Marfan syndrome in children and adolescents: an adjusted nomogram for screening aortic root dilatation

Published in: Heart

DOI:
10.1136/hrt.79.1.69

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Marfan syndrome in children and adolescents: an adjusted nomogram for screening aortic root dilatation

Lieke Rozendaal, Maarten Groenink, Mies S J Naeff, Raoul C M Hennekam, Augustinus A M Hart, Ernst E van der Wall and Barbara J M Mulder

Heart 1998;79:69-72

Updated information and services can be found at:
http://heart.bmj.com/cgi/content/full/79/1/69

These include:

References
This article cites 24 articles, 5 of which can be accessed free at:
http://heart.bmj.com/cgi/content/full/79/1/69#BIBL

4 online articles that cite this article can be accessed at:
http://heart.bmj.com/cgi/content/full/79/1/69#otherarticles

Rapid responses
You can respond to this article at:
http://heart.bmj.com/cgi/eletter-submit/79/1/69

Email alerting service
Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

Notes

To order reprints of this article go to:
http://www.bmjjournals.com/cgi/reprintform

To subscribe to Heart go to:
http://www.bmjjournals.com/subscriptions/
Marfan syndrome in children and adolescents: an adjusted nomogram for screening aortic root dilatation

Lieke Rozendaal, Maarten Groenink, Mies S J Naef, Raoul C M Hennekam, Augustinus A M Hart, Ernst E van der Wall, Barbara J M Mulder

Abstract
Objective—To construct an adjusted nomogram for the echocardiographic screening of aortic root diameter in children with possible Marfan disease.

Design—In 91 children (42 boys, 49 girls, age range 3.2 to 18.4 years) undergoing Marfan screening from 1983 until 1996, the diagnosis Marfan syndrome and any other aortic pathology was definitely ruled out. These served as a control population to set appropriate reference standards.

Results—Compared with a standard Dutch reference population, body surface area of the control subjects (mean (SD)) was above the 50th centile (boys 0.09 (0.20) m², range −0.28 to 0.69 m²; girls 0.09 (0.17) m², range −0.17 to 0.69 m²). Echocardiographically determined aortic root diameter and body surface area showed a linear relation and a greater variability of aortic root diameter in these relatively tall subjects (n = 91, \( R^2 = 0.62 \) than in the standard nomogram (n = 56, \( R^2 = 0.93 \)). In 24% of cases (n = 22), the aortic root exceeded the upper limit of normal in the standard nomogram, by 2.2 (2.0) mm. An adjusted nomogram was constructed with a higher upper limit.

Conclusions—A Marfan screening population differs from the unselected population in body surface area and aortic root size variability. An adjusted nomogram should therefore be used to detect a truly enlarged aortic root.

(Heart 1998;79:69–72)

Keywords: Marfan syndrome; aorta; nomogram; children

Marfan syndrome is an autosomal dominant connective tissue disorder, associated with mutations in the fibrillin I gene, in which ocular, skeletal, cardiovascular, integumentary, pulmonary, and neurological features may be present. The prevalence has been estimated to be 1 in 3–5000, 15–30% of whom are new mutations.

Until recently, the diagnosis was based on fulfillment of diagnostic criteria established in Berlin in 1986. In 1995, these criteria were revised in Gent. The criteria are still based on a combination of major and minor clinical manifestations in different organ systems and on family history. The manifestations vary in onset and in severity, and show a variable rate, particularly in children. Usually signs are not clearly present at birth but develop during childhood and adolescence. Therefore, diagnosis of Marfan syndrome in children is often difficult and long term follow up examinations are necessary before a definite diagnosis can be made.

Because aortic root dilatation is one of the major criteria for the diagnosis of Marfan syndrome, screening and follow up of the cardiovascular system relies on accurate measurement of aortic root size. M mode and cross sectional echocardiographic dimensions are related to height, weight, and body surface area. At present, body surface area is considered to be the most important independent determinant of aortic root diameter. Roman et al proposed a nomogram based on cross sectional echocardiographic aortic root diameters of children and adults in the normal population. However, a remarkably large number of subjects in whom Marfan syndrome or any other aortic disease was definitely ruled out after screening by a multidisciplinary team in our institution showed aortic root diameters exceeding the upper limit of this standard nomogram with M mode echocardiography. Subjects referred for screening for Marfan syndrome are not usually entirely comparable in body size with gender and age matched subjects from the unselected population. Usually these children are taller and thinner, and have a relatively larger body surface area. There is, however, a possibility that systematic differences between M mode and cross sectional echocardiography are responsible for the deviation from the standard nomogram. Therefore a comparison between the two methods was made in Marfan patients and controls, in whom both M mode and cross sectional echocardiographic aortic root measurements were performed simultaneously.

The aim of our study was to develop a nomogram adjusted to the actual control population to screen children and adolescents for Marfan disease.

Methods
From 1983 until 1996, 250 children had been referred to the multidisciplinary Marfan team of the Academic Medical Centre of Amsterdam. Indications for screening included family history, excessive height, chest or spine anomalies, hypermobile joints, and lens subluxation.

None of these subjects was referred for aortic root enlargement. The diagnosis of Marfan
Table 1  Population characteristics

<table>
<thead>
<tr>
<th></th>
<th>Boys (n=42)</th>
<th>Girls (n=49)</th>
<th>Total (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age (years)</td>
<td>12.7 (4.4)</td>
<td>13.0 (3.2)</td>
<td>12.9 (3.8)</td>
</tr>
<tr>
<td>Range</td>
<td>3.2 to 18.0</td>
<td>5.3 to 18.4</td>
<td>3.2 to 18.4</td>
</tr>
<tr>
<td>Mean (SD) BSA (m²)</td>
<td>1.53 (0.45)</td>
<td>1.51 (0.31)</td>
<td>1.52 (0.38)</td>
</tr>
<tr>
<td>Range</td>
<td>0.60 to 2.32</td>
<td>0.85 to 2.14</td>
<td>0.60 to 2.32</td>
</tr>
<tr>
<td>Mean (SD) aortic root diameter (mm)</td>
<td>27.6 (5.7)</td>
<td>25.9 (3.9)</td>
<td>26.7 (4.8)</td>
</tr>
<tr>
<td>Range</td>
<td>18.0 to 38.3</td>
<td>18.5 to 35.0</td>
<td>18.0 to 38.3</td>
</tr>
</tbody>
</table>

p not significant for boys vs girls for all variables.

BSA, body surface area.

The 95% prediction intervals were calculated as:

\[ \log(\text{BSA}) = \log(W) \cdot 0.425 + \log(H) \cdot 0.725 + 1.8564 \]

where BSA is body surface area in cm², W is weight in kg, and H is height in cm.23 It was correlated with age and subsequently compared with body surface area growth curves of the Dutch population in the years 1989 to 1992.24

Echocardiographic measurements of the aortic root diameter were made by M mode echocardiography at the level of the sinuses of Valsalva, according to the recommendations of the American Society of Echocardiography (ASE)25 and guided by cross sectional echocardiography. Only the most recent measurement of aortic root diameter per subject was used.

Body surface area and aortic root diameter were correlated by linear regression analysis. The 95% prediction intervals were calculated as:

\[ y_\pm \left( 2 \cdot \text{SD} \cdot R \right) + \text{SQRT} \left[ 1 + 1/91 + (\text{BSA} - \text{BSA}_m)^2 / \Sigma (\text{BSA} - \text{BSA}_m)^2 \right], \]

in which \( y \) is aortic root diameter predicted from the linear regression, SD is standard deviation of aortic root diameters, R is square root of the correlation’s least squares fit, BSA is body surface area, and BSA_\( _m \) is mean BSA.

For comparison of the M mode and cross sectional echocardiographic measurements of the aortic root, Bland-Altman analysis26 was applied to 56 Marfan patients and 58 control subjects. In these subjects cross sectional and M mode echocardiographic measurements were made during the same imaging procedure. One randomly chosen aortic root diameter per subject measured by both modes was used for this analysis. The characteristics in range and mean (SD) of the patients and control subjects are shown in table 2.

Table 2  Population characteristics for Bland-Altman analysis

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=56)</th>
<th>Control subjects (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female (%)</td>
<td>48/52</td>
<td>46/54</td>
</tr>
<tr>
<td>Mean (SD) age (years)</td>
<td>13.1 (5.7)</td>
<td>13.1 (3.6)</td>
</tr>
<tr>
<td>Range</td>
<td>0.01 to 26.4</td>
<td>3.2 to 18.4</td>
</tr>
<tr>
<td>Mean (SD) BSA (m²)</td>
<td>1.58 (0.42)</td>
<td>1.50 (0.34)</td>
</tr>
<tr>
<td>Range</td>
<td>0.22 to 2.48</td>
<td>0.61 to 2.18</td>
</tr>
<tr>
<td>Diameter of aortic root at the level of the sinus of Valsalva</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M mode (mm)</td>
<td>36.2 (8.6)</td>
<td>26.7 (4.4)</td>
</tr>
<tr>
<td>Range</td>
<td>12.0 to 58.5</td>
<td>18.0 to 37.0</td>
</tr>
<tr>
<td>2D (mm)</td>
<td>35.8 (8.8)</td>
<td>25.5 (4.5)</td>
</tr>
<tr>
<td>Range</td>
<td>9.8 to 55.0</td>
<td>17.0 to 37.0</td>
</tr>
</tbody>
</table>

BSA, body surface area. 2D, cross sectional echocardiography.

AORTIC ROOT DIAMETER

Although our data showed roughly the same linear regression (\( y = 9.9x + 11.6 \)) as the standard body surface area nomogram (\( y = 9.8x + 10.2 \)), we found a weaker correlation (\( R^2 = 0.62 \) vs 0.93), although more subjects were studied. In 22 of 91 children (24%), the aortic root diameter exceeded the upper limit of the standard body surface area nomogram by 0.1 to 6.8 mm (mean 2.4 (2.2) mm). The adjusted nomogram, based on our data,
Nomogram for aortic root dilatation in Marfan syndrome

Discussion

Aortic root dilatation is one of the major criteria for assessing the diagnosis of Marfan syndrome. Patients with Marfan syndrome are at risk of sudden death from aortic dissection or rupture. Marfan patients with non-enlarged aortic roots are thought to be at low risk of these complications. Hence, both for accurate assessment of the diagnosis of Marfan syndrome and for recognition of a group of Marfan patients with low risk of severe aortic problems, it is critical to define whether the aortic root is really enlarged.

Echocardiography

Echocardiographic measurements of the aortic root in our population did not show complete agreement with the nomogram used as the standard for children proposed by Roman et al. Our data, however, were obtained from M mode echocardiography, whereas Roman’s nomogram was based on cross sectional echocardiography. Information about differences in the diameter of the aortic root between the two modes is limited, though Roman et al, who studied 52 normal children with both echocardiographic approaches, observed that the aortic root diameters at the level of the sinuses of Valsalva were systematically larger when assessed by cross sectional echocardiography than by M mode, by a mean of 2 mm. Of 58 available cross sectional measurements of our population, however, 11 aortic root diameters (19%) also exceeded the upper limit of the standard nomogram. We also compared M mode and cross sectional echocardiographic aortic root measurements in our own population using Bland–Altman analysis. No systematically relevant difference between the two methods was found. The prediction interval presented in fig 4 indicates that 95% of all differences will be between −4.4 mm and 2.8 mm. Factors such as two different technicians, intraobserver and interobserver variability, the use of different recorders and transducers, and different patient positioning largely account for the distribution of these differences in measurement results. Consequently, the two modes can be used interchangeably. Two different nomograms for either cross sectional or M mode echocardiography do not appear to be necessary.

Population and body surface area

Several investigators have proposed nomograms for standardisation of aortic root size in relation to body surface area. The nomogram proposed by Roman et al is currently the most widely used and is recommended by de Paepe et al in the revised diagnostic criteria for Marfan syndrome. Our study population consisted of subjects referred for screening for Marfan syndrome in whom the diagnosis was definitely excluded on the basis of repeated evaluation of the diagnostic criteria.
for all organ systems. These children may have a
deviant body surface area, excessive growth,
and marfanoid body appearance, which are
important reasons why subjects are referred for
Marfan screening. A possible explanation for
the upward scatter of our data could be the
selection of a tall subgroup in a standard popu-
lation, in which aortic root dimensions are
larger than expected. Reed et al. constructed
a body surface area nomogram for aortic root
dimensions in tall adults (exceeding the 95th
centile for height) between 17 and 26 years of
age. There was a much weaker linear correla-
tion ($n = 182$, $R^2 = 0.54$) between body sur-
face area and aortic root diameter (showing a
larger scatter, as in the present study) than in
the population of Roman et al. To our knowl-
edge, a nomogram for tall children has not yet
been reported. Although we do not have full
details of the body size measurements done in
the population reported by Roman et al, the
mean body surface area at nine years of age was
1.1 m$^2$, which is 0.5 m$^2$ below the regression
line of our data in fig 1. Therefore it seems
likely that, in relation to age, there are
differences in body surface area between our
population and that of Roman et al. This can
only partially be explained by possible geo-
ographical differences in body surface area at a
particular age between The Netherlands and
the USA, because comparisons using a stan-
dard Dutch reference population still show an
upward shift of the correlation, roughly follow-
ing the 75th percentile of body surface area.
So, as in tall adults, a wider range of aortic
root diameter should be considered normal in
tall children compared to an average unse-
lected population.

CONCLUSIONS

We conclude that a Marfan screening popula-
tion differs from an unselected echocardiogra-
phy population in aortic root size variability.
This is probably due to differences in anthro-
pometric measurements in this specific popu-
lation. The use of an adjusted nomogram rather
than a standard nomogram seems appropriate
for routine clinical screening in this specific
group of patients with deviant body surface
areas. There were no clinically relevant differ-
ces between M mode and cross sectional
echocardiography in the assessment of aortic
root diameters.

1 Lee B, Godfrey M, Vitale E, Hor I, Mattei M-G, Sarafarazi
M, et al. Linkage of Marfan syndrome to a phenotypically
related disorder to two different fibrillin genes. Nature
2 McKusick VA. The cardiovascular aspects of Marfan’s
syndrome: a heritable disorder of connective tissue.
3 Pyeritz RE, McKusick VA. The Marfan syndrome: diagno-
4 Pyeritz RE. Disorders of fibrillins and microfibrillogenesis:
Marfan syndrome, MASS phenotype, connective tissue
dysfunction and related conditions. In: Emery AE, Rimoin
DL, David L, Connor JM, Pyeritz RE, eds. Principles and
practice of medical genetics, 3rd ed. New York: Churchill Liv-
ingstone, 1996.
5 Brightton P, de Paepe A, Danss D, Finodori G, Gedele-Dahl
6 Morse RP, Rockenmacher S, Pyeritz RE, Sanders SP, Bieber
FR, Lin A, et al. Diagnosis and management of infantile
7 De Paepe A, Devereux RB, Dietz HC, Hennekam RCM,
Pyeritz RE. Revised diagnostic criteria for the Marfan
8 Oostrhuy JWE, Naeff MSJ, Hennekam RCM, Bleeker-
syndrome: a multidisciplinary clinical study of 91 patients.
9 Shell MLK, Jenkins O, Sholder GF. Echocardiographic
assessment of aortic root dimensions in normal children
based on measurement of a new ratio of aortic size
10 Vasan RS, Larson MG, Levy D. Determinants of echocar-
diographic aortic root size. The Framingham Heart Study.
11 Henry WL, Gardin JM, Ware JH. Echocardiographic meas-
urements in normal subjects from infancy to old age.
12 Salim MA, Alpert BS, Ward JC, Pyeritz RE. Effect of beta-
adrenergic blockade on aortic root rate of dilation in the
13 Jeremy RW, Huang H, Hwa J, McCarron H, Hughes CF,
Richards JG. Relation between age, arterial distensibility,
and aortic dilation in the Marfan syndrome. Am J Cardiol
14 Roman MJ, Devereux RB, Kramer-Fox R, O’Laughlin J.
Two-dimensional echocardiographic aortic root dimen-
sions in normal children and adults. Am J Cardiol 1989;64:
507–12.
15 Roman MJ, Rosen SE, Kramer-Fox R, Devereux RB. Prog-
nostic significance of the pattern of aortic root dilation in the
16 Snider AR, Enderlein MA, Teitel DF, Juster RP. Two-
dimensional echocardiographic assessment of aortic and
pulmonary artery sizes from infancy to adulthood in
17 Henry WL, Ware J, Gardin JM, Heppner SI, McKay J,
Weiner M. Echocardiographic measurements in normal
subjects. Growth-related changes that occur between
18 Gutgesell HP, Rembold CM. Growth of the human heart
19 Reed CM, Riecy PA, Pulliam DA, Soomes GW, Alpert BS.
Aortic dimensions in tall men and women. Am J Cardiol
20 Rogé C.LL, Silverman NH, Hart PA, Ray RM. Cardiac
structure growth pattern determined by echocardiography.
21 Vetter U, Mayerhofer R, Lang D, von Bernuth G, Rank
MB, Schmaltz AA. The Marfan syndrome—analysis of
growth and cardiovascular manifestation. Eur J Pediatr
1990;149:452–6.
22 Geva T, Sanders SP, Diogenes MS, Rockenmacher S, Van
Vraagh R. Two-dimensional and Doppler echocardiogra-
phy and pathologic characteristics of the infantile
23 Du Bois D, Du Bois EF. A formula to estimate the approxi-
mate surface area if height and weight be known. Arch
24 Verweij GCG. Height and weight of children and adoles-
cents up to 21 years, 1981–1992. Maandblad gezond-
25 Sahn DJ, DeMarco A, Kassof J, Weyman A. The committe
on M-mode standardization of the American Society of
Echocardiography. Recommendations regarding quantita-
tion in M-mode echocardiography: results of a survey
of echocardiographic measurements. Circulation 1978;58:
1072–93.
26 Bland JM, Altman DG. Statistical methods for assessing
agreement between two methods of clinical measurement.
27 Armittage P, Berry G. Linear regression. In: Statistical
methods in medical research, 2nd ed. Oxford: Blackwell,
28 Leggett ME, Unger TA, O’Sullivan CK, Zwik TR, Bennett
RL, Byers PH, et al. Aortic root complications in Marfan’s
syndrome: identification of a lower risk group. Heart 1996;
75:389–95.
29 Pietro DA, Voelkel AG, Ray BJ, Parisi MD. Reproducibility
of echocardiographic exam: a study evaluating the variabil-
ity of serial echocardiographic measurements. Chest 1981;79:
29–32.
30 Ichida F, Aubert A, Bene F, Dumoulin M, van der
Hauwaert LG. Cross sectional echocardiographic assess-
ment of great artery diameters in infants and children. Br