

## CARDIOVASCULAR MEDICINE

# Safety and cardiac chronotropic responsiveness to the early injection of atropine during dobutamine stress echocardiography in the elderly

J M Tsutsui, F Cerqueira Lario, D R Fernandes, I Kowatsch, J C Sbrano, J A Franchini Ramires, W Mathias Jr



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See end of article for authors' affiliations

Correspondence to:  
Dr Jeane M Tsutsui, Heart Institute (InCor), University of Sao Paulo Medical School, Av Dr Enéas Carvalho de Aguiar, 44, Sao Paulo, Brazil, CEP 05403-000; jeanetsutsui@msn.com

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**Objective:** To determine the safety and cardiac chronotropic responsiveness to early atropine dobutamine stress echocardiography (DSE) in the elderly.

**Design:** Retrospective study of 258 patients  $\geq 70$  years who underwent early atropine DSE and 290 patients  $\geq 70$  years who underwent conventional DSE. In the early atropine protocol, atropine was started at 20  $\mu\text{g}/\text{kg}/\text{min}$  of dobutamine if heart rate was  $< 100$  beats/min, up to 2 mg. The cardiac chronotropic responsiveness in the elderly was compared with a control group of patients  $< 70$  years matched for sex, myocardial infarction, diabetes, and treatment with  $\beta$  blockers and calcium channel blockers.

**Results:** The dose of dobutamine given to elderly patients was lower during early atropine than during conventional DSE (mean (SD) 29 (7) v 38 (4)  $\mu\text{g}/\text{kg}/\text{min}$ ,  $p = 0.001$ ). Early atropine DSE resulted in diminished incidence of ventricular extrasystoles, non-sustained ventricular tachycardia, bradycardia, and hypotension compared with conventional DSE. In comparison with patients  $< 70$  years, elderly patients required lower doses of dobutamine and atropine and achieved a higher percentage of predicted maximum heart rate (92 (9)% v 88 (10)%,  $p = 0.0001$ ). Except for more common hypotension (16% v 10%,  $p = 0.004$ ), no other difference in adverse effects was observed between patients  $\geq 70$  and  $< 70$  years.

**Conclusions:** Early atropine DSE is a safe strategy in the elderly resulting in lower incidence of minor adverse effects than with the conventional protocol. Elderly patients presented adequate cardiac chronotropic responsiveness to early injections of atropine, requiring lower doses of drugs to reach test end points.

Coronary artery disease (CAD) is highly prevalent and the leading cause of cardiac morbidity and mortality in the elderly.<sup>1,2</sup> Because of some limitations to exercise, dobutamine stress echocardiography (DSE) has become a widely used method for the non-invasive evaluation of CAD in this population.<sup>3-5</sup> Recent modifications in the DSE protocols include earlier injection of atropine in patients with poor chronotropic response to dobutamine.<sup>6,7</sup> This strategy has been shown to be safe and effective in reducing the test duration, maintaining similar diagnostic accuracy for detecting angiographically significant CAD to that with the conventional protocol.<sup>8</sup> No data exist, however, about the safety profile of this strategy in the elderly. Moreover, some concerns remain regarding the presence of a diminished adrenergic responsiveness with aging. Although the chronotropic response to bolus injections of isoproterenol in older animals and senescent humans was shown to be decreased,<sup>9-11</sup> no evidence for a reduced cardiac response to dobutamine was found in healthy elderly subjects.<sup>12</sup> In this study, we sought to determine the safety and efficacy of the early injection of atropine during DSE in elderly patients with known or suspected CAD, as compared with the conventional protocol. In addition, we evaluated the differences in cardiac chronotropic responsiveness to early atropine DSE between patients  $\geq 70$  and  $< 70$  years old.

## METHODS

### Patients

We retrospectively studied 290 patients  $\geq 70$  years old (mean (SD) age 74 (3) years) who underwent conventional DSE

from July 1991 to December 1999 and 258 patients  $\geq 70$  years old (mean (SD) age 75 (4) years) who underwent early atropine DSE from January 2000 to June 2003. Patients were referred for DSE because of known or suspected CAD. The following exclusion criteria were observed: haemodynamic instability, unstable angina, recent myocardial infarction, submaximal tests performed for evaluation of myocardial viability, and contraindications to any drug used in the study.<sup>13</sup> To evaluate the effect of aging on the adverse effects and chronotropic responsiveness to early atropine DSE, we also studied 258 patients  $< 70$  years old (mean (SD) age 58 (6) years) who underwent the same protocol, in the same period of time. Both groups  $\geq 70$  and  $< 70$  years old were matched for sex, history of myocardial infarction, diabetes mellitus, and medication with  $\beta$  blockers and calcium channel blockers. All patients in the early atropine DSE protocol received at least one dose of 0.25 mg of atropine either at 20 or 30  $\mu\text{g}/\text{kg}/\text{min}$  of dobutamine. Table 1 describes the clinical characteristics of patients in the conventional and early atropine DSE groups. The prevalence of risk factors for CAD did not differ between patients  $\geq 70$  and  $< 70$  years old in the early atropine DSE groups, except for cigarette smoking.

### Dobutamine stress protocol

During conventional DSE, intravenous dobutamine was infused at a starting dose of 5  $\mu\text{g}/\text{kg}/\text{min}$  followed by

**Abbreviations:** CAD, coronary artery disease; DSE, dobutamine stress echocardiography; PMHR, predicted maximum heart rate

**Table 1** Characteristics of patients undergoing dobutamine stress echocardiography (DSE)

Variable	Early atropine DSE		Conventional DSE
	≥70 years (n = 258)	<70 years (n = 258)	≥70 years (n = 290)
Men*	107 (39%)	107 (39%)	140 (48%)
Hypertension	175 (68%)	183 (71%)	157 (54%)
Cigarette smoking	25 (10%)	56 (22%)†	43 (17%)‡
Dyslipidaemia	131 (51%)	146 (56%)	89 (31%)‡
Diabetes mellitus*	63 (24%)	63 (24%)	57 (20%)
Previous myocardial infarction*	49 (19%)	49 (19%)	91 (31%)‡
Previous coronary bypass surgery	44 (17%)	38 (15%)	43 (15%)
Previous PCI	51 (20%)	34 (13%)	56 (19%)
Medications			
β Blockers*	85 (33%)	85 (33%)	75 (26%)
Calcium channel blockers*	53 (20%)	53 (20%)	92 (32%)‡
Left ventricular ejection fraction (%)	62 (13)	63 (14)	59 (13)

Data are mean (SD) or number (%) of patients.

\*Groups ≥70 and <70 years old in the early atropine DSE were matched for these clinical characteristics;

†p<0.05 between patients ≥70 and <70 years old in early atropine DSE; ‡p<0.05 between patients ≥70 years old in early atropine and conventional DSE.

PCI, percutaneous coronary intervention.

increasing doses of 10, 20, 30, and up to a maximum of 40 µg/kg/min in three minutes stages.<sup>13</sup> In patients without signs of myocardial ischaemia who did not achieve 85% of predicted maximum heart rate (PMHR) (220 in men, and 200 in women) with the maximum dose of dobutamine, atropine was administered in doses of 0.25 mg each minute, up to a maximum of 1.0 mg. During early atropine DSE, dobutamine was infused in a similar way, but atropine was started at the beginning of the 20 µg/kg/min of dobutamine stage if the heart rate was < 100 beats/min, in doses of 0.25 mg each minute, up to 2 mg.<sup>8</sup> When a heart rate ≥ 100 beats/min had already been achieved at the beginning of the 20 µg/kg/min stage, atropine was injected with 30 µg/kg/min of dobutamine. Blood pressure, heart rate, and 12 lead ECG were monitored at each stage of dobutamine infusion. End points of the tests were achievement of target heart rate,<sup>4, 12</sup> maximum dobutamine and atropine doses, development of severe or extensive wall motion abnormalities, ST elevation > 0.1 mV at an interval of 80 ms after the J point in patients without a previous myocardial infarction, sustained arrhythmias, severe angina, or intolerable side effects.<sup>13</sup> Metoprolol (5–15 mg) was injected intravenously to reverse the effects of dobutamine if they did not revert quickly after test termination.

### Image acquisition and analysis

Images were acquired at rest, low dose of dobutamine, peak stress, and recovery phases and displayed side by side in a quad screen format. All images were recorded on videotape and digitised in continuous loop format for later analysis. Left ventricular ejection fraction was estimated at rest by two dimensional echocardiography with the modified Simpson's rule. The stress tests were considered positive for myocardial ischaemia if they showed new or worsening of pre-existing wall motion abnormalities in ≥ 2 contiguous segments.<sup>13</sup> The tests were considered diagnostic either if they were positive for ischaemia or achieved the target heart rate, and non-diagnostic when they were prematurely interrupted because of significant adverse effect or did not achieve the target heart rate despite maximum doses of dobutamine and atropine.

### Safety

Hypertension was defined as blood pressure > 230/120 mm Hg. Hypotension was defined as systolic blood pressure < 100 mm Hg or a drop > 20 mm Hg from

baseline.<sup>4, 14</sup> Symptomatic hypotension was defined as hypotension associated with significant symptoms causing test termination. Major adverse effects were defined as those that would potentially cause a life threatening situation or that led to new hospital admission.<sup>15</sup>

### Statistical analysis

Continuous variables were expressed as mean (SD) and categorical variables as proportions. Two tailed unpaired and paired Student's *t* tests were used for intergroup and intragroup comparisons, respectively. Fisher's exact and  $\chi^2$  tests were used for comparison of proportions. All data were analysed by SPSS statistical package (SPSS 11.0 for Windows; SPSS Inc, Chicago, Illinois, USA). A probability value of *p* < 0.05 was considered significant.

## RESULTS

### Safety and efficacy of early atropine versus conventional DSE in the elderly

The mean maximum dose of dobutamine used during early atropine DSE was lower than during the conventional protocol (29 (7) v 38 (4) µg/kg/min, *p* = 0.001). Only 21% of patients required the 40 µg/kg/min stage to achieve the stress end points. During conventional DSE 85% of patients received this high dose of dobutamine (table 2). The test duration was significantly shorter during early atropine than during conventional DSE (12 (2) min v 15 (2) min, *p* < 0.001). Patients reached similar rates of PMHR at peak stress in both protocols (92% (9%) v 91% (14%), *p* = 0.98). The test was diagnostic in 243 (94%) patients undergoing early atropine DSE and in 260 (89%) of patients undergoing conventional DSE (*p* = 0.06 between groups). Table 3 describes the adverse effects observed in elderly patients who underwent early atropine and conventional DSE. The incidence of ventricular extrasystoles, non-sustained ventricular tachycardia, bradycardia, and hypotension were significantly lower in the early atropine than in the conventional DSE groups. Arrhythmias were terminated spontaneously or after administration of metoprolol. Symptomatic hypotension leading to test termination was more common in conventional than in early atropine DSE. On the other hand, hypertension was observed more often in the early atropine protocol. No myocardial infarction, death, sustained ventricular tachycardia, or ventricular fibrillation occurred in either group during or immediately after dobutamine stress tests.

**Table 2** Drugs used in DSE with early injection of atropine

Drug	Early atropine DSE		Conventional DSE
	≥70 years (n = 258)	<70 years (n = 258)	≥70 years (n = 290)
Total dobutamine dose (µg/kg/min)	29 (7)	31 (6)*	38 (4)†
Total atropine dose (mg)	0.6 (0.5)	0.8 (0.5)*	0.4 (0.2)†
Atropine dose (mg) at each stage of dobutamine (µg/kg/min)			
20	0.3 (0.2)	0.4 (0.2)	
30	0.4 (0.3)	0.5 (0.3)	
40	0.5 (0.3)	0.6 (0.4)*	0.4 (0.2)
Atropine started at 20 µg/kg/min of dobutamine	226 (87%)	223 (86%)	
Atropine started at 30 µg/kg/min of dobutamine	32 (13%)	35 (14%)	
Stage of 40 µg/kg/min of dobutamine needed to achieve test end points	55 (21%)	69 (27%)*	247 (85%)†

Data are mean (SD) or number (%) of patients.

\* $p < 0.05$  between patients  $\geq 70$  and  $< 70$  years old in early atropine DSE; † $p < 0.05$  between patients  $\geq 70$  years in early atropine and conventional DSE.

### Early atropine DSE in patients $\geq 70$ and $< 70$ years old

The doses of dobutamine (29 (7)  $\nu$  31 (6) µg/kg/min,  $p = 0.001$ ) and atropine (0.6 (0.5)  $\nu$  0.8 (0.5) mg,  $p = 0.001$ ) required to achieve test end points were lower in patients  $\geq 70$  than in patients  $< 70$  years old who underwent early atropine DSE. However, when considering each stage of dobutamine separately, no difference was observed in the dose of atropine used between both groups (table 2). The percentage of diagnostic tests was similar between patients  $\geq 70$  and  $< 70$  years old (94%  $\nu$  90%,  $p = 0.07$ ). Although patients had a similar prevalence of hypertension and other clinical variables, blood pressure at baseline was higher in older than in younger patients. At peak stress, systolic blood pressure levels were maintained in patients  $\geq 70$  years old ( $p = 0.15$ ) and diastolic blood pressure decreased significantly relative to baseline ( $p < 0.001$ ). On the other hand, in younger patients systolic blood pressure increased significantly at peak stress ( $p < 0.001$ ). Although the rate–pressure product was similar between groups at baseline, at peak stress patients  $< 70$  years old reached a significantly higher rate–pressure product than did patients  $\geq 70$  years old (table 4). Arrhythmias, chest pain, or hypertension did not differ between the groups. However, hypotension was more often observed in older patients (table 4).

### Cardiac chronotropic responsiveness to early atropine DSE

The analysis of chronotropic responsiveness at each stage of dobutamine infusion showed that the heart rate was similar

between older and younger patients at baseline (69 (12)  $\nu$  69 (12) beats/min,  $p = 1.0$ ), at 10 µg/kg/min of dobutamine (78 (15)  $\nu$  78 (17) beats/min,  $p = 0.98$ ), and at 20 µg/kg/min of dobutamine (107 (26)  $\nu$  107 (27) beats/min,  $p = 0.81$ ) (fig 1). At the end of the 20 µg/kg/min stage of dobutamine infusion, a higher proportion of patients  $\geq 70$  years old had already reached the target heart rate than had patients  $< 70$  years old (21%  $\nu$  13% of younger patients,  $p < 0.001$ ). The heart rate at the end of 30 µg/kg/min of dobutamine was lower in patients  $\geq 70$  years old (126 (20) beats/min) than in patients  $< 70$  years old (136 (21) beats/min,  $p < 0.001$ ). However, the percentage PMHR was significantly higher in older patients (fig 2). In a similar way, at 40 µg/kg/min of dobutamine the heart rate was lower (125 (14)  $\nu$  138 (18) beats/min,  $p = 0.001$ ) but the percentage PMHR was higher (95%  $\nu$  91%,  $p = 0.01$ ) in patients  $\geq 70$  than in patients  $< 70$  years old.

### DISCUSSION

As a result of prolonged mean life expectancy and improvements in treatment approaches, non-invasive evaluation of CAD has increasingly been required in elderly patients. DSE has proved to be an accurate method for detecting CAD and predicting cardiac events in this patient population.<sup>4 5 14</sup> Although the injection of atropine in early stages of dobutamine has been recently incorporated into DSE protocols,<sup>16</sup> no data exist regarding the appropriateness of this strategy in the elderly. In the present study we assessed the safety profile of the early injection of atropine during DSE in 258 patients  $\geq 70$  years old with known or suspected CAD.

**Table 3** Adverse effects

Adverse effect	Early atropine DSE		Conventional DSE
	≥70 years (n = 258)	<70 years (n = 258)	≥70 years (n = 290)
Cardiac arrhythmias			
Ventricular extrasystoles	67 (25.9%)	60 (23.2%)	105 (36.2%)†
Supraventricular extrasystoles	35 (13.6%)	25 (9.7%)	42 (14.5%)
Non-sustained VT	4 (1.6%)	1 (0.4%)	15 (5.2%)†
Atrial fibrillation	5 (1.9%)	3 (1.2%)	4 (1.3%)
Symptomatic bradycardia	0	2 (0.7%)	6 (2.1%)†
Chest pain	26 (10.1%)	23 (8.9%)	38 (13.1%)
Nausea	1 (0.4%)	4 (1.5%)	7 (2.4%)
Hypotension	42 (16.2%)	23 (9.6%)*	66 (22.3%)†
Symptomatic hypotension	3 (1.2%)	5 (1.9%)	11 (3.7%)†
Hypertension	9 (3.5%)	10 (3.9%)	2 (0.7%)†

Data are number (%) of patients.

\* $p < 0.05$  between patients  $\geq 70$  and  $< 70$  years old in early atropine DSE; † $p < 0.05$  between patients  $\geq 70$  years in early atropine and conventional DSE.

VT, ventricular tachycardia.

**Table 4** Haemodynamic data

	Early atropine DSE		Conventional DSE
	≥70 years (n = 258)	<70 years (n = 258)	≥70 years (n = 290)
<b>Baseline</b>			
Heart rate (beats/min)	69 (12)	69 (12)	69 (11)
Systolic blood pressure (mm Hg)	140 (22)	136 (20)*	138 (17)
Diastolic blood pressure (mm Hg)	81 (10)	84 (10)*	80 (11)
Rate-pressure product (mm Hg/min)	9 662 (2 148)	9 379 (2 311)	9 431 (2 521)
<b>Peak</b>			
Heart rate (beats/min)	133 (15)	142 (18)*	129 (17)†
% Predicted maximum heart rate	92 (9)	88 (10)*	91 (14)
Systolic blood pressure (mm Hg)	143 (29)	143 (29)	144 (30)
Diastolic blood pressure (mm Hg)	72 (16)	78 (17)*	64 (17)
Rate-pressure product (mm Hg/min)	19 033 (4 282)	20 324 (4 642)*	18 989 (4 284)

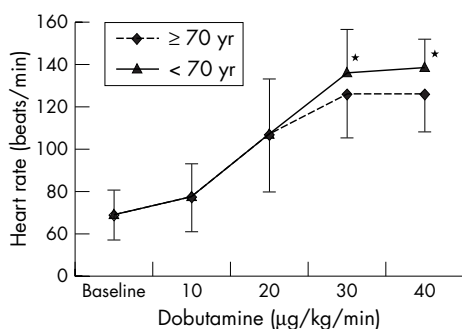
Data are mean (SD).

\* $p < 0.05$  between patients  $\geq 70$  and  $< 70$  years old in early atropine DSE; † $p < 0.05$  between patients  $\geq 70$  years in early atropine and conventional DSE.

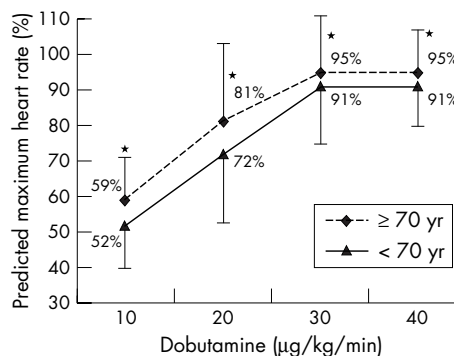
Additionally, the differences in chronotropic responsiveness to early atropine DSE were assessed in patients  $\geq 70$  and  $< 70$  years old matched for sex and other clinical characteristics known to influence the chronotropic response to dobutamine.<sup>4 17 18</sup> Although early injection of atropine has been recently proposed for DSE, no standardised recommendations exist. The report of the British Society of Echocardiography<sup>16</sup> recommends that atropine should be considered when heart rate has not increased after administration of 20  $\mu\text{g}/\text{kg}/\text{min}$ . Marwick<sup>19</sup> recommends starting atropine when heart rate has not increased by  $> 10\%$  or remains at  $< 70$  beats/min at the stage of 20  $\mu\text{g}/\text{kg}/\text{min}$ , since these patients will almost certainly need atropine. In the present study, we followed the same protocol being used in our institution since January 2000.<sup>5</sup> We showed that early atropine DSE resulted in a lower incidence of minor side effects than with conventional DSE. Although the efficacy of the test was the same, this reduction in minor adverse effects may favour the use of early atropine DSE in the elderly. Previous studies have shown an increased incidence of exercise induced<sup>20</sup> and dobutamine induced arrhythmias with aging. Hiro *et al*<sup>4</sup> reported a higher incidence of ventricular arrhythmias during conventional DSE in patients  $\geq 75$  years old. Elhendy *et al*<sup>14</sup> reported that patients  $\geq 70$  years old had a higher incidence of supraventricular arrhythmias and ventricular extrasystoles during myocardial perfusion scintigraphy according to the conventional protocol of dobutamine stress. In our study, early atropine resulted in a lower incidence of arrhythmias than did conventional DSE, but no differences were observed between older and younger

patients who underwent early atropine DSE. By starting atropine in the early stages of dobutamine infusion, the maximum dose of dobutamine required to achieve test end points was significantly lower than in the conventional protocol. The diminished exposure of patients to high doses of an adrenergic stimulant drug probably accounted for these findings.

Elderly patients had a lower incidence of hypotension during early atropine DSE than during conventional DSE but more patients  $\geq 70$  than  $< 70$  years old experienced this adverse effect. Although patients had a similar prevalence of hypertension and treatment with  $\beta$  blockers and calcium channel blockers, a different haemodynamic profile during early atropine DSE was observed between patients  $\geq 70$  and  $< 70$  years old. The higher rates of dobutamine stress induced hypotension in the elderly had already been described by other investigators.<sup>14 17</sup> In our study, younger patients had lower levels of resting systolic blood pressure, which increased at peak stress. On the other hand, more of the patients  $\geq 70$  years old had episodes of hypotension during stress. Limiting hypotension was more often observed in elderly patients who underwent conventional DSE (3.7%) than in patients who underwent early atropine DSE (1.2%). The possible mechanisms underlying this phenomenon include diminished baroreflex sensitivity and abnormal blood pressure homeostasis in the elderly,<sup>21</sup> resulting in higher susceptibility of these patients to the peripheral vasodilatation that occurs by dobutamine stimulation of  $\beta_2$  receptors. Furthermore, it has already been established that stress induced hypotension is not related to the degree of CAD.<sup>17 22</sup>



**Figure 1** Heart rate at each stage of dobutamine in patients  $\geq 70$  years old and  $< 70$  years old who underwent early injection of atropine during dobutamine stress echocardiography. Note that the heart rate achieved at 30 and 40  $\mu\text{g}/\text{kg}/\text{min}$  of dobutamine was lower in patients  $\geq 70$  years old. \* $p < 0.05$  between groups.



**Figure 2** Percentage of predicted maximum heart rate reached at each stage of dobutamine in patients  $\geq 70$  years old and  $< 70$  years old who underwent early injection of atropine during dobutamine stress echocardiography. \* $p < 0.05$  between groups.

No major complications from the stress test were observed in any group, confirming previous reports in the literature.<sup>15 23 24</sup>

### Chronotropic responsiveness to dobutamine and atropine

Atropine is a muscarinic cholinergic antagonist with parasympatholytic and vagolytic activity.<sup>25</sup> The possible effects of early atropine injection during DSE on chronotropic responses in the elderly had not been tested before. The ability of DSE to detect myocardial ischaemia depends on an adequate increase in myocardial oxygen consumption, which is directly related to the heart rate achieved at peak stress. Previous animal studies have raised concerns regarding a diminished  $\beta$  adrenoceptor mediated responsiveness to bolus injections of isoproterenol in older rats.<sup>9 10</sup> A reduced chronotropic response to isoproterenol was also reported in elderly subjects with low risk for CAD.<sup>11</sup> Elderly patients with diabetes, hypertension, smoking, and previous myocardial infarction were shown to have a decreased sensitivity to dobutamine, but no evidence for reduced  $\beta$  adrenoceptor responsiveness to dobutamine was found in healthy elderly subjects who underwent DSE.<sup>12</sup> Our study population had some clinical characteristics associated with diminished sensitivity to dobutamine and included a significant number of patients taking  $\beta$  blockers. However, a high percentage of patients achieved the target heart rate, probably due to the lower calculated PMHR for older patients, resulting in achievement of the target rate heart with lower doses of drugs. By performing a stepwise analysis of heart rate at each stage of dobutamine, we showed that older patients achieved a lower heart rate during stress than younger patients. However, the PMHR reached at peak stress was higher, and test end points were achieved with lower doses of dobutamine and atropine.

### Conclusions

Our study showed that early injection of atropine during DSE is a safe strategy in patients  $\geq 70$  years old with known or suspected CAD. Cardiac chronotropic responsiveness to early atropine DSE is adequate in elderly patients, requiring lower doses of drugs to achieve test end points.

### Authors' affiliations

J M Tsutsui, F Cerqueira Lario, D R Fernandes, I Kowatsch, J C Sbrano, J A Franchini Ramires, W Mathias Jr, Echocardiography Laboratory, Heart Institute (InCor), University of São Paulo Medical School, Sao Paulo, Brazil

Ethics approval: The study was approved by ethical committee of the Heart Institute (InCor) and written consent form was obtained from all participants.

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