



Noninvasive and invasive evaluation of pulmonary arterial pressure in highlanders

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ABSTRACT: The purpose of the present study was to evaluate Doppler echocardiography for the detection of pulmonary hypertension in high-altitude inhabitants.

In total, 60 (55 male) patients aged 18–71 yrs were recruited from an ECG screening programme applied to 1,430 inhabitants living at an altitude of 2,500–3,600 m in Kyrgyzstan. Of these, 44 met ECG criteria for right ventricular hypertrophy. All underwent Doppler echocardiography followed by a cardiac catheterisation within 7 days of arrival in Bishkek (Kyrgyzstan; altitude 760 m). Pulmonary flow acceleration time and the maximum velocity of tricuspid regurgitation were measured.

Sufficient quality tricuspid regurgitant jets were recovered in only 28% of the patients. Therefore, pulmonary artery pressure was estimated from the pulmonary flow acceleration time, which was recovered in 100% of the patients. It was found that 37 (62%) of the patients had pulmonary hypertension on echocardiography. Pulmonary hypertension was confirmed in 29 patients on catheterisation. Pulmonary hypertension was detected with 70% sensitivity and 88% specificity by echocardiography, as compared to 59% sensitivity and 81% specificity by ECG. The correlation coefficient between echocardiography and catheterisation studies was $r^2=0.78$.

It is concluded that a combination of ECG and echocardiography may be useful for screening high-altitude pulmonary hypertension.

KEYWORDS: ECG, echocardiography, high-altitude pulmonary hypertension, pulmonary circulation, right heart catheterisation

High-altitude pulmonary hypertension (HAPH) is a public health problem in mountainous areas of the world. In Kyrgyzstan, the Tien-Shan and Pamir mountains occupy ~90% of the territory and more than 200,000 people live >2500 m above sea level. Previous studies have suggested that 4–6% of Kyrgyz highlanders with pulmonary hypertension develop right ventricular failure [1].

HAPH is characterised by increased pulmonary arterial pressure (P_{pa}) and pulmonary vascular remodelling involving all elements of the vessel wall, including endothelial and smooth muscle cells and fibroblasts [2–4]. Diagnosing the condition is dependent on accurate measurement of P_{pa} . Direct measurement by cardiac catheter remains the gold standard but there are practical problems with using this technique at altitude and it is unacceptable for routine screening. ECG and Doppler echocardiography assessments are alternative approaches but their sensitivity and specificity remain uncertain.

The purpose of the current study was to determine the value of Doppler echocardiography in screening for HAPH.

METHODS AND MATERIALS

Patients

The study population was recruited from 1,430 ethnic Kyrgyz residents (aged 18–86 yrs) of four villages in the Naryn region (altitudes 2,500–3,000 m) and Ak-Say plateau (altitude 3,600 m) of Kyrgyzstan who underwent health screening by history, physical examination, blood pressure measurement, spirometry and ECG (fig. 1). Subjects were invited for further investigation by echocardiography and cardiac catheterisation in Bishkek (altitude 760 m) if they met the following criteria. 1) ECG signs of right ventricular hypertrophy (ECG-RVH), defined later, without obvious cause and an otherwise normal medical examination. Alternatively, normal ECG and medical examination and in the same age group as subjects with ECG-RVH. 2) Willing to travel to Bishkek. In total, 63 subjects volunteered

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STATEMENT OF INTEREST

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but three were subsequently excluded on rescreening in Bishkek because of an atrial septal defect (two subjects) or coronary vascular disease (one subject). Of the remaining 60, none had evidence of coexisting disease (table 1). Forty-four (mean \pm SD aged 51 ± 16 yrs) had ECG-RVH and 16 (aged 47 ± 15 yrs) had a normal ECG. The ethics committee of the National Center of Cardiology and Internal Medicine (Bishkek, Kyrgyzstan) approved the study and all subjects gave informed consent.

ECG

Standard 12-lead ECG was performed at high altitude and repeated in Bishkek in the 60 highlanders volunteering for further investigation. RVH was diagnosed using one of the following patterns [5]: right axis deviation, defined as a frontal plane QRS axis of ≥ 90 (pattern A); R wave in lead V_1 of ≥ 5 mm, an R/S ratio of >1 , and $S > R$ in V_5 or V_6 (pattern B); a leftward shift in the transition zone (pattern C).

Doppler echocardiography

Doppler echocardiography was performed using a commercially available portable Doppler echocardiograph (Sequoia 256; Acuson Corporation, Mountain View, CA, USA) and a transducer array of 2.5 MHz. Images were obtained from standard parasternal views (long axis and short axis) and an apical four-chamber view. The subjects were placed in the left

lateral decubitus position for the parasternal views and in a supine position for the apical four-chamber view. Patients were investigated in the morning after 30 min of rest. Recordings were made on S-VHS videotape with simultaneous tracing of the ECG. The recordings were analysed by two independent echocardiographers, who were unaware of the clinical histories or cardiac catheter results. Right ventricle end-systolic and end-diastolic diameters were measured by M-mode echocardiography from the left parasternal short- and long-axis views. Continuous Doppler tricuspid regurgitant jets were recorded and analysed for the estimation of systolic P_{pa} [6]. A pulsed Doppler pulmonary blood flow velocity signal was sampled in the right ventricular outflow tract for the estimation of mean P_{pa} [7]. For this purpose, an acceleration time was defined as the time interval from the onset of forward flow in the pulmonary artery to the peak velocity of this flow [7]. HAPH was diagnosed if resting mean P_{pa} was ≥ 25 mmHg [4]. A right ventricular anterior wall thickness >0.5 cm was taken as evidence of RVH [8].

Right heart catheterisation

Right heart catheterisation was performed in Bishkek within 24 h of the echocardiography with a Swan-Ganz thermodilution catheter (Baxter Healthcare, Compton, UK) introduced *via* an internal jugular vein. The investigator was unaware of the echocardiography data. Patients were investigated in the supine position, in the morning after 30 min of rest. Baseline measurements consisted of systolic, diastolic and mean P_{pa} and pulmonary artery wedge pressure. Cardiac output was measured by continuous thermodilution with a Vigilance Monitor (Baxter Healthcare). Arterial oxygen saturation, ECG and blood pressure were monitored throughout. HAPH was diagnosed if resting mean P_{pa} was ≥ 25 mmHg [4].

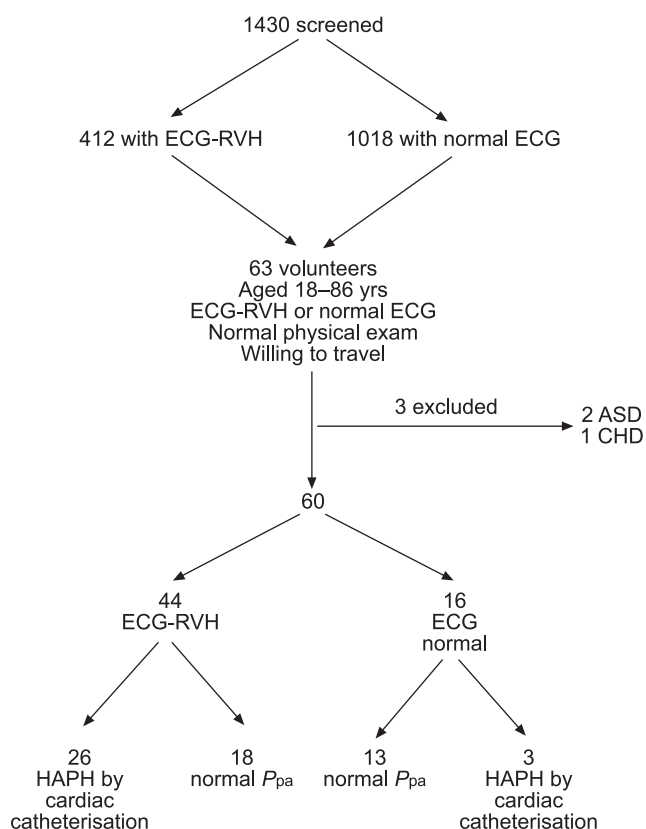


FIGURE 1. Flow of study subjects from screening to diagnosis of high-altitude pulmonary hypertension (HAPH) by cardiac catheterisation. ECG-RVH: right ventricular hypertrophy on ECG; P_{pa} : pulmonary artery pressure; ASD: atrial septal defect; CHD: coronary heart disease.

TABLE 1 Patient characteristics

	Total catheterised	ECG-RVH	Normal ECG
Subjects n	60	44	16
Age yrs	49.8 (18–71)	50.9 (18–71)	47.3 (26–70)
Sex			
Male	55	39	16
Female	5	5	0
Resident altitude 2500–3000 m	38	26	12
Resident altitude 3000–3600 m	22	18	4
BMI kg·m⁻²	26 \pm 5	26 \pm 5	26 \pm 3
Systolic BP mmHg	125 \pm 16	123 \pm 18	128 \pm 16
Diastolic BP mmHg	77 \pm 8	77 \pm 7	79 \pm 7
FEV1 % pred	93 \pm 16	93 \pm 17	91 \pm 13
FVC % pred	94 \pm 16	94 \pm 18	94 \pm 9
Smokers	5	0	5

Data are presented as n, median (range) or mean \pm SD. ECG-RVH: right ventricular hypertrophy on ECG; BMI: body mass index; BP: blood pressure; FEV1: forced expiratory volume in one second; % pred: % predicted; FVC: forced vital capacity.

Study protocol

Thus, 60 Kyrgyz highlanders were recruited, 44 with ECG-RVH and 16 with a normal ECG; all with no other clinical or spirometric evidence of cardiovascular or respiratory disease. The sensitivity and specificity of the ECG for the detection of RVH was evaluated on the basis of echocardiographic measurement of right ventricular wall thickness in all the subjects. The sensitivity and specificity of Doppler echocardiography for the detection of pulmonary hypertension was evaluated on the basis of invasive measurements of P_{pa} .

Statistical analyses

Results are expressed as mean \pm SD. $P < 0.05$ was taken as evidence of significance. An unpaired t-test was used for the comparisons between groups. A paired t-test was used for comparisons within groups. Data from catheterisation and echocardiography studies were examined using Spearman and Bland-Altman analyses [9]. The performance of ECG data with respect to the diagnosis of RVH and HAPH, and echocardiography data in the diagnosis of HAPH was assessed by calculating sensitivity (true positives/(true positives+false negatives)), specificity (true negatives/(true negatives+false positives)), and positive (true positives/(true positives+false positives)) and negative predictive values (true negatives/(true negatives+false negatives)).

RESULTS

ECG

Of the 1,430 high-altitude residents (age 38 ± 1 yrs; 660 male) screened, 412 (29%; 290 male) subjects had one or more ECG-RVH pattern. Pattern A was observed in 124 (8.7%) subjects, pattern B in 11 (0.8%) and pattern C in 167 (11.6%; fig. 1). Additionally, 86 (6%) subjects had a combination of patterns A and C, three (0.2%) had a combination of patterns A and B and 21 (1.5%) had a combination of patterns A, B and C. The prevalence of ECG-RVH was related to the altitude of residency; 23.3% of subjects living at altitudes 2,500–3,000 m and 55.3% of subjects residing higher than 3,000 m above sea level had ECG-RVH ($p < 0.01$).

Echocardiography study

Although tricuspid regurgitation was identified in 42 out of 60 (69%) subjects, a signal of sufficient quality for unequivocal reading of a maximum velocity was recovered in only 17 (28%) of them. On the other hand, a satisfactory pulmonary flow velocity signal was recovered in all 60 (100%) subjects. Therefore, only the acceleration time of pulmonary blood flow velocity was used for the estimation of P_{pa} . Calculated mean P_{pa} ranged 14–44 mmHg (mean P_{pa} 26 ± 7 mmHg). In total, 37 subjects were considered to have HAPH based on a mean $P_{pa} \geq 25$ mmHg and 23 were regarded as normal (table 2). Right ventricular dimensions and right ventricular anterior wall thickness in patients with HAPH were significantly greater than in normal subjects (2.6 ± 0.6 versus 2.1 ± 0.5 cm; $p < 0.001$ and 0.5 ± 0.1 versus 0.4 ± 0.05 cm; $p < 0.001$).

Right heart catheterisation study

Mean P_{pa} measured at right heart catheterisation ranged 15–54 mmHg (26 ± 8 mmHg). Mean P_{pa} was ≥ 25 mmHg in 29 highlanders and was normal in 31 (table 3). Mean age in the group diagnosed with HAPH was higher than in the normal

TABLE 2 ECG study

Parameters	HAPH	Normal
Subjects n	37	23
AcT ms	91 ± 3	$120 \pm 2^{\#}$
P_{pa} mmHg	30 ± 6	$19 \pm 3^{\#}$
fc beats·min ⁻¹	68 ± 10	64 ± 8

Data are presented as n or mean \pm SD. HAPH: high-altitude pulmonary hypertension; AcT: acceleration time; P_{pa} : pulmonary arterial pressure, fc: cardiac frequency. #: $p < 0.001$ compared with HAPH group.

group ($p < 0.001$). Mean and systolic P_{pa} and pulmonary vascular resistance (PVR) were also significantly higher in HAPH patients compared with the normal controls ($p < 0.001$). Cardiac output and frequency did not significantly differ between these two groups.

Sensitivity and specificity of ECG in diagnosis of RVH and HAPH

In 44 subjects with one or more ECG-RVH patterns, the right ventricular anterior wall thickness was >0.5 cm on echocardiographic study in 22 subjects, giving an ECG sensitivity for diagnosing RVH of 50%. In 16 subjects with a normal ECG, the right ventricular wall thickness was normal (0.4 ± 0.05 cm), giving a specificity of 100%. Negative predictive value by ECG was 42% and positive predictive value was 100%.

In 44 subjects with ECG-defined RVH, pulmonary hypertension was confirmed by direct invasive measurement in 26 subjects. Thus, the sensitivity of ECG for detecting HAPH was 59%. In 16 subjects with a normal ECG, pulmonary hypertension was diagnosed at right heart catheterisation in three subjects, giving a specificity for ECG of 81%. Negative predictive value of ECG was 42% and positive predictive value was 90%.

TABLE 3 Right heart catheterisation study

Parameters	HAPH	Normal
Subjects n	29	31
Age yrs	58.3 ± 9.8	$41.7 \pm 15.9^{\#}$
P_{pa} mmHg	33 ± 7	$20 \pm 3^{\#}$
Systolic P_{pa} mmHg	49 ± 11	$32 \pm 5^{\#}$
PVR dyne·sec ⁻¹ ·cm ⁻⁵	374 ± 159	$194 \pm 56^{\#}$
CO L·min ⁻¹	5.4 ± 1.2	5.3 ± 1.2
fc beats·min ⁻¹	67 ± 9	66 ± 11

Data are presented as n or mean \pm SD. HAPH: high-altitude pulmonary hypertension; P_{pa} : pulmonary arterial pressure; PVR: pulmonary vascular resistance; CO: cardiac output; fc: cardiac frequency. #: $p < 0.001$ compared with HAPH subjects.

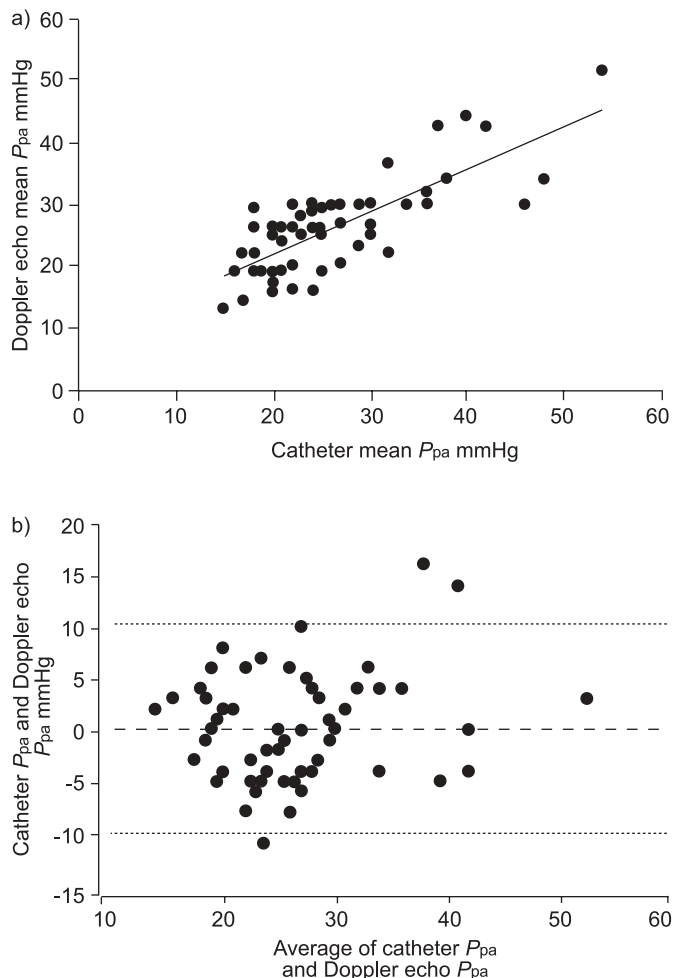


FIGURE 2. a) Correlation between mean pulmonary arterial pressure P_{pa} estimated by Doppler echocardiography (Doppler echo P_{pa}) and mean P_{pa} measured invasively by right heart catheterisation (catheter P_{pa}). The correlation coefficient between echocardiography and catheterisation studies was $r^2=0.78$ (—). b) Bland-Altman plot of the same data. ---: mean;: $\pm 1.96SD$.

Sensitivity and specificity of echocardiography in diagnosis of HAPH

A total of 12 subjects from the pulmonary hypertension group diagnosed at echocardiography (echocardiography mean P_{pa} 27 ± 2 mmHg) had a normal mean P_{pa} on cardiac catheterisation (22 ± 2 mmHg; $p < 0.001$). Four subjects with normal mean P_{pa} on echocardiography (21 ± 2 mmHg) had pulmonary hypertension on direct measurement (mean P_{pa} 28 ± 3 mmHg; $p < 0.005$). Thus, the sensitivity of echocardiography for HAPH was 70% and the specificity was 88%. The negative predictive value of echocardiography was 72% and the positive predictive value was 88%. The correlation coefficient between echocardiography and catheterisation studies was $r^2=0.78$, and the Bland-Altman analysis showed a satisfactory agreement between the two methods of measurement (fig. 2).

DISCUSSION

The present results show that a combination of clinical examination, ECG and echocardiography can be useful for

noninvasive screening for pulmonary hypertension in high-altitude populations.

P_{pa} can be estimated from Doppler echocardiographic measurements of tricuspid regurgitation or pulmonary flow waves [10]. The most commonly used echocardiographic method relies on the measurement of maximum velocity of tricuspid regurgitation and calculating the trans-tricuspid pressure gradient using the simplified form of the Bernoulli equation:

$$\Delta P_{RV-RA} = 4(V_{TR})^2 \quad (1)$$

where ΔP is pressure difference, RV the right ventricle, RA the right atrium and V_{TR} the maximum velocity of tricuspid regurgitation [6]. Systolic P_{pa} is then estimated by adding the clinically determined mean jugular venous pressure to the pressure gradient between the right ventricle and atrium [6]. This method has been widely used in patients with a variety of cardiac diseases, with reported correlation coefficients between Doppler and catheter measurements ranging 0.89–0.97, accurate prediction of P_{pa} over a wide range of pressures and low interobserver variability [10]. A good agreement between catheter and Doppler tricuspid regurgitation measurements of systolic P_{pa} has even been reported in high-altitude environments [11]. However, as illustrated by the present study, the recovery rate of sufficient quality Doppler velocity envelopes for an accurate determination of maximum velocity of regurgitation decreases with the severity of pulmonary hypertension, down to 24–50% in normal subjects and in patients with mild pulmonary hypertension secondary to chronic lung diseases [10]. This may be the reason for a high proportion of false positives and negatives reported in screening programmes for pulmonary hypertension using Doppler studies of tricuspid regurgitation [12].

The alternative, though less popular, Doppler echocardiographic method for the estimation of P_{pa} is based on the analysis of the morphology of pulmonary artery flow waves [7]. The acceleration time of pulmonary flow has been repeatedly showed to be inversely correlated to mean P_{pa} , with correlation coefficients ranging 0.65–0.96 in a variety of cardiac and pulmonary conditions [10]. The intraobserver and interobserver variabilities and errors on the estimate are somewhat higher than on the maximum velocities of tricuspid regurgitation, but the recovery rate of adequate signals is higher, in the range 81–98%, even in patients with chronic obstructive lung disease [10], and may attain 100% in normal subjects [13]. Acceleration time is affected by heart rate, but this only matters outside the normal range: $< 60 \cdot \text{min}^{-1}$ or $> 100 \cdot \text{min}^{-1}$ [14], which did not occur in the present study. In the present selected group of altitude inhabitants, the recovery rate of adequate quality Doppler pulmonary artery flow waves was 100%, and there was a correlation of $r^2=0.78$, showing a good agreement with invasively measured mean P_{pa} . The sensitivities and specificities of 70 and 88%, respectively, appear to be adequate for a screening programme, although admittedly this should be systematically evaluated on a larger patient population than in the present investigation.

A recognised limitation of the study is that the echocardiography and catheterisations were performed within the first 7 days after the patients were brought down to 760 m. This would certainly reverse hypoxia-induced increase in pulmonary vascular tone,

and less so pulmonary vascular remodelling, as indicated by persistently increased P_{pa} in the patients with HAPH. The current authors assume that the agreement between echocardiographic and catheter measurements observed at 760 m would stay the same at higher altitudes.

It is important to emphasise that the present study also relied on ECG as a screening tool for high-altitude pulmonary hypertension. The ECG is affected by right ventricular hypertrophy, itself a consequence of sustained elevation in pulmonary arterial pressure. The ECG is generally believed to be insensitive to the presence of pulmonary hypertension, as reported sensitivities have been as low as 20% [8]. In the present study, the sensitivity of the ECG for the detection of right ventricular hypertrophy was 50%, but the specificity was 100%. As for the detection of catheter-confirmed pulmonary hypertension, the sensitivity and specificity of the ECG were 59 and 81%, respectively. These numbers compare favourably with general belief that ECG cannot be used for the screening for pulmonary hypertension. Therefore, it may be worth re-evaluating the performance of ECG, both alone and in combination with echocardiography, in larger numbers of patients at risk of pulmonary hypertension.

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