of PH. Fourth, this was a single-center, retrospective study. The number of patients included in the present study was small, which could have obscured the results of the present study. Fifth, the wall thickness of the RV was measured by echocardiography in only 10% of the patients that made us unable to evaluate the correlation between the degrees of RVH and PH in our study population.

Conclusions

The diagnostic criteria derived from the synthesized right-sided chest ECG provided a better diagnostic accuracy than the known conventional criteria from the standard 12-lead ECG. The R wave amplitude in the synthesized right-sided ECG correlated with the PASP. This technique described in the present study may be useful for the diagnosis and evaluation of PH.

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