Pulmonary hypertension secondary to chronic mitral valve disease in dogs: prevalence and echocardiographic aspects

Hipertensão arterial pulmonar secundária à doença valvar mitral crônica em cães: prevalência e aspectos ecocardiográficos

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ABSTRACT
Objectives: To evaluate the prevalence of pulmonary arterial hypertension (PAH) in dogs with mitral valve disease and to determine the correlation between pulmonary arterial pressure (PAP) and certain echocardiographic indexes that reflect the severity of the disease. Materials and methods: A retrospective study of the echocardiographic records of dogs with chronic mitral valve disease. Results: This study evaluated 359 dogs with mitral valve disease. Of these, 89 (24.8%) had some degree of PAH. A total of 59 animals (66.3%) had mild PAH (G2a) with an estimated pulmonary arterial pressure of 43.7 ± 5.9 mmHg. Twenty-five animals (28.1%) had moderate PAH (G2b) with an estimated PAP of 68.2 ± 8.4 mmHg and 5 animals (5.6%) had significant PAH (G2c) with an estimated PAP of 102.2 ± 37.6 mmHg. PAH secondary to mitral valve disease develops in small dogs of older age with progression of valve degeneration and in animals with significant diastolic dysfunction. Statistically significant correlations between systolic pulmonary arterial pressure and the aortic-to-left atrial diameter ratio as well as between systolic pulmonary arterial pressure and the E and A wave of transmitral flow were detected. Conclusion: Our results suggest that these indexes could be used as predictors of PAH.

Keywords: echocardiography, canine, mitral valve, pulmonary hypertension.

RESUMO
Objetivo: avaliar a prevalência de hipertensão arterial pulmonar em cães com doença valvar mitral crônica e determinar a correlação entre a pressão arterial pulmonar e certos índices ecocardiográficos que refletem a severidade da doença valvar mitral. Foi realizado um estudo retrospectivo de registros ecocardiográficos de cães com doença valvar mitral. Materiais e métodos: Foram avaliados 359 cães com doença valvar mitral dos quais 89 (24,8%) apresentavam algum grau de HAP. Resultados: Um total de 59 animais (66,3%), apresentaram HAP discreta (G2a) com pressão arterial pulmonar (PAP) estimada de 43,7 ± 5,9 mmHg, 25 animais (28,1%) HAP moderada (G2b) com PAP estimada de 68,2 ± 8,4 mmHg e 5 animais (5,6%) com HAP importante (G2c) com PAP estimada de 102,2 ± 37,6 mmHg. A hipertensão arterial pulmonar secundária a doença valvar mitral se desenvolveu principalmente em cães de pequeno porte, com idade mais avançada e, concomitantemente com a progressão da degeneração valvar, principalmente naqueles animais com disfunção diastólica importante. Foi observada uma correlação significativa entre a pressão sistólica na artéria pulmonar e a relação Ao/AE e entre a pressão sistólica na artéria pulmonar e a relação E/A do fluxo transmitral. Conclusão: Os resultados sugerem que esses índices possam ser utilizados como preditivos para o desenvolvimento da HAP.

Palavras-chave: ecocardiografia, cães, valva mitral, hipertensão pulmonar

1 INTRODUCTION
In mitral regurgitation caused by degenerative valve disease, chronic elevation of the left atrial pressure with subsequent pulmonary venous hypertension is considered one of the major causes of PAH (Pyle et al. 2004, Stepień 2009, Reinerο et al. 2020). The increased preload is the main factor responsible for the retrograde congestion, making the blood initially accumulate in the pulmonary veins, the lungs, the pulmonary arteries and the right heart chambers, which may lead to findings such as tricuspid insufficiency and pulmonary hypertension in the most severe cases of mitral regurgitation (Stepień 2009). The pathophysiological mechanisms that have been proposed to explain pulmonary
hypertension are related to retrograde transmission of the left atrial pressure (passive pulmonary hypertension), reactive arterial vasoconstriction (reactive pulmonary hypertension) and structural alterations (remodelling) of the pulmonary vascular bed and the interaction of several vasoactive substances secreted by the endothelial cells (Chiavegato et al. 2009, Stepien 2009).

The echocardiogram is a part of evaluation of animals with PAH. The diagnosis can be made by measuring the pulmonary pressure by Doppler echocardiography and by detection of indirect signs of elevated pulmonary pressure (Almeida-Filho 2007, Stepien 2009, Kellihan et al. 2010). The indirect signs on the echocardiogram are pulmonary artery and RV dilation, which can evolve with systolic dysfunction, paradoxical movement of IVS and rectification of the pulmonary valve (Almeida-Filho 2007, Mancuso et al. 2008). The Doppler echocardiography evaluation is more sensitive and specific because it allows estimation of the pulmonary artery pressure. Of the methods employed to evaluate PAP, the most reliable is measurement of the velocity of tricuspid regurgitation, which estimates the pulmonary systolic artery pressure based on the pressure gradient between the right ventricle and the atrium during systole (Johnson et al. 1999, Boon 2006; Serres et al. 2006, Mancuso et al. 2008).

The objective of this study was to evaluate the prevalence of PAH in dogs with mitral valve disease and determine the correlation between pulmonary arterial pressure and echocardiographic indexes that reflect the severity of mitral valve disease.

2 MATERIALS AND METHODS

Echocardiographic records from a diagnostic centre were scanned for cases of dogs presenting with compatible echocardiographic findings and mitral valve disease from April to July 2010. The project was certified by the ethics committee of XXXXX process number 077/12. The echocardiographic records of 359 dogs with mitral valve disease were obtained. The median age of the dogs was 10.8 ± 2.6 years and 172 were male and 187 were female.

The criteria adopted for the inclusion of echocardiographic records in this study were the presence of thickening of the mitral valve leaflets with or without leaflet prolapse and identification of mitral valve regurgitation by evaluation with colour Doppler, confirming the presence or absence of insufficiency with pulse Doppler. A minimum value of 30% was established for the shortening fraction (SF) to minimise the possibility of including animals with a compatible case of dilated cardiomyopathy. Animals with congenital heart diseases were excluded.

Transthoracic echocardiograms were performed with a GE Medical Systems Ultrasound device model Vivid 3 using 1.5-3.6 MHz and 3.6-8 MHz multi-frequency sector probes according to the size
of the animal. The animals were conscious during the examinations (no sedation) and positioned in the left lateral position. The images were obtained through the right parasternal and left parasternal cranial and caudal acoustic windows (Boon 2006). Qualitative and quantitative analyses were performed using the mono-dimensional (M mode) and bi-dimensional (B mode) echocardiographic modes, and analysis of the transvalvular and regurgitant flows was performed using colour, pulsed and continuous Doppler imaging, according to Boon (2006) (Fig. 1A).

To estimate the pressure in the right ventricle and pulmonary artery (P_{RV/PA}), the pressure estimated in the right atrium (RA) (normal: 5 mmHg; increased: 10 mmHg; increased with signs of heart failure: 15 mmHg) was added to the pressure gradient obtained by the Bernoulli equation (Stepien 2009, Milan et al. 2010). The PAH was classified into three degrees of severity (Table 1).

The values of the echocardiographic parameters were subjected to descriptive statistical analysis to calculate the mean, median and standard deviation using Microsoft Office Excel® software. The Kolmogorov-Smirnov test was performed to verify whether the quantitative variables were normally distributed. For normally distributed parameters, the parametric test was conducted, whereas for parameters with heterogeneous distribution, a non-parametric test was utilised. Student’s t test was used for the 2 independent samples, in which age and the cardiac frequency of the animals with mitral valve disease with and without PAH were compared. The Mann-Whitney test for 2 independent samples was used to compare the maximum velocity parameters in the pulmonary artery (V_{max} pulmonary flow), the Ao/LA ratio and the E/A ratio of transmitral flow between the groups of animals without and with PAH (G1 and G2, respectively). Spearman’s correlation test (non-parametric test) was performed to evaluate if there was an association between the variables of group G2: the estimated pressure at the pulmonary artery (PA) and the E/A ratio of the transmitral flow, the V_{max} pulmonary flow and the E/A ratio of transmirtal flow, and the estimated PA pressure and the V_{max} pulmonary flow. Calculations were performed using Biostat 5.0 software. The values are presented as the means ± standard deviation and were considered significant when p<0.05.

3 RESULTS

Of the 359 animals assessed, 89 (24.8%) showed some degree of pulmonary arterial hypertension. Of these 89 animals, 45 were male and 44 were female, with a median age 12.1±2.6 years. The evaluated animals were divided into two groups. Group G1 was composed of animals that presented mitral valve disease without PAH, and group G2 was composed of animals that presented PAH. The data obtained from the animals of these two groups were compared to choose a parameter that could be used as a predictive factor regarding the development of PAH (Table 2). Some
Echocardiograph records did not contain information for all the parameters that were used in the analysis; therefore, we chose to exclude these animals from comparisons using the missing parameter.

According to the criteria adopted in this study and previously described, group G2 was divided into three sub-groups: G2a (mild PAH), G2b (moderate PAH) and G2c (severe PAH) (Table 3).

In addition, a few qualitative and quantitative morphofunctional aspects were taken into account to more effectively characterise the animals belonging to the sub-groups G2a, G2b and G2c (Table 4). To determine which factors were predictive for PAH, Spearman's correlation test was used to determine if there were associations between the variables of group G2 (the estimated PA pressure, \( V_{\text{max}} \) pulmonary flow, Ao/LA ratio, E/A ratio of the transmitral flow). Because some records did not contain all the analysed parameters and given the specific need for paired samples to perform this test, the animals that did not have values recoded for all the parameters in question were excluded. Fifty-seven samples in group G2 were utilised for this test.

There was a positive correlation between the estimated pressure in the PA and the E/A ratio \((r=0.3324; p=0.0115)\) (Fig.1B) and a negative correlation between the estimated pressure in the PA and the Ao/LA ratio \((r=-0.3273; p=0.0129)\) (Fig.1C). Both correlations were statistically significant. The parameters \( V_{\text{max}} \) pulmonary flow, E/A ratio and Ao/LA ratio presented negative \((r= -0.4778; p=0.0002)\) (Fig. 1D) and positive correlations \((r=0.4317; p=0.0008)\) (Fig.1E), respectively. No statistically significant correlation was observed between the parameters estimated PA pressure (mmHg) and \( V_{\text{max}} \) pulmonary flow \((G2; n=57; r= -0.1989; p=0.1380)\) (Fig.1F).

4 DISCUSSION

Three hundred fifty-nine dogs with mitral valve disease were evaluated including 172 males and 187 females with a median age of 10.8±2.6 years. The dogs were mostly from breeds that are small in size; the most prevalent breed was Poodle \((n=144; 40.1\%)\). These data are similar to those described by Ware (2006) and Castro et al. (2009); however, we must consider the popularity of this breed.

Of the 359 evaluated dogs, 89 (24.8%) showed some degree of PAH, which is a much higher prevalence than described by Serres et al. (2006) and smaller than described by Borgarelli et al. (2015). This specific group of animals (G2) followed the same breed distribution pattern as the group with mitral valve disease without PAH (G1), but it was composed of older animals \((12.1±2.6\) years; \(p<0.0001)\), which indicates that the prevalence and severity of mitral valve disease increases with age (Borgarelli 2010).
In the group of animals with PAH, 59 dogs (66.3%) presented with mild PAH (G2a) with an estimated pulmonary arterial pressure (PAP) of 43.7±5.9 mmHg; 25 animals (28.1%) had moderate PAH (G2b) with an estimated PAP of 68.2±8.4 mmHg; and 5 dogs (5.6%) showed significant PAH (G2c) with an estimated PAP of 102.2±37.6 mmHg. These animals, especially those in groups G2b and G2c, displayed additional features in their echocardiographic findings indicating right ventricular dysfunction including anomalous SIV motion, thickening of the pulmonary valve and enlargement of the right heart chambers (Almeida-Filho 2007, Borgarelli 2010).

The right ventricle (RV) presents a spatial conformation that complicates echocardiographic evaluation (Boon 2006, Almeida-Filho 2007), however, in order to evaluate RV systolic function in dogs with pulmonary hypertension has been used as indicator the RV end-diastolic area (RVEDA) as a 2-dimensional indicator of RV size, and the tricuspid annular plane systolic excursion (TAPSE), the fractional area change (FAC) and pulmonary artery distensibility index (Borgarelli et al. 2015, Visser et al. 2016, Vezzosi et al. 2018, Reinero et al. 2020). In this study, when the RV remained smaller than the LV it was considered a slight increase; when the area of the RV was similar in size to the LV it was considered a moderate increase; and when the area of the RV was larger than that of the LV it was considered a significant increase (Almeida-Filho 2007). This study demonstrated that most of the animals with PAH (74%) had right heart chambers (RA and RV) with normal dimensions on the echocardiogram, corroborating the observations of Serres et al. (2006) and allowing us to infer that dogs with mitral valve disease, even in the absence of the clinical and echocardiographic signs associated with right cardiac dilation, should not be excluded from a more in-depth evaluation to determine the presence of PAH. In small-breed dogs that present with left-sided congestive heart failure, pulmonary hypertension should be disregarded as the cause of cough, even if there is no evident increase in the right heart (Bonn 2006).

The motion pattern of IVS is another parameter considered relevant in the evaluation of PAH (Boon 2006, Borgarelli et al. 2010). The IVS motion usually follows the movement of the other walls of the LV because it follows the centre of the mass of the heart. When there is an increase in RV secondary to volume and/or pressure overload, the mass of this chamber increases, and the centre of the mass of the organ is displaced to the RV, leading to several degrees of septal dyssynergy (Almeida-Filho 2007).

The interventricular septum had increased movement (hyperkinesia) in 39% of the animals from group G2 and paradoxical motion in only one animal with severe PAH. This finding contradicts the literature, and studies that consider that the motion can range from mild to significantly paradoxical, depending on the ratio between the sizes of the LV and RV (Boon 2006).
The augmented size of the left atrium was a consequence of mitral valve regurgitation and progressive diastolic dysfunction, which leads to a progressive increase in atrial pressure and, consequently, in pressure in the pulmonary veins. When this condition becomes chronic, it may lead to an increase in arterial pressure with a potential effect on the right heart (Boon 2006, Chiavegato et al. 2009, Borgarelli et al. 2015, Reinero et al. 2020).

Several studies have shown an association between abnormalities in left ventricular relaxation and specific patterns of blood flow velocity (Almeida-Filho 2007). The blood flow velocity between the left atrium and ventricle is determined by the pressure gradient between these chambers (Boon 2006). During the initial phases of heart disease, the first diastolic abnormality observed is the pattern known as "abnormal relaxation", which is characterised by the prolongation of the isovolumetric relaxation time (IVRT) and the E wave deceleration time as well as a reduction in the velocity of the E wave and an increase in the A wave, producing an E/A ratio<1. This phenomenon is commonly attributed to a reduction in the rate of intraventricular pressure decline as a consequence of dysfunction of left ventricular myocardium relaxation with flattening of the AE/VE pressure gradient at the end of diastole (Boon 2006).

A change in relaxation (E<A), indicated by the inversion of the E/A waves, was observed in 27.1% of the animals in group G1 and in 17.6% of the animals in group G2. Although it is a predictive factor of mitral valve disease evolution, it is only important as a predictor for the development of PAH when the E/A ratios are lower than 0.59±0.16 (r=0.3324; p=0.0115) as demonstrated in this study by the correlation test. In a study using a multivariate analysis to evaluate the factors related to the length of survival in 558 animals monitored for 22.7±13.6 months, the most commonly recognized transmitral flow filling pattern was of the E/A ratio > 2. Diastolic dysfunction was referred to as an indicator of a high risk of death in dogs with mitral valve disease (Borgarelli et al. 2008).

With the progressive deterioration of diastolic function, the pressure in the LA gradually increased; this acts as a triggering force, which is responsible for opening the mitral valve and causes a reduction in IVRT and an increase in the velocity of the E wave, making the E/A ratio equal to 1. Simultaneously, the pressure in the LV is elevated, leading to a pattern known as pseudonormal pattern (Almeida-Filho 2007), which was not observed in this study. A restrictive-type pattern was verified (E>>A) in 14% of the animals from group 2, whereas in group G1 it was observed in only 1.7% of cases. The restrictive pattern is considered the most serious phase of diastolic dysfunction, with a significant increase in the pressure of the LA and a reduction of left ventricular compliance. Many studies consider this pattern a factor in a poor prognosis (Boon 2006, Borgarelli et al. 2010). All the animals from group G2 that presented the restrictive-type pattern belonged to the sub-groups...
classified as having moderate PAH (G2b) or significant PAH (G2c). Therefore, it is a parameter that should be taken into account in the evaluation of the severity of PAH.

In this study, we identified an optimal correlation between the estimated pressure in the PA and the parameters of the E/A ratio (r=0.3324; p=0.0115) and the Ao/LA ratio (r= -0.3273; p=0.0129), which are related to the progression of mitral valve disease (Schober et al. 2006, Chiavegato et al. 2009, Borgarelli et al. 2015, Reinero et al. 2020). This observation is critical because it indicates that an increase in the E/A ratio and reduction in the Ao/LA ratio in successive echocardiograms can serve as positive predictive factors for the development of PAH (Chiavegato et al. 2009).

Morphofunctional evaluation of the RV is difficult to perform because of its spatial conformation, which is similar to the letter "U", making echocardiography laborious. Several methods and many approaches have been developed to measure the real volume of the RV and estimate its systolic performance; however, quantitative evaluations present methodological limitations (Almeida-Filho 2007).

During routine echocardiograms, such as those performed in this study, the RV is evaluated semi-quantitatively, which sometimes makes it impossible to precisely evaluate the functional status of this heart chamber. This finding could justify the absence of a statistically significant correlation between the echocardiographic parameters of the estimated pressure in the PA and Vmax pulmonary flow because some of the animals with PAH evaluated in this study could present systolic dysfunction in the RV. This dysfunction might affect the values obtained for the velocity of pulmonary flow, making this finding a limitation of this study. There was a correlation between the Vmax pulmonary flow, the E/A ratio (r= -0.4778; p=0.0002) and the Ao/LA ratio (r=0.4317; p=0.0008), indicating that as the E/A ratio decreases, the Ao/LA elevates, i.e., mitral valve disease progresses, leading to increased left atrial pressure. Consequently, in the pulmonary vascular bed, the velocity of the pulmonary blood flow increases, indicating that this parameter might be useful as a predictor for PAH in animals that already have indirect signs of elevated pulmonary pressure.

5 CONCLUSION

We concluded that PAH is a frequent finding in dogs with mitral valve disease, with an approximate prevalence of 25%, especially in small and elderly dogs. Pulmonary arterial hypertension secondary to mitral valve degeneration has a direct and statistically significant correlation with the E/A indexes of the transmitral flow and the Ao/LA ratio, thereby qualifying them as predictive factors for the development of PAH.
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Figures and Legends:

**Figure 1 A.** Echocardiographic image utilised with continuous Doppler to evaluate regurgitate flow of the tricuspid valve to measure the pressure gradient between the right ventricle and the right atrium ($\Delta P_{RV-RA}$) during systole in an animal from group G2 (PAH) (left caudal parasternal window, apical 4-chamber view).

**B.** Correlation between the parameters estimated PA pressure (mmHg) and E/A ratio of the transmitral flow (G2; n=57; $r=0.3324$; $p=0.0115$).

**C.** Correlation between the parameters estimated PA pressure (mmHg) and Ao/LA ratio (G2; n = 57; $r= -0.3273$; $p=0.0129$).

**D.** Correlation between the parameters E/A ratio of the transmitral flow and $V_{max}$ pulmonary flow (G2; n=57; $r=0.4779$; $p=0.0002$).

**E.** Correlation between the parameters Ao/LA ratio and $V_{max}$ pulmonary flow (G2; n=57; $r=0.4317$; $p=0.0008$).

**F.** Correlation between the parameters estimated PA pressure (mmHg) and $V_{max}$ pulmonary flow (G2; n=57; $r= -0.1989$; $p=0.1380$).
Table 1. Classification of the degree of PAH severity based on the maximum velocity of the regurgitant flow associated with the pressure gradient (Borgarelli et al. 2015; Visser et al. 2016; Vezzosi et al. 2018)

| Mild | Moderate | Important |
|------|----------|-----------|
| $V_{IT}$ (m/s) | >3.0 to < 3.5 | >3.5 - 4.3 | > 4.3 |
| $\Delta P_{PA,RV}$ (mmHg) | > 36 to < 50 | 50 - 75 | > 75 |

$V_{IT}$: maximum velocity of tricuspid regurgitant flow; $\Delta P_{PA,RV}$: pressure gradient between the right ventricle and the right atrium.

Table 2. Comparison parameters between groups G1 and G2 for choosing a predictive factor for the development of PAH

| G1 | Mitral valve disease without PAH | G2 | Mitral valve disease with PAH |
|----|---------------------------------|----|--------------------------------|
| Age (years) | 10.8 ± 2.6 | 12.1 ± 2.6 | $^1 p < 0.0001$ |
| Heart rate (bpm) | 118.4 ± 33.7 | 134.1 ± 34.2 | $^1 p = 0.0002$ |
| $V_{max}$ pulmonary flow (m/s)* | 1.0 ± 0.28 | 0.89 ± 0.21 | $^2 p = 0.0018$ |
| Ao/LA ratio | 0.82 ± 0.13 | 0.66 ± 0.16 | $^2 p < 0.0001$ |
| E/A ratio** | 1.08 ± 0.41 | 1.35 ± 0.38 | $^2 p = 0.0004$ |
| Normal | 171 (71.2%) | 39 (68.4%) |
| E<A | 65 (27.1%) | 10 (17.6%) |
| E>>A | 4 (1.7%) | 8 (14.0%) |

* $V_{max}$ pulmonary flow: Mitral valve disease without PAH (n = 262).
**E/A ratio: mitral valve disease without PAH (n = 240) and mitral valve disease with PAH (n = 57).
$^1$ Student’s t test; $^2$ Mann-Whitney test; E<A: mitral flow with abnormal relaxation pattern; E>>A: restrictive mitral flow pattern

Table 3. Distribution of animals from group G2 according to the degree of PAH severity based on the maximum velocity of the regurgitating flow associated with the pressure gradient

| Mild PAH (≥ 36 to < 55 mmHg) | Moderate PAH (55 - 80 mmHg) | Severe PAH (> 80 mmHg) |
|------------------------------|-------------------------------|-------------------------|
| Mean | 43.7 | 68.2 | 102.2 |
| Standard deviation | 5.9 | 8.4 | 37.6 |
| N | 59 (66.3%) | 25 (28.1%) | 5 (5.6%) |
Table 4. Qualitative and quantitative variables obtained by echocardiographic evaluation. Values are expressed as the percentage (mean followed by the standard deviation)

| Aspect of the pulmonary valve | G2a mild PAH (n = 59) | G2b moderate PAH (n = 25) | G2c severe PAH (n = 5) |
|-----------------------------|-----------------------|---------------------------|-----------------------|
| Normal                      | 94.9%                 | 76.0%                     | 40.0%                 |
| Thickened                   | 5.1%                  | 20.0%                     | 20.0%                 |
| Rectified                   | 0.0%                  | 4.0%                      | 40.0%                 |

| Dimension of the RA          |                       |                           |                       |
|-----------------------------|-----------------------|---------------------------|-----------------------|
| Normal                      | 89.8% (53/59)         | 52.0% (13/25)             | 40.0% (1/5)           |
| ↑ mild                      | 8.5% (5/59)           | 28.0% (7/25)              | 60.0% (3/5)           |
| ↑ moderate                  | 1.7% (1/59)           | 16.0% (4/25)              | 20.0% (1/5)           |
| ↑ severe                    | 0.0%                  | 4.0% (1/25)               | 20.0% (1/5)           |

| Dimension of the RV          |                       |                           |                       |
|-----------------------------|-----------------------|---------------------------|-----------------------|
| Normal                      | 88.1% (52/59)         | 52.0% (13/25)             | 20.0% (1/5)           |
| ↑ mild                      | 8.5% (5/59)           | 32.0% (8/25)              | 40.0% (2/5)           |
| ↑ moderate                  | 1.7% (1/59)           | 16.0% (4/25)              | 20.0% (1/5)           |
| ↑ severe                    | 0.0%                  | 4.0% (1/25)               | 20.0% (1/5)           |

| Motion of the IVS            |                       |                           |                       |
|-----------------------------|-----------------------|---------------------------|-----------------------|
| Normal                      | 59.3%                 | 60.0%                     | 60.0%                 |
| Increased                   | 40.7%                 | 40.0%                     | 20.0%                 |
| Paradoxical                 | 0.0%                  | 0.0%                      | 20.0%                 |

| Degree of tricuspid regurgitation |                       |                           |                       |
|-----------------------------------|-----------------------|---------------------------|-----------------------|
| Mild                              | 86.4%                 | 40.0%                     | 0.0%                  |
| Moderate                          | 10.2%                 | 40.0%                     | 40.0%                 |
| Severe                            | 3.4%                  | 20.0%                     | 60.0%                 |

| V<sub>max</sub> pulmonary flow (m/s) |                       |                           |                       |
|-------------------------------------|-----------------------|---------------------------|-----------------------|
| Normal                              | 0.94 ± 0.18           | 0.77 ± 0.21               | 0.95 ± 0.30           |

| Ao/LA ratio                        |                       |                           |                       |
|------------------------------------|-----------------------|---------------------------|-----------------------|
| Normal                             | 0.69 ± 0.16           | 0.59 ± 0.16               | 0.58 ± 0.11           |

| E/A ratio** (n = 57)               |                       |                           |                       |
|------------------------------------|-----------------------|---------------------------|-----------------------|
| Normal                             | 1.2 ± 0.48            | 1.61 ± 0.64               | 2.20 ± 0.61           |
| E<A                                | 71.1% (27/38)         | 64.7% (11/17)             | 50% (1/2)             |
| E>>A                               | 23.7% (9/38)          | 5.9% (1/17)               |                       |
| E>>A                               | 5.3% (2/38)           | 29.4% (5/17)              | 50% (1/2)             |