Cardiovascular involvement in osteogenesis imperfecta

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ABSTRACT While aortic root dilatation and valvular dysfunction have been well-documented in osteogenesis imperfecta (OI), the nature and extent of cardiovascular involvement in OI have not been clearly delineated. A clinical and echocardiographic survey involving 109 individuals with various nonlethal OI syndromes from 66 separate families was undertaken. Clinically discernible valvular dysfunction was encountered in only four of the 109 individuals (aortic regurgitation in two, aortic stenosis in one, and mitral valve prolapse in one), none of whom were related. Aortic root dilatation was recognized echocardiographically in eight (12.1%) of 66 individuals comprising a subset of the sample in which each family was represented by a single individual. The extent of the aortic root dilatation was mild (the largest dimension measuring 4.3 cm) and was unrelated to the age of the individual. Dilatation was seen in each of the different OI syndromes but was strikingly segregated within certain families (p < .001). In the same subset of 66 individuals, mitral valve prolapse was encountered in two or 6.9% of the 29 individuals aged 15 years or greater in whom adequate studies were obtained. This observed frequency was not different from that seen in a normal adult population. Aortic root dilatation appears to represent a distinct phenotypic trait in patients with OI that is nonprogressive and occurs in about 12% of affected individuals. Whether mitral valve prolapse should be considered as a part of the cardiovascular phenotype in OI, or alternately segregates as an independent autosomal dominant trait has yet to be determined.


OSTEOGENESIS IMPERFECTA (OI) is a group of heritable disorders of the connective tissue.1,2 Although bone fragility is the most widely recognized aspect of the clinical phenotype, the alterations in the connective tissue of affected individuals may be manifest in several extraskeletal tissues, including those of the sclerae, middle and inner ear, tendons and ligaments, integument, dentine, and cardiovascular structures. A considerable clinical and biochemical heterogeneity exists both between and within the different OI syndromes.3 In the few variants of OI studied in detail, specific mutations leading to either a quantitative or qualitative defect in type I procollagen synthesis have been delineated.3,4 While serious sequelae of structural alterations in the cardiovascular tissues have been reported infrequently in patients with OI, aortic root dilatation and valvular dysfunction (aortic regurgitation and mitral valve dysfunction) have been well-documented in affected individuals.5–11 The present study was undertaken to examine the prevalence of aortic root dilatation and valvular dysfunction in the nonlethal OI syndromes. An analysis of the influence of age, gender, clinical phenotype, and kinship on aortic root dimension provided a further delineation of the nature of the lesion underlying aortic root dilatation in this group of connective tissue disorders. A similar analysis with respect to valvular dysfunction in OI was limited by the small numbers of individuals with these lesions in our sample.

Materials and methods

One hundred and nine individuals with OI from 66 separate families were identified by two of the investigators (P. T. and J.
R. S.). These individuals had been referred to one of three clinical centers (Montreal Children’s Hospital, Middlesex General-University Hospital, or the Clinical Centre, NIH) for genetic counseling. The diagnosis of OI was based on the clinical presentation of fractures with or without skeletal deformity and a characteristic radiographic appearance of the skeletal tissues. In several cases, a family history of OI and the presence of one or more extraskeletal manifestations of this disorder (e.g., blue sclera, prenecise hearing loss, dentinogenesis imperfecta) served to reinforce the diagnosis. There were no clinical features that would have suggested a diagnosis of the Marfan’s syndrome in any of the families included in our sample. Informed consent was obtained from each participant in the study.

There were 56 male and 53 female patients included in the sample, ranging in age from 1 to 75 years (mean = 27 years). The classification proposed by Sillence et al. (table 1) was used to categorize each individual with respect to clinical phenotype. The sample comprised 83 individuals from 47 families with type I disease, 10 individuals from three families with type IV disease, and 16 individuals with type III disease. In these latter individuals with OI type III, there were no affected relatives.

The cardiovascular assessment was part of a more extensive protocol that included a complete medical and orthopedic history, a clinical examination, dental evaluation, audiometry, and an M mode echocardiographic examination. The weight, height, and blood pressure were recorded. An estimate of the mean arterial pressure (MAP) was calculated from the sphygmomanometric measurements of systolic and diastolic pressures with the following equation:

\[
\text{MAP} = \text{Diastolic pressure} + \frac{\text{Systolic} - \text{diastolic pressure}}{3}
\]

Auscultation was completed with the subject lying in a supine and left decubitus position, and immediately on sitting or standing.

An M mode echocardiogram was obtained with the subject lying supine or in a left decubitus position and was recorded at a paper speed of 50 mm/sec. The transducer was held perpendicular to the chest wall at the left sternal edge in the interspace (usually the fourth), which allowed optimal visualization of the mitral valve within the left ventricular cavity. The aortic valve was visualized with a superomedial angulation of the transducer. The mitral valve leaflets were then visualized over their entire cephalocaudal extent by scanning the echo beam from aortic root toward the left ventricular apex. When neither mitral nor aortic valves could be adequately delineated from the sternal edge, a subxiphoidal approach was used to visualize the aortic valve.

Measurements of cardiac dimensions from the M mode echocardiographic recordings in the 109 individuals studied were made by a single observer following the standards recommended by the American Society of Echocardiography. While aortic root dimension was of particular interest, left atrial and left ventricular dimensions were also recorded. In 45 individuals, these same dimensions were measured by the second investigator involved in the echocardiographic assessment. A repeated-measures analysis of variance, using the intraclass correlation coefficient as an index of observer concordance, was undertaken in this set of paired observations (table 2). Subsequent analyses of cardiovascular dimensions within the entire sample were limited to the three echocardiographic parameters (aortic root, left atrial, and left ventricular diastolic dimensions) for which there was no evidence of any systematic bias with respect to their measurement in tracings judged adequate by both observers. The measured aortic root, left atrial, and left ventricular diastolic dimensions were expressed as percentages of the mean predicted dimensions from age and weight based on the data of Henry et al. in normal individuals.

The echocardiographic recordings were also examined for evidence of mitral valve prolapse. Mitral valve motion was assessed at a point at which the free edges of the mitral valve leaflets were seen to coapt in early systole.
graphic diagnosis of mitral valve prolapse required the presence of a definite posterior buckling of the mitral valve leaflets in midsystole (i.e., late systolic prolapse) or a posterior displacement of the mitral valve leaflets from a line connecting valve closure and opening measuring at least 2 mm (holosystolic prolapse). 17, 18

Analysis of data. A preliminary analysis of the distribution of aortic root dimension among the 109 individuals suggested that kinship might be an important determinant of this aspect of the cardiovascular phenotype. There was a considerable range in the number of affected individuals available for study from any one family. Because the disparity in numbers of affected members available from different families would distort the observed frequency of aortic root dilatation in the analyses, the frequency distribution of aortic root dimension was examined within a subset in which each of the 66 families identified in the study was represented by a single family member. This subset comprised all individuals representing the single available family member in the data base (n = 48), and a single individual randomly selected (by use of the study identification number and a random number table) in each of the families in which two or more members had been studied (n = 18). While an alternate sampling technique in these latter families might have been the use of the propositus, the referral of an entire family for genetic counseling often precluded a clear delineation of the propositus

The distribution of age and gender within the subset of 66 individuals representing their respective families was not significantly different from that in the entire study group (unpaired t analysis and Fisher’s exact probability, respectively). 19

A considerable overlap exists in the clinical phenotype of types I and IV OI (table 1), and the number of families with type IV disease in our sample was small. Accordingly, those individuals with types I and IV disease were considered as a single group and were compared with the remaining individuals with the more severely deforming type III disease.

Aortic root dilatation was considered to exist in those individuals in whom the measured aortic root dimension lay outside the 99% confidence interval about the mean predicted dimension (i.e., aortic root dimension, expressed as a percentage of the mean predicted dimension from age and weight greater than 127% predicted). 20

Within the subset of 66 individuals representing their respective families, the distribution of discrete variables (gender and clinical phenotype) in the group of individuals with aortic root dilatation was compared with that in the remainder of the subset with Fisher’s test of exact probability. 19 In a separate analysis, the differences in the distribution of aortic root dimensions within seven separate families with types I or IV disease were examined by a one-way analysis of variance and Scheffe’s procedure for multiple comparisons. 20, 21 The influence of age and mean arterial pressure on aortic root dimension was examined in four of the families in which several individuals had been available for study. These data were analyzed with a linear regression model using the least sum of squares and Pearson’s correlation coefficient. 19

The prevalence of mitral valve prolapse (MVP) in OI and the distributions of left atrial and left ventricular diastolic dimensions were also examined within the smaller sample of the 66 individuals representing their respective families. The prevalence of MVP in otherwise normal children is less than that seen in the normal adult population. 22, 23 Using a three-dimensional penetrance model to describe the variation in expression of MVP with age, Straham et al. 23 estimated the mean and standard deviation of the age of phenotypic expression to be 8.8 ± 2.6 years. In other words, one could presume that MVP would be unlikely to emerge in an individual in whom it was not manifest by age 15 years. The observed frequency of MVP in our analy-

ses was therefore expressed as a fraction of the number of adequate studies in individuals less than 15 years old, and as a fraction of the number of adequate studies in individuals 15 years old or greater. The latter observed frequency served as our estimate of the prevalence of MVP in OI and was compared with published data pertaining to the prevalence of MVP in the normal adult population. 24-26

Results

Among the 109 individuals identified in the study, clinically discernible valvular dysfunction was encountered in only four subjects, none of whom were related. Aortic regurgitation was noted in two individuals and mild aortic stenosis was evident in another. MVP (a nonejection systolic click without a murmur) was noted in a fourth individual. While none had any cardiorespiratory limitation, three of these individuals (two with aortic regurgitation and one with mitral valve prolapse) required antihypertensive medication.

The actual measurements of aortic root dimension ranged from 1.1 to 4.3 cm in the entire study group. Aortic root dimension, expressed as a percentage of the mean predicted dimension based on weight and age (ARD%), ranged from 82% to 148%. Aortic root dilatation (ARD% > 127% predicted) was seen in eight (12.1%) of the 66 individuals representing the separate families within the sample. The ARD% in these eight individuals was distributed about a mean of 135.3% (range = 130% to 148%). These individuals with aortic root dilatation were represented in a second peak within the upper tail of the frequency distribution of ARD%, distinct from the principal peak at 105% (figure 1). A similar bimodal distribution of ARD% was also evident within the separate clinical phenotypes

![Aortic Root Dimension (% predicted)](image-url)
(figure 2). The eight individuals with aortic root dilatation were compared with the remaining 58 individuals with respect to age, gender, and clinical phenotype (table 3). The ages of the members of the two groups were similar, ranging from 5 to 64 years in the group with increased ARD% and from 1 to 74 years in the remaining individuals. The proportion of male and female subjects and the proportion of individuals with type III or types I and IV disease represented in each group were not significantly different (p = .16 and .18, respectively). Doliostenomelia or arachnodactyly, "marfanoid" features that have been described in some individuals with OI, were not seen in any of the individuals with aortic root dilatation.

A striking segregation in the distributions of aortic root dimension was noted when different families were analyzed (table 4). In two of the eight individuals with ARD% greater than 127%, there were additional family members available for study. The distributions of ARD% in the families of these two individuals (families I-A and IV-A) were compared with the distributions of ARD% in the families of five other individuals with ARD% less than 127%, in which three or more family members had been studied (families I-B through I-E and family IV-B). Values for ARD% within the families I-A and IV-A were distributed about significantly greater means than in the remaining families (p < .001; figure 3).

**TABLE 3**
Characteristics of the groups with and without significant aortic root dilatation

<table>
<thead>
<tr>
<th></th>
<th>ARD% &gt;127%</th>
<th>ARD% ≤127%</th>
<th>Total</th>
<th>p value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 8)(^b)</td>
<td>(n = 58)</td>
<td>(n = 66)</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>24</td>
<td>30</td>
<td>0.16</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>34</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>58</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Phenotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Types I and IV</td>
<td>4</td>
<td>46</td>
<td>50</td>
<td>0.18</td>
</tr>
<tr>
<td>Type III</td>
<td>4</td>
<td>12</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>58</td>
<td>66</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)ARD% >127% predicted exceeds the 99% confidence interval about the mean predicted dimension in normal individuals.\(^{16}\)

\(^b\)By Fisher's exact probability test.

The analyses of the relationship between aortic root dimension and both age and systemic arterial pressure were limited to the four families in which several members had been studied (table 4). Reliable measurement of systolic and diastolic pressures had been obtained in 29 of the 31 individuals available for study in these four families. There was no relationship between ARD% and age within any of these families. In the three families in which aortic root dilatation was not a part of the phenotype, there was no correlation be-

**FIGURE 2.** Frequency distributions of aortic root dimension, expressed as ARD% in individuals with (left) types I and IV OI (n = 50) and (right) type III OI (n = 16). The upper limit of the 99% confidence interval is again denoted with a broken line.
TABLE 4
Differences in distribution of aortic root dimension in families with OI

<table>
<thead>
<tr>
<th>Family</th>
<th>n</th>
<th>Age (yr)</th>
<th>MAP (mm Hg)</th>
<th>Aortic root dimension (ARD%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Proband</td>
</tr>
<tr>
<td>I-A</td>
<td>6</td>
<td>39.4 ± 17.4</td>
<td>89.0 ± 5.2</td>
<td>134</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(9-51)</td>
<td>(80-93)</td>
<td></td>
</tr>
<tr>
<td>I-B</td>
<td>12</td>
<td>38.7 ± 22.3</td>
<td>96.1 ± 9.4</td>
<td>127</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(4-75)</td>
<td>(84-109)</td>
<td></td>
</tr>
<tr>
<td>I-C</td>
<td>6</td>
<td>27.8 ± 21.8</td>
<td>90.3 ± 14.5</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2-61)</td>
<td>(72-110)</td>
<td></td>
</tr>
<tr>
<td>I-D</td>
<td>3</td>
<td>26.3 ± 21.4</td>
<td>—</td>
<td>107</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(13-51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-E</td>
<td>3</td>
<td>23.0 ± 2.6</td>
<td>—</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(20-25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV-A</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>139</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(24, 51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV-B</td>
<td>7</td>
<td>33.7 ± 25.4</td>
<td>91.4 ± 11.0</td>
<td>109</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(10-74)</td>
<td>(78-108)</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD, with range in parentheses.

Aortic root dimension expressed as a percentage of the mean predicted dimension.16

Aortic root dimension in the families I-A and IV-A was distributed about a significantly greater mean than in the remaining families (multiple comparison analysis/Scheffé procedure, p < .001).

between ARD% and the estimate of mean arterial pressure. However, in the family in which aortic root dilatation did exist, there was a tendency for ARD% to be greater in those individuals with higher mean arterial pressures (r = .78, p = .07). None of the individuals in this latter family was considered hypertensive.

There was not a clear association between aortic root dilatation and aortic regurgitation. The largest actual measurement of aortic root dimension in our sample (4.3 cm, ARD% = 144%) was seen in one of the two individuals with aortic regurgitation. However, the aortic root dimension in the second individual with aortic regurgitation, while prominent (ARD% = 118%), was within normal limits.

A satisfactory recording of mitral valve motion was obtained in 19 of the 24 individuals less than 15 years old and in 29 of the 42 individuals 15 years old or greater (table 5). MVP was diagnosed in one individual with type I OI and a second individual with type III disease. Both were adults (aged 39 and 56 years, respectively) and in the second case, the echocardiographic findings confirmed the clinical diagnosis of MVP. These two individuals comprised 6.9% of the 29 individuals aged 15 years or greater in whom adequate studies were obtained. There were no cases of MVP in the younger age group. The two individuals with MVP represented the single affected members of their respective families available for study. Among the affected relatives excluded from the subset (n = 43), one further case of MVP was seen in the 32 adequate studies obtained. The absence of affected relatives of individuals with MVP in our sample precluded a more detailed examination of the pattern of phenotypic expression of this lesion.

Left atrial dimensions within the subset in which each family was represented by a single individual were somewhat less than expected in a normal population (mean ± SD 88.2 ± 11.4% predicted) and left ventricular dimensions were slightly greater than expected (mean ± SD 103.2 ± 11.5% predicted). There was no suggestion of a bimodal distribution of these cardiac dimensions. Neither was there any relationship between the severity of aortic root dilatation and the extent to which either left atrial dimension was decreased or left ventricular dimension increased.

The aortic root dimension in our analysis was in-

<table>
<thead>
<tr>
<th>Families</th>
<th>I-A (n=6)</th>
<th>I-B (n=12)</th>
<th>I-C (n=6)</th>
<th>I-D (n=3)</th>
<th>I-E (n=3)</th>
<th>IV-A (n=2)</th>
<th>IV-B (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic Root Dimension (% predicted)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>110</td>
<td>120</td>
<td>130</td>
<td>140</td>
<td>150</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 3. Distributions of aortic root dimension, expressed as ARD% in affected members of seven families with OI. The mean ± SD is shown.

TABLE 5
Mitrval prolapse

<table>
<thead>
<tr>
<th>Age ≥15 yr (n = 42)</th>
<th>Adequate study (n = 48)</th>
<th>Inadequate study (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No MVP</td>
<td>MVP</td>
<td>Total</td>
</tr>
<tr>
<td>Age ≥15 yr (n = 42)</td>
<td>24 1 25 9</td>
<td></td>
</tr>
<tr>
<td>Types I and IV (n = 34)</td>
<td>3 1 4 4</td>
<td></td>
</tr>
<tr>
<td>Type III (n = 8)</td>
<td>27 2 29 13</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>13 — 13 3</td>
<td></td>
</tr>
<tr>
<td>Age &lt;15 yr (n = 24)</td>
<td>13 — 6 2</td>
<td></td>
</tr>
<tr>
<td>Types I and IV (n = 16)</td>
<td>6 — 6 2</td>
<td></td>
</tr>
<tr>
<td>Type III (n = 8)</td>
<td>19 — 19 5</td>
<td></td>
</tr>
</tbody>
</table>
dexed to body weight (ARD%) rather than body surface area (BSA). Aortic root dimension expressed as a percentage of the mean predicted dimension from age and BSA\(^6\) was equal to ARD% (based on weight) \(\pm 5\%\) in 52 of the 66 individuals representing each of the families in the sample. The four subjects with autosomal dominant disease (types I and IV) and significant aortic root dilatation were among these 52 individuals. In the remaining 14 subjects, the aortic root dimension expressed as a percent predicted from BSA exceeded ARD% by more than 5% (range 6% to 15%). Twelve of these 14 individuals, including the four remaining individuals with aortic root dilatation, had type III disease.

Discussion

The biochemical lesions in patients with OI have been examined in studies of procollagen biosynthesis in vivo in human fibroblast tissue cultures.\(^3,4\) These investigations identified a biochemical heterogeneity among the various OI phenotypes. It would appear that the defect in many of the OI syndromes involves a mutation in either the proα1(I) or proα2(I) chains of type I procollagen. These mutations may result in the synthesis of unstable procollagen molecules or alternately, the secretion of a structurally abnormal heteropolymer. Type I collagen is the predominant fibrillar collagen in humans and is well represented in both skeletal and nonskeletal tissues, including the cardiovascular connective tissues.\(^22\) Biochemical alterations have also been identified in noncollagenous structural proteins of bone in an animal preparation of OI.\(^28\) It has been suggested that similar defects in noncollagenous bone proteins may exist in some variants of OI in humans.\(^28\) In such cases, one would not expect systemic manifestations of the biochemical alteration and certainly no cardiovascular involvement.

Aortic and mitral valvular regurgitation in individuals with OI has been the subject of several case reports that have been reviewed recently by different authors.\(^5,6,10\) The frequency with which clinically discernible valvular dysfunction has been noted in either retrospective\(^7,8\) and prospective\(^9,10\) surveys has been small.

Aortic regurgitation was encountered in only two of the 109 affected individuals in our sample. Pyeritz and Levin\(^9\) and White et al.\(^10\) noted similarly small numbers of individuals with aortic regurgitation in their surveys (two of 109 and one of 20 individuals, respectively). A dilatation of the aortic root and valve anulus has been implicated in the pathogenesis of this lesion in OI.\(^11\) However, aortic root dilatation was not a consistent finding in the 11 patients with aortic regurgitation reviewed by Acar et al.\(^6\) in whom surgical or postmortem descriptions of the aortic valve and ascending aorta were available. A similar disparity existed in the aortic root dimensions of the two individuals in our sample with aortic regurgitation. As Acar et al.\(^6\) have suggested, the dysplastic nature of the valvular tissue is probably an equally important determinant of aortic valve integrity in this group of connective tissue disorders.

Mitral regurgitation has been reported less often than aortic valvular dysfunction in patients with OI.\(^5,6\) While neither White et al.\(^10\) nor ourselves encountered mitral regurgitation in our respective samples, Pyeritz and Levin\(^9\) identified this lesion in three of the 109 affected individuals in their survey. The preeminence of the group at Johns Hopkins\(^9\) in the management of cardiovascular complications of connective tissue disorders may underlie the discrepancy in the observed frequencies of mitral regurgitation among these separate surveys.

MVP has been recognized both clinically and echocardiographically in OI with a somewhat greater frequency than mitral regurgitation. MVP is also one of the most common Mendelian cardiovascular traits in humans, exhibiting an autosomal dominant inheritance with age-dependent expression.\(^22,23\) Pyeritz and Levin\(^9\) were unable to discern a significant difference in the frequency with which MVP was observed in individuals with OI or their unaffected relatives. In our sample, the frequency with which MVP was identified in affected individuals 15 years old or greater (6.9%) was not significantly different from the 4%\(^24,26\) and 8%\(^25\) that have been reported in normal adult populations. These observations raise the possibility that MVP in individuals with OI may simply represent the expression of an autosomal dominant trait that is prevalent among otherwise healthy individuals. A larger sample of affected individuals and further analysis of the prevalence of MVP in both affected and unaffected relatives would provide a clearer delineation of the relationship between MVP and this group of connective tissue disorders.

Until recently, aortic root dilatation had been recognized almost exclusively in the context of clinically discernible aortic regurgitation. With echocardiographic studies, the relatively frequent occurrence of aortic root dilatation without associated valvular dysfunction has been appreciated.\(^9,10\) The frequency with which aortic root dilatation was encountered in our sample (8/66 or 12.1%) represents an estimate of the prevalence of this lesion in individuals with OI. The
mild extent of the enlargement of aortic root noted in the present study and in the earlier clinical and echocardiographic surveys of OI clinic populations. It is in marked contrast to the striking aortic root dilatation seen in another group of connective tissue disorders, the Marfan syndrome.

Aortic root dilatation would appear to represent a specific phenotypic trait in OI. While it was seen in each of the different nonlethal OI syndromes included in our sample, the bimodal distribution of ARD% and the segregation in the distribution of ARD% between separate families is consistent with the presence of a distinct lesion in the connective tissue of the aortic root in those individuals with aortic root dilatation. The recognition of aortic root dilatation in each of the different OI syndromes would suggest that more than one structural defect in type I procollagen may predispose to this lesion in OI. The difference noted by Pyeritz and Levin in the frequency with which aortic root dilatation was observed in male or female patients was not as evident in our analyses.

The similarity in age range within the groups with or without significant aortic root dilatation and the absence of any relationship between age and ARD% in four large families (including the family I-A in whom significant aortic root dilatation existed) suggests that aortic root dilatation in OI is associated with a very different natural history than that seen in the Marfan syndrome. A longitudinal study of aortic root dimension in these individuals would be required to confirm the impression that aortic root dilatation is a nonprogressive phenomenon in OI.

The analysis of the relationship between ARD% and the estimate of mean arterial pressure within the four families allowed us to examine the influence of systemic arterial pressure on aortic root dimension within four relatively homogenous groups. The observation that a relationship between ARD% and mean arterial pressure existed only in that family in which aortic root dilatation was a part of the phenotype may be a further reflection of the differences in the connective tissue of the aortic root that presumably underlie this aspect of the cardiovascular phenotype.

The present analysis differs from the reports cited previously in that aortic root dimension was indexed to body weight rather than BSA. Henry et al. found that the predicted echocardiographic dimensions derived from regression equations based on weight were nearly identical to those obtained with BSA. The discrepancy in the more severely affected individuals in the sample between the aortic root dimension expressed as a percent predicted from weight (ARD%) and that expressed as a percent predicted from BSA undoubtedly reflects an underestimate of BSA related to disturbances in growth and the skeletal deformities in these individuals.

In summary, cardiovascular involvement in the nonlethal OI syndromes is often clinically inapparent. The frequency with which clinically discernible valvular dysfunction was encountered in our sample was small. However, aortic root dilatation was delineated by M mode echocardiography in 12% of affected individuals. This lesion appeared to represent a distinct phenotypic trait in OI, seen in each of the different OI syndromes but strikingly segregated within certain families. The frequency with which MVP was noted in our survey was similar to that seen among otherwise healthy adults. Whether MVP in this group of disorders represents a distinct aspect of the OI cardiovascular phenotype, or alternately segregates in OI as an independent autosomal dominant trait that is prevalent in the population at large, has yet to be determined.

Systemic arterial pressure may influence aortic root dimension in those individuals in whom significant aortic root dilatation is a part of the clinical phenotype. While the use of propanolol has been advocated in patients with the Marfan syndrome as a means of slowing the progression of aortic root dilatation, the mild and apparently nonprogressive nature of this lesion in OI would argue against the use of β-adrenergic blockade in affected individuals in the absence of systemic arterial hypertension.

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