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Dobutamine stress echocardiography in pulmonary arterial hypertension☆

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ABSTRACT

Background: There is a growing interest in exploring the concept of right ventricular functional reserve in patients with pulmonary arterial hypertension. However, it is still unclear how it should be assessed. Aim of the study was to investigate the determinants of the changes in cardiac output and in pulmonary pressure during dobutamine stress echocardiography in pulmonary arterial hypertension.
Methods: Low-dose dobutamine stress echocardiography was performed in 55 patients and 28 controls. Tricuspid annular plane systolic excursion, its ratio to systolic pulmonary artery pressure, right ventricular area change, degree of tricuspid regurgitation, right ventricular end-systolic pressure-area ratio, cardiac output were assessed at rest and at peak stress.
Results: According to the stress induced increase in cardiac output, patients were classified into 2 groups: above/equal to the median of 2.8 L/min (high cardiac output) or below the median (low cardiac output). High cardiac output patients were characterized by a greater increase in heart rate ($+45.1 \pm 17.5$ vs $+21.3 \pm 17.7$ bpm), a greater improvement in tricuspid annular plane systolic excursion ($+4.2 \pm 3.3$ vs $+1.9 \pm 2.6$ mm, $P = 0.005$) and a decrease in tricuspid regurgitation ($P = 0.010$) as compared to low cardiac output patients. Changes in pulmonary pressure were not associated with changes in indicators of right ventricular function but only with changes in heart rate.
Conclusions: The increase in cardiac output during dobutamine is associated with an improvement in longitudinal right ventricular function, a decrease in tricuspid regurgitation and an increase in heart rate. Changes in pulmonary pressure only reflect the changes in heart rate.

1. Introduction

Over the past twenty years, it has been consistently shown that left ventricular contractile reserve is useful to predict outcome in coronary artery disease, in heart failure and in valvular heart disease. In fact, the response of the left ventricle to exercise or to dobutamine portends a greater prognostic power than left ventricular functional parameters at rest, whichever is the clinical outcome considered (i.e. survival, recovery after surgery or response to cardiac resynchronization therapy) [1–3].

More recently researchers began to explore the concept of contractile reserve in patients with pulmonary arterial hypertension (PAH). In PAH survival depends on the capability of the right ventricle to adapt to chronically elevated pulmonary artery pressure. Therefore, an accurate evaluation of RV pump function is crucial for diagnosis and follow-up assessment. The concept of right ventricular (RV) contractile reserve has been prompted by a study where it was assumed that it could be indirectly assessed by the increase in pulmonary artery pressure (PAP) during exercise; the study demonstrated that the inability to augment PAP during exercise was associated with poorer survival [4]. The hypothesis that changes in PAP indicate changes in RV contractility has subsequently been questioned by a pathophysiological study which failed to demonstrate exertional RV contractile reserve in PAH patients and concluded that rest-to-exercise response in PAP only reflects the rest-to-exercise response in heart rate [5]. A recent study paid a greater attention to the exercise induced changes in the right

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ventricle but it only included healthy subjects [6]. In theory, dobutamine stress echocardiography has potential advantages over exercise (since patient cooperation with exercise is not required and acquisition of RV image is facilitated); however, few small studies used dobutamine as a stressor to estimate RV contractile reserve [7–9] and a precise characterization of the changes in RV function and of the changes in pulmonary artery pressure induced by dobutamine is still lacking.

In the present study, standard two-dimensional and Doppler echocardiography was used to obtain a description of the response of the right heart to stress in PAH patients, in order to gain information on which are the determinants of the increase in cardiac output and which are the determinants of the increase in pulmonary artery pressure during stress.

2. Methods

2.1. Patients

The study includes 58 PAH patients aged >18 yo diagnosed according to Guidelines recommendations [10], admitted to a referral center for pulmonary arterial hypertension. Twenty-eight healthy controls were included with age similar to that of the patients, no history of cardiorespiratory conditions, normal electrocardiogram and normal baseline transthoracic echocardiography.

The investigation conforms to the principles outlined in the Declaration of Helsinki. All patients signed an informed consent to collect data for scientific purpose, and subsequently the Ethical Committee gave the approval for the analysis (protocol no 20130003777 del 12/08/13) and all participants provided written informed consent. There is no potentially overlapping work.

2.2. Dobutamine stress echocardiography

Echocardiography images were acquired by a Vivid 7 system (GE Healthcare) with a 3.5 MHz transducer by an experienced echocardiographist. All patients underwent continuous dobutamine infusion using a low-dose protocol. Dobutamine was increased at increments of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ at 3-min intervals up to a maximum of 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The pre-specified infusion end-points were either reaching the maximum dobutamine dose, heart rate > 140 beats·min^{-1} or side-effects requiring cessation such as hypotension (systolic blood pressure < 90 mm Hg), chest pain, new onset arrhythmias. A standard echocardiogram was performed at baseline and repeated at peak stress. The examination included TAPSE (measured by M-mode tracing with 2D-echo guidance) as a robust indicator of RV function and its ratio by systolic pulmonary artery pressure (TAPSE/sPAP) [11]; RV areas and RV fractional area change (RVFAC); peak gradient between the right ventricle and the right atrium esimated from the peak tricuspid regurgitation velocity (TRV) using the Bernoulli equation; right atrial pressure (RAP) estimated on the basis of the inferior vena cava diameter and collapsibility; sPAP estimated as tricuspid gradient + estimate of RAP. The degree of tricuspid regurgitation was assesses on the basis of the area of the regurgitant jet. Stroke volume (SV) was estimated from the left ventricular outflow tract (LVOT) diameter and LVOT velocity time integral (stroke volume = LVOT velocity time integral × π (LVOT diameter / 2)); cardiac output was obtained as SV × HR. The ratio of TAPSE to PASP was calculated as a simplified indicator of the right ventricle to pulmonary circulation coupling. The RV end-systolic pressure-area ratio (RVESPAR) was calculated as a surrogate of RV contractility [12]. Mean pulmonary artery pressure (mPAP) was estimated from sPAP measurements using the Chemla formula: mPAP = 0.61 × sPAP + 2 and the mPAP/CO ratio was calculated as a surrogate measure of resistance to flow in the pulmonary circulation [13]. At each step of the dobutamine infusion systolic and diastolic blood pressure (BP) were measured by cuff and HR was recorded.

2.3. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as absolute and relative frequencies. Comparisons between PAH patients and control subjects were performed using independent *t*-test for normally distributed data and, Mann-Whitney *U* test for not normally distributed data. Chi-square tests were used to analyze dichotomous variables. Comparisons of rest-to-stress response were obtained using dependent *t*-test for normally distributed data while Wilcoxon test was used for not normally distributed data. McNemar test was applied to analyze rest-to-stress response of dichotomous variables. Statistical analyses were performed using SPSS version 21 (IBM Corp., Armonk, NY). A P value <0.05 was considered statistically significant.

3. Results

In 3 patients dobutamine stress echocardiography was prematurely stopped because of the appearance of left ventricular outflow tract obstruction (with the patients remaining asymptomatic). No cases of repetitive ventricular or supraventricular arrhythmias were observed. The baseline demographic characteristics of the 28 control subjects and of the 55 patients who completed the test are shown in Table 1. The diagnostic categories of PAH included idiopathic PAH (60%), scleroderma-associated PAH (24%) and other etiologies in the remaining 16% of patients. Baseline disease characteristics encompassed a range of severity as demonstrated by invasive haemodynamics, 6-min walk distance and WHO functional class. All patients were receiving targeted PAH therapies at the time of study.

Baseline and peak stress echocardiographic data in control subjects and PAH patients are shown in Table 2. Control subjects had a greater increase in SV and CO; PAH patients had a greater increase in sPAP and mPAP; both in control subjects and in PAH patients the mPAP/CO index slighltly decreased during dobutamine infusion.

According to the stress induced increase in CO, PAH patients were classified into 2 groups: above/equal to the median of 2.8 L/min (high CO) or below the median (low CO). At baseline, the only difference between the two groups was a lower heart rate in high CO patients than in low CO patients (respectively 70,2 ± 11,1 bpm vs 78,0 ± 14,9 bpm, P = 0.042). The changes at peak stress are shown in Table 3. In brief, high CO patients were characterized by a greater increase in HR, a greater improvement in TAPSE and a greater number of patients decreasing the degree of TR (all P = 0.010) as compared to low CO patients. Fig. 1 shows the increase in TAPSE and the disappearance of TR occurring in a single patient during stress.

According to the stress induced increase in sPAP, patients were classified into 2 groups: above/equal to the median of 21 mm Hg (high sPAP) or below the median of 21 mm Hg (low sPAP). High sPAP patients were characterized by greater changes in HR from rest to peak dobutamine; all other parameters were similar (Table 4). There was a significant correlation between the change in sPAP and the change in HR from rest to peak dobutamine (ΔsPAP and ΔHR, r = 0.415, R2 = 0.172, P = 0.005). A similar correlation was observed between the change in mPAP and the change in HR from rest to peak dobutamine (ΔmPAP and ΔHR, r = 0.416, R2 = 0.173, P = 0.004). No correlation was observed between the changes in mPAP and sPAP and the change in TAPSE from rest to peak dobutamine (ΔmPAP and ΔTAPSE, r = 0.105, R2 = 0.011, P = 0.495; ΔsPAP and ΔTAPSE, r = 0.104, R2 = 0.011, P = 0.496).

Table 1
Baseline characteristics.

	PAH patients (n = 55)	Control subjects (n = 28)
Age (years)	56 ± 16	59 ± 14
Gender F/M (n)	39/16	8/20
WHO class I/II/III (n)	7/40/8	
BNP pg/ml	241 ± 266	
6MWT (m)	450 ± 97	
Etiology: IPAH/APAH/others (n)	33/13/9	
Hemodynamic parameters		
CI (L/min/mq)	2,62 ± 0,64	
sPAP (mm Hg)	81 ± 24	
mPAP (mm Hg)	51 ± 17	
dPAP (mm Hg)	33 ± 15	
PVR (WU)	9,7 ± 4,2	
RAP (mm Hg)	6,4 ± 3,3	
PAH specific treatment		
Monotherapy (n)	15	
Double oral combination therapy	32	
Triple combination therapy	8	

Legenda: BNP = brain natriuretic peptide; 6MWT = 6 min walk test; IPAH = idiopathic pulmonary arterial hypertension; APAH = associated pulmonary arterial hypertension; sPAP systolic pulmonary artery pressure; mPAP = mean pulmonary artery pressure; dPAP = diastolic pulmonary artery pressure; PVR = pulmonary vascular resistances; RAP = right atrial pressure; PAH = pulmonary arterial hypertension.

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