

**NONINVASIVE AND INVASIVE EVALUATION OF PULMONARY ARTERIAL  
PRESSURE IN KYRGYZ HIGHLANDERS**

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**SHORT TITLE:**

**PULMONARY ARTERY PRESSURE IN HIGHLANDERS**

## ABSTRACT

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

Sixty (55 male) patients aged 18 to 71 years were recruited from an electrocardiographic screening program applied to 1430 inhabitants living between 2500 and 3600 m in Kyrgyzstan. Forty-four met electrocardiographic criteria for right ventricular hypertrophy. All underwent a Doppler echocardiography followed by a cardiac catheterization within 7 days of arrival in Bishkek (760m). Pulmonary artery pressure was estimated from the pulmonary flow acceleration time and from the maximum velocity of tricuspid regurgitation.

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. Thirty-seven of the patients (62%) had pulmonary hypertension on echocardiography. Pulmonary hypertension was confirmed in 29 on catheterization. Pulmonary hypertension was detected with 70% sensitivity and 88% specificity by echocardiography, as compared to 59 % sensitivity and 81 % specificity of electrocardiography. The correlation coefficient between echocardiography and catheterization studies was  $r^2=0.78$ .

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

**Key words:** echocardiography, electrocardiography, high altitude pulmonary hypertension, pulmonary circulation, right heart catheterization.

## INTRODUCTION

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

High altitude pulmonary hypertension is characterized by increased pulmonary arterial pressure (PAP) and pulmonary vascular remodeling 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 PAP. 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. Electrocardiography (ECG) and Doppler-echocardiography assessments are alternative approaches, but their sensitivity and specificity remain uncertain.

The purpose of this study was to determine the value of Doppler-echocardiography for the screening for high altitude pulmonary hypertension.

## MATERIALS AND METHODS

### Patients

The study population was recruited from 1430 ethnic Kyrgyz residents (aged 18 to 86 years) of four villages in the Naryn region (altitudes 2500-3000 m) and Ak-Say plateau (altitude 3600 m) of Kyrgyzstan who underwent health screening by history, physical examination, blood pressure measurement, spirometry and ECG (Figure 1). Subjects were invited for further investigation by echocardiography and cardiac catheterization in Bishkek (altitude 760m) if they met the following criteria: (a) ECG signs of right ventricular hypertrophy, defined below, without obvious cause and an otherwise normal medical examination or (b) normal ECG and medical examination and in the same age group as subjects with ECG signs of right ventricular hypertrophy and (c) willing to travel to Bishkek. Sixty-three subjects volunteered but 3 were subsequently excluded on rescreening in Bishkek because of an atrial septal defect (2 subjects) or coronary vascular disease (1 subject). Of the remaining 60, none had evidence of co-existing disease (Table 1). Forty-four (aged  $51 \pm 16$ , mean  $\pm$  SD years) had ECG criteria for right ventricular hypertrophy and 16 (aged  $47 \pm 15$  years) had a normal ECG. The ethics committee of the National Center of Cardiology and Internal Medicine (Bishkek, Kyrgyz Republic) approved the study and all subjects gave informed consent.

### Electrocardiography

Standard 12-lead ECG was performed at high altitude and repeated in Bishkek in the 60 highlanders volunteering for further investigation. Right ventricular hypertrophy was diagnosed using one of the following patterns [5]: right axis deviation, defined as a frontal plane QRS axis of  $\geq 90$  (pattern A); R wave in lead  $V_1$  of  $\geq 5$  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, USA) and a transducer array of 2.5 MHz. Images was 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 minutes rest. Recordings were made on S-VHS videotape with simultaneous tracing of the electrocardiogram. The recordings were analyzed 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 PAP (6). A pulsed Doppler pulmonary blood flow velocity signal was sampled in the right ventricular outflow tract for the estimation of mean PAP (7). For this purpose, an acceleration time (AcT) defined as the time from the onset to peak pulmonary velocity flow (7). High altitude pulmonary hypertension was diagnosed if resting mean PAP was  $\geq 25$  mmHg [4]. A right ventricular anterior wall thickness  $>0.5$ cm was taken as evidence of right ventricular hypertrophy [8].

### **Right heart catheterization**

Right heart catheterization was performed in Bishkek within 24h 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 minutes rest. Baseline measurements were made of systolic, diastolic and mean PAP and pulmonary artery wedge pressure. Cardiac output was measured by continuous thermodilution with a Vigilance Monitor (Baxter Healthcare, Compton, USA). Arterial oxygen saturation, ECG and blood pressure were monitored throughout. High altitude pulmonary hypertension was diagnosed if resting mean PAP was  $\geq 25$  mmHg [4].

### **Study protocol**

Thus 60 Kyrgyz highlanders were recruited, 44 with an ECG suggestive of right ventricular hypertrophy, and 16 with a normal ECG, and otherwise no clinical or spirometric evidence of cardiovascular or respiratory disease. The sensitivity and specificity of the ECG for the detection of right ventricular hypertrophy 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 pulmonary artery pressures.

### **Statistical analyses**

Results are expressed as mean  $\pm$  SD.  $p < 0.05$  was taken as an evidence of significance. The unpaired Student's *t*-test was used for the comparisons between groups. A paired *t*-test was used for within group comparisons. Data from catheterization and echocardiography studies were examined using Spearman and Bland–Altman analyses (9). The performance of ECG data with respect to the diagnosis of right ventricular hypertrophy and high altitude pulmonary hypertension and echocardiography data in the diagnosis of high altitude pulmonary hypertension 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

**Electrocardiography:** Of the 1430 high altitude residents (mean age  $38\pm 1$  years, 660 male) screened, 412 (290 male) subjects (29%) had one or more ECG patterns of right ventricular hypertrophy. Pattern A was observed in 124 subjects (8.7%), pattern B in 11 (0.8%), pattern C in 167 subjects (11.6%) (Figure 1). Eighty-six subjects had a combination of patterns A and C (6%), 3 (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 signs of right ventricular hypertrophy was related to the altitude of residency; 23.3% of subjects living at altitudes 2500-3000 m above sea level and 55.3% of subjects resident higher than 3000 m above sea level had ECG signs of right ventricular hypertrophy ( $p<0.01$ ).

**Echocardiography study:** Although a tricuspid regurgitation was identified in 42 of our 60 highlanders (69 %), and a sufficient quality signal for unequivocal reading of a maximum velocity was recovered in only 17 of them (28 %). On the other hand, a satisfactory pulmonary flow velocity signal was recovered in all of our 60 highlanders (100 %). Therefore, only the acceleration time of pulmonary blood flow velocity was used for the estimation of PAP. Calculated mean PAP ranged from 14 to 44 mm Hg (mean PAP =  $26\pm 7$  mm Hg). Thirty-seven highlanders were considered to have high altitude pulmonary hypertension based on a mean PAP  $\geq 25$  mmHg and 23 were regarded as normal (Table 2). Right ventricular dimensions and right ventricular anterior wall thickness in patients with high altitude pulmonary hypertension were significantly greater than in normal subjects ( $2.6\pm 0.6$  vs  $2.1\pm 0.5$ ,  $p<0.001$  and  $0.5\pm 0.1$  vs  $0.4\pm 0.05$  cm,  $p<0.001$  respectively).

**Right heart catheterization study.** Mean PAP measured at right heart catheterization ranged from 15 to 54 mm Hg ( $26\pm 8$  mm Hg). Mean PAP was  $\geq 25$  mm Hg in 29 highlanders and was normal in 31 highlanders (Table 3). Mean age in the group diagnosed with high altitude

pulmonary hypertension was higher than in the normal group ( $p<0.001$ ). Mean and systolic PAP and pulmonary vascular resistance (PVR) were also significantly higher in high altitude pulmonary hypertensive patients compared with the normal controls ( $p<0.001$ ). Cardiac output and heart rate did not significantly differ between these two groups.

**Sensitivity and specificity of ECG in diagnosis of right ventricular hypertrophy and high altitude pulmonary hypertension.** In 44 highlanders with one or more ECG patterns of right ventricular hypertrophy, the right ventricular anterior wall thickness was  $> 0.5$  cm on echocardiographic study in 22 subjects, giving an ECG sensitivity for diagnosing right ventricular hypertrophy of 50%. In 16 highlanders with a normal ECG the right ventricular wall thickness was normal ( $0.4\pm 0.05$  cm), giving a specificity of 100%. Negative predictive value by ECG was 42% and positive predictive value was 100%.

In 44 highlanders with ECG-defined right ventricular hypertrophy, pulmonary hypertension was confirmed by direct invasive measurement in 26 subjects. Thus, the sensitivity of ECG for detecting high altitude pulmonary hypertension was 59%. In 16 highlanders with a normal ECG, pulmonary hypertension was diagnosed at right heart catheterisation in 3 subjects, giving a specificity for ECG of 81%. Negative predictive value of ECG was 42% and positive predictive value was 90%.

**Sensitivity and specificity of echocardiography in diagnosis of HAPH.** Twelve highlanders from the pulmonary hypertension group diagnosed at echocardiography (echocardiography mean PAP =  $27\pm 2$  mm Hg) had a normal mean PAP on cardiac catheterization (mean PAP  $22\pm 2$  mm Hg,  $p<0.001$ ). Four highlanders with normal mean PAP on echocardiography (echocardiography mean PAP =  $21\pm 2$  mm Hg) had pulmonary hypertension on direct measurement (mean PAP  $28\pm 3$  mm Hg,  $p<0.005$ ). Thus, the sensitivity of echocardiography for high altitude pulmonary hypertension 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 catheterization studies was  $r^2=0.78$ , and the Bland and



Altman analysis showed a satisfactory agreement between the two methods of measurement (Figure 2).

## DISCUSSION

The present results show that a combination of clinical examination, electrocardiography and echocardiography can be useful to the non-invasive screening for pulmonary hypertension in high altitude populations.

Pulmonary artery pressure can be estimated from Doppler echocardiographic measurements of tricuspid regurgitation or pulmonary flow waves (10). The most commonly echocardiographic method relies on the measurement of a maximum velocity of tricuspid regurgitation and calculating the trans-tricuspid pressure gradient using the simplified form of the Bernoulli equation:  $\Delta P_{RV-RA} = 4(V_{TR})^2$ , where  $\Delta P$  is pressure difference, RV the right ventricle, RA the right atrium and  $V_{TR}$  the maximum velocity of tricuspid regurgitation (6). Systolic PAP 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 between 0.89 and 0.97, accurate prediction of PAP over a wide range of pressures, and low interobserver variability (10). A good agreement between catheter and Doppler tricuspid regurgitation measurements of systolic PAP 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 a maximum velocity of regurgitation decreases with the severity of pulmonary hypertension, down to 24 to 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 programs for pulmonary hypertension using Doppler studies of tricuspid regurgitation (12).

The alternative, though less popular, Doppler echocardiographic method for the estimation of PAP is based on the analysis of the morphology of pulmonary artery flow waves (7). The acceleration time of pulmonary flow has been repeatedly shown to be inversely correlated to mean PAP, with correlation coefficients ranging from 0.65 to 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 of 81 % to 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 matters only out of the normal range, below 60/min or above 100/min (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 tight correlation ( $r^2=0.78$ ) a good agreement with invasively measured mean PAP. The sensitivities and specificities of 70 % and 88 % respectively appear to be adequate for a screening program, although admittedly this should be systematically evaluated on a larger patient population than in the present investigation.

A recognized limitation of the study is that the echocardiography and catheterizations were performed within the first 7 days after the patients were brought down to 760m. This would certainly reverse hypoxia-induced increase in pulmonary vascular tone, less so pulmonary vascular remodelling, as indicated by persistently increased PAP in the patients with high altitude pulmonary hypertension. We assume that the agreement between echocardiographic and catheter measurements observed at 760 m would stay the same at higher altitudes.

It is important to emphasize that the present study also relied on the 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 PAP. The ECG is generally believed to be insensitive to the presence of pulmonary hypertension, as reported sensitivities have been as low as down to 20 % (8). In the present study, the sensitivity of the ECG for the detection of right ventricular hypertrophy was 50 %, but the specificity 100 %. As for the detection of catheter-confirmed pulmonary hypertension, the sensitivity and specificity of the ECG were respectively of 59 % and 81 %. These numbers compare favorably with general belief that the ECG cannot be used for the screening for pulmonary hypertension. It may be worth therefore to reevaluate the performance of ECG, alone and in combination with echocardiography, on larger numbers of patients at risk of pulmonary hypertension.

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**Figure legends:**

Figure 1. Flow of study subjects from screening to diagnosis of HAPH by cardiac catheterisation. ECG-RVH, right ventricle hypertrophy on ECG; PAP, pulmonary artery pressure; ASD, atrial septal defect; CHD, coronary artery disease.

Figure 2 (a). Correlation between mean pulmonary artery pressure (PAP) estimated by Doppler-echocardiography (mean PAP by Doppler-echo) and mean PAP measured invasively by right heart catheterization (mean PAP by cath). The correlation coefficient between echocardiography and catheterization studies was  $r^2=0.78$ . (b) Bland-Altman plot of the same.

**Table 1. Patients characteristics**

	<b>All catheterised ( 60)</b>	<b>ECG-RVH (44)</b>	<b>Normal ECG (16)</b>
<b>Age (range)</b>	49.8 (18-71)	50.9 (18-71)	47.3 (26-70)
<b>Gender (M:F)</b>	55 M 5 F	39 M 5 F	16 M
<b>Resident altitude 2500-3000m</b>	38	26	12
<b>Resident altitude 3000-3600m</b>	22	18	4
<b>BMI (kg/m<sup>2</sup>)</b>	26±5	26±5	26±3
<b>Systolic BP (mmHg)</b>	125±16	123±18	128±16
<b>Diastolic BP (mmHg)</b>	77±8	77±7	79±7
<b>FEV<sub>1</sub> (% predicted)</b>	93±16	93±17	91±13
<b>FVC (% predicted)</b>	94±16	94±18	94±9
<b>Smokers (number)</b>	5	0	5

Legend: RVH: right ventricular hypertrophy; ECG: electrocardiogram; BP: blood pressure; FEV<sub>1</sub>: forced expiratory volume in one second; FVC: forced vital capacity

**Table 2. Echocardiography Study**

<b>Parameters</b>	<b>HAPH (n=37)</b>	<b>Normal (n=23)</b>
<b>AcT (ms)</b>	91±3	120±2*
<b>mPAP (mm Hg)</b>	30±6	19±3*
<b>HR (beats/min)</b>	68±10	64±8

Legend: HAPH: high altitude pulmonary hypertension; AcT – acceleration time, mPAP – mean pulmonary arterial pressure, HR – heart rate. \*p>0.001 – compared with HAPH group.



**Table 3. Right Heart Catheterization Study**

<b>Parameters</b>	<b>HAPH (n=29)</b>	<b>Normal (n=31)</b>
<b>Age (years)</b>	58.3±9.8	41.7±15.9*
<b>mPAP (mm Hg)</b>	33±7	20±3*
<b>sPAP (mm Hg)</b>	49±11	32±5*
<b>PVR (dyne sec cm<sup>-5</sup>)</b>	374±159	194±56*
<b>CO (l/min)</b>	5.4±1.2	5.3±1.2
<b>HR (beats/min)</b>	67±9	66±11

HAPH: high altitude pulmonary hypertension; mPAP – mean pulmonary arterial pressure, sPAP – systolic pulmonary arterial pressure, PVR – pulmonary vascular resistance, CO- cardiac output, HR – heart rate, \*p<0.001– compared with HAPH subjects

**Figure 1**

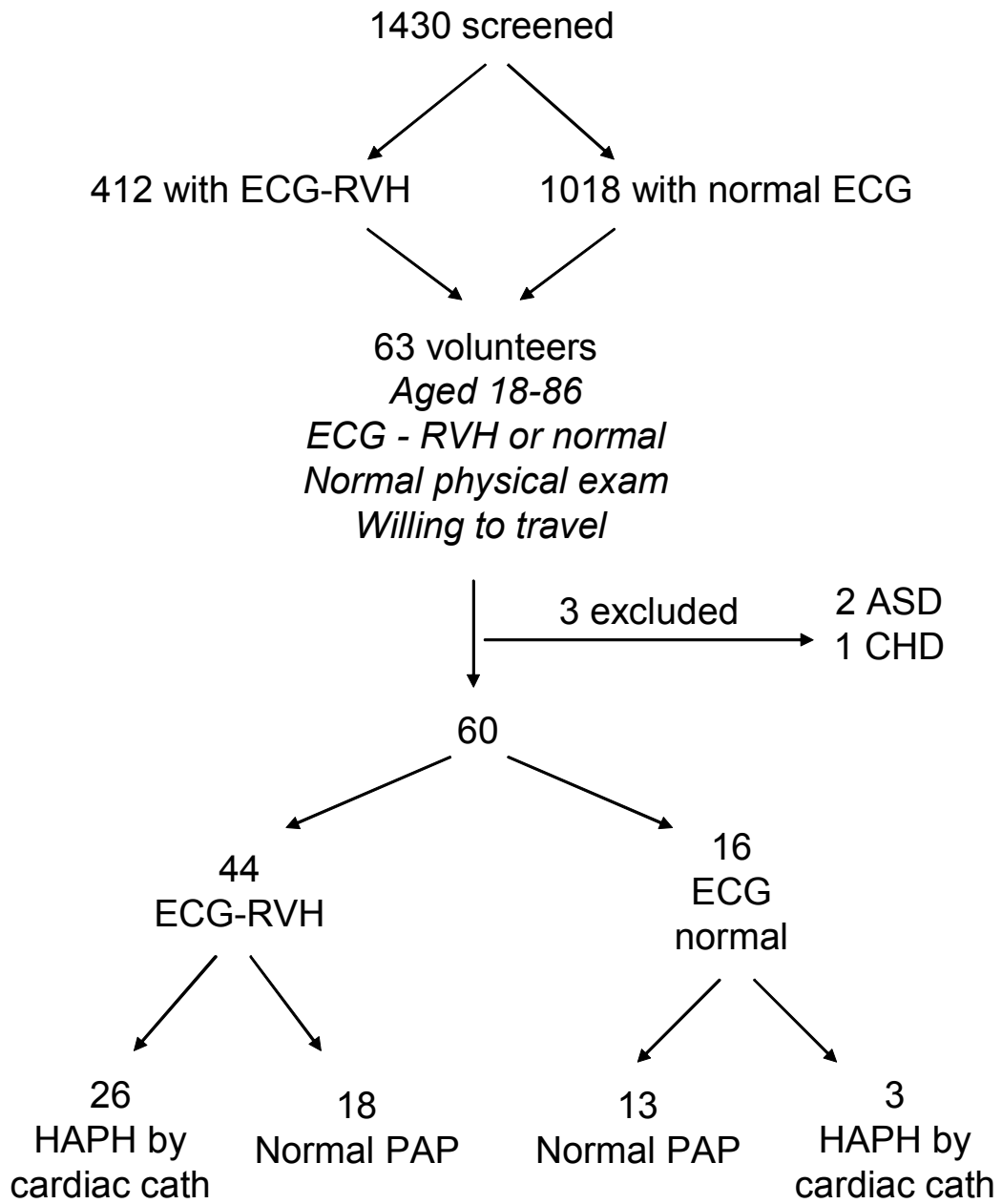


Figure 2

(a)

