Isolated mitral valve prolapse is an independent predictor of aortic root size in a general population

José R. Matos-Souza†, Mariana E. Fernandes-Santos†, Eduardo L. Hoehne2, Kleber G. Franchini1, and Wilson Nadruz Jr†*

1Department of Internal Medicine, School of Medicine, University of Campinas, Cidade Universitária 'Zeferino Vaz', 13081-970 Campinas, SP, Brazil; and 2Department of Preventive Medicine, School of Medicine, University of Campinas, Brazil

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Aims
Mitral valve prolapse (MVP) is associated with aortic root (AoR) enlargement in patients with inherited connective tissue disorders. This report evaluated whether MVP is related to AoR dimension in a large population with otherwise normal echocardiographic parameters.

Methods and results
We retrospectively analysed echocardiograms performed by a single echocardiographer between 2001 and 2007 for various clinical indications. Six hundred and twenty-seven subjects with isolated MVP were found and then matched by sex, age, and body mass index to 627 individuals without MVP. The whole sample included 454 men and 800 women with an average age of 37.9 ± 0.3 years and a body mass index of 23.7 ± 0.1 kg/m². MVP subjects had a higher AoR diameter (30.4 ± 0.1 vs. 29.5 ± 0.1 cm; P < 0.0001) compared with controls. Furthermore, multivariate analyses demonstrated an independent association between MVP and AoR size (P < 0.0001) in a model that included age, gender, body mass index, body surface area, blood pressure levels, and left ventricular mass index as confounding variables.

Conclusion
Isolated MVP is an independent predictor of greater AoR size in a large population with otherwise normal echocardiographic parameters.

Keywords
Mitral valve prolapse • Aortic root • Echocardiography

Introduction
Mitral valve prolapse (MVP) is a common echocardiographic variation that may be detected in 2–4% of some populations. Although MVP is most frequently a primary condition, it has often been associated with osteoarticular abnormalities, such as shallow chest and articular hypermobility, leading to the suggestion that MVP might be actually a manifestation of collagen modification.

In accordance with this assumption, MVP is also associated with heritable disorders of connective tissue, such as Marfan and Ehlers–Danlos syndromes. Although subjects with such disorders comprise <1–2% of MVP cases, they provide relevant information regarding the potential phenotypic spectrum related to MVP. In this context, several lines of evidence demonstrated that aortic root (AoR) dilatation is usually seen along with MVP in subjects with heritable disorders of connective tissue, indicating that abnormalities in mitral valve and AoR structures may represent a phenotypic continuum. Nevertheless data available to date have failed to detect significant changes in AoR diameter in subjects with primary MVP. It is noteworthy, however, that these aforementioned studies included a small number of subjects, which probably limited the statistical power of such analyses. Thus, the aim of the present report was to evaluate whether the presence of MVP influences AoR dimension in a large sample of subjects with normal AoR size and normal cardiac parameters.

†Both authors contributed equally to this study.
* Corresponding author. Tel: +55 19 3521 7836, Fax: +55 19 3521 7836, Email: wilnj@fcm.unicamp.br
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Table 1  Characteristics of studied subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n = 1254)</th>
<th>MVP (n = 627)</th>
<th>Controls (n = 627)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>37.9 ± 0.3</td>
<td>37.9 ± 0.5</td>
<td>37.9 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>454/800</td>
<td>227/400</td>
<td>227/400</td>
<td>NS</td>
</tr>
<tr>
<td>Height, cm</td>
<td>166.9 ± 0.3</td>
<td>167.5 ± 0.4</td>
<td>166.4 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>66.2 ± 0.4</td>
<td>66.3 ± 0.5</td>
<td>66.2 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.7 ± 0.1</td>
<td>23.6 ± 0.1</td>
<td>23.9 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.75 ± 0.01</td>
<td>1.76 ± 0.01</td>
<td>1.75 ± 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>125.0 ± 0.6</td>
<td>124.7 ± 0.7</td>
<td>125.3 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>79.8 ± 0.3</td>
<td>79.5 ± 0.4</td>
<td>80.1 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Left atrium diameter, mm</td>
<td>31.8 ± 0.1</td>
<td>31.3 ± 0.1</td>
<td>32.2 ± 0.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AoR diameter, mm</td>
<td>30.0 ± 0.1</td>
<td>30.4 ± 0.1</td>
<td>29.5 ± 0.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AoR/body surface area, mm/m²</td>
<td>17.06 ± 0.06</td>
<td>17.27 ± 0.08</td>
<td>16.86 ± 0.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Left ventricular mass index, g/m²</td>
<td>89.1 ± 0.5</td>
<td>89.2 ± 0.6</td>
<td>89.1 ± 0.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

AoR, aortic root; MVP, mitral valve prolapse. NS, non-significant. P-values are related to the comparison between MVP vs. controls.

Methods

Study population

We performed a retrospective analysis of echocardiograms performed by a single echocardiographer (Dr Matos-Souza) between January 2001 and March 2007 for various clinical indications at a single cardiology/echocardiography centre. Inclusion criteria were age over 18 years and normal left ventricular and left atrial (LA) dimensions according to the American Society of Echocardiography. Echocardiographic exclusion criteria were: (i) valvular disease, except MVP or minimal mitral regurgitation; (ii) left ventricular hypertrophy, defined as left ventricular mass index >110 g/m² for women and >125 g/m² for men; (iii) signs of left ventricular diastolic, systolic, or segmental dysfunction; (iv) signs of pulmonary hypertension; (v) congenital heart disease; and (vi) AoR dilatation. The study was approved by the Ethics Committee of the University of Campinas.

Six hundred and twenty-seven subjects with isolated MVP fulfilled the inclusion criteria for the study. A similar number of individuals without MVP matched by sex, age, and body size were then randomly selected as controls from the database. Clinical evaluated variables were extracted from patient records and included age, sex, height, weight, and blood pressure levels. Body mass index was calculated as body weight divided by height squared (kg/m²), while body surface area was calculated according to the Dubois formula. Blood pressure was measured using mercury sphygmomanometers with the subjects in the sitting position before the echocardiographic examination.

Echocardiography

Echocardiography studies were performed on each subject at rest in the left lateral decubitus position using a Vivid 3 apparatus (General Electric) equipped with a 2.5 MHz transducer as previously described. AoR and LA diameters as well as left ventricular mass were assessed according to the American Society of Echocardiography recommendations. AoR diameter was measured at the level of Val- salva’s sinuses by M-mode tracings under two-dimensional control as the maximal distance between the two leading edges of the anterior and posterior AoR walls, while LA maximal diameter was measured in the anteroposterior position. The reproducibility of measuring AoR and LA diameters and left ventricular mass as well as diagnosing MVP was determined in recordings obtained from 20 healthy subjects (10 with MVP). Intraobserver left ventricular mass, LA diameter, and AoR diameter variabilities were <6, <4, and <3% respectively, whereas interobserver variabilities of these parameters were <10, <7, and <5% respectively. Intraobserver and interobserver correlations for echocardiographic MVP diagnosis was >0.90.

The echocardiographic criterion for the diagnosis of MVP was based on that reported by Freed et al. Briefly, subjects were classified as having MVP if displacement of mitral leaflets exceeded 2 mm. AoR was considered normal when its diameter was equal to or smaller than 36 mm in women and 39 mm in men. These cut-off points were below the 98th percentile values in a group of 356 normotensive, non-obese (body mass index between 20 and 25 kg/m²), apparently normal adults (196 women and 160 men; mean age 56.0 ± 6 years) evaluated in the same unit for a cardiovascular check-up in the previous 3 years. The thickness of the mitral leaflets during diastasis was measured from the leading to the trailing edge of the thickest area of the midportion of the leaflet, excluding focal areas of thickness and chordae.

Statistical analysis

Descriptive statistical results are given as the mean ± standard error. χ² test and unpaired t-test were used to compare categorical and continuous variables, respectively. Univariate correlations between variables were assessed by Pearson’s or Spearman’s methods. Multiple linear regression analysis with stepwise forward method was used to assess the independent relationships between AoR and studied parameters. A P-value of <0.01 was considered significant.

Results

Clinical and echocardiographic features of the studied sample are shown in Table 1. Although no differences in age, sex, anthropometric measurements, blood pressure levels, and left ventricular mass index were detected, subjects with MVP presented higher AoR diameter, AoR/body surface area, as well as lower LA diameter in comparison to controls. Among subjects with MVP, 55% (n = 345) presented mitral valve leaflets thickening ≥5 mm. However, no differences in clinical and echocardiographic features were detected between MVP individuals with thickened leaflets.
and MVP subjects with valve leaflets thickening < 5 mm (data not shown).

Univariate regression analyses were performed in order to evaluate relationships between AoR diameter and clinical/echocardiographic variables (Table 2). AoR diameter exhibited a direct correlation with MVP in the whole sample \( r = 0.13; P < 0.0001 \), while age, male gender, height, weight, body mass index, body surface area, blood pressure levels, and left ventricular mass index displayed significant correlation coefficients with AoR diameter in the whole sample as well as in both studied subgroups \( r \approx 0.20–0.60; \) all \( P < 0.0001 \).

A stepwise regression model was constructed to evaluate the independent contribution of different factors to AoR size (Table 3). This model included age, gender, body mass index, body surface area, systolic blood pressure, diastolic blood pressure, left ventricular mass index, and the presence of MVP as independent variables. Male gender and age were found to be the foremost predictors of AoR diameter, while left ventricular mass index and MVP contributed to explain its variance to a lesser extent.

### Discussion

MVP and enlarged AoR frequently coexist in patients with inherited connective tissue disorders, indicating that these echocardiographic alterations may represent a phenotypic continuum.\(^5\)\(^–\)\(^7\) Previous studies have also investigated whether AoR diameter is increased in individuals with primary MVP.\(^5\)\(^–\)\(^11\) Nevertheless, they failed to find significant differences in AoR diameter according to the presence or not of MVP. Noticeably, these latter reports enrolled a small number of subjects with isolated MVP, which varied from 10 to 100 individuals per study. Such feature probably limited the statistical power of the analysis. In the present report we evaluated a much larger sample (627 subjects with isolated MVP) and detected higher average AoR diameter and AoR/body surface area compared with measurements obtained from a similar number of individuals without MVP. In addition, results of multivariate analysis revealed that MVP was an independent predictor of greater AoR diameter in the whole sample. Overall, these data support the notion that alterations in mitral valve and AoR structure may indeed comprise a phenotypic continuum even in individuals with isolated MVP. In accordance with this hypothesis, previous studies have also described decreased elastic properties in the aorta of subjects with MVP.\(^5\)\(^–\)\(^7\)\(^,\)\(^17\)\(^–\)\(^18\)

One potential limitation to the assumption that greater AoR size is related to isolated MVP was that we did not know whether the enrolled individuals had diagnoses of inherited connective tissue disorders, since there were a variety of reasons for examination referral. Thus, inclusion of subjects with such diseases in the MVP group could have contributed to increase the average AoR diameter in this population.\(^5\)\(^–\)\(^7\) However, this hypothesis seems less probable since primary MVP is much more prevalent than secondary MVP to established connective tissue disorders.\(^2\)\(^,\)\(^3\)\(^,\)\(^19\) In this context, it has been estimated that no more than 1–2% of patients with MVP have an associated connective tissue disorder.\(^4\) Moreover, the presence of MVP in adults with heritable disorders of connective tissue is usually associated with AoR dilatation,\(^5\)\(^–\)\(^7\)\(^,\)\(^20\) an echocardiographic feature excluded from our analysis.

It was noteworthy that MVP subjects presented a smaller LA diameter in comparison to controls. However, we believe that this finding might not represent a real reduction in LA dimension. LA diameter was measured in the anteroposterior position according to echocardiographic guidelines.\(^12\) Noticeably, this evaluation may underestimate LA dimension since expansion of the LA can be limited by the thoracic cavity between the sternum and the spine. In this regard, increases in the AoR diameter are known to compress the adjacent LA, leading to a reduction in the anteroposterior diameter of this latter chamber.\(^21\) Given that the MVP and control groups had a similar body size, it is possible that the higher AoR diameter in the MVP group was responsible for the observed lower LA size in this population. This hypothesis is further supported by our findings showing that the average increase in AoR diameter in MVP was of 0.9 cm, which was quite comparable to the average decrease in LA diameter in comparison to controls.
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Some potential limitations of the present study deserve further comments. First, our data were extracted from databases, therefore, the examinations or the diagnoses could not be reviewed. However, we reduced this bias by only including exams carried out by a single echocardiographer. Moreover, intraobserver and interobserver correlations were performed and revealed high reproducibility in echocardiographic examinations. Second, we had no access to clinical features such as prevalence of hypertension, smoking, and diabetes, which are acknowledged markers of cardiovascular risk. Nevertheless, several reports have demonstrated that these variables are not consistent determinants of AoR size, suggesting that the lack of clinical characterization on these topics played no major influence in our results.

In conclusion, the present report demonstrated that MVP is an independent determinant of the greater AoR size in a large population with otherwise normal echocardiographic parameters. This result supports the notion that alterations in the mitral valve and AoR structures may represent a phenotypic continuum in subjects with isolated MVP.

Conflict of interest: none declared.

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