Exercise and sports participation in patients with thoracic aortic disease: a review


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Exercise and sports participation in patients with thoracic aortic disease: a review


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ABSTRACT

Introduction: Current guidelines recommend patients with thoracic aortic disease (TAD) including inherited aortopathies to avoid heavy exercise. However, evidence supporting the negative advice on exercise is scarce. We aimed to provide an up-to-date systematic review of the available evidence on risks and benefits of exercise and sports participation in TAD patients.

Areas covered: A systematic search was performed in Medline, Embase and Web of Science: thoracic aortic aneurysm or thoracic aortic dissection or inheritable aortopathies including Marfan Syndrome (MFS), Loeys-Dietz syndrome, Turner Syndrome, Ehlers-Danlos syndrome, bicuspid aortic valve (BAV) and sports, exercise or athletes. The resulting 1,652 manuscripts were reviewed by two independent observers. Eventually, 26 studies and 12 case-reports were included, reporting on thoracic aortic dimensions in athletes, exercise related acute aortic dissections, and exercise in BAV and MFS patients.

Expert opinion: Blood pressure elevation during exercise may be associated with an increased risk of acute aortic dissection; however, no controlled trials have longitudinally evaluated the effect of exercise on survival or the risk of aortic dissection in TAD patients. Mouse-model studies suggest beneficial effects of exercise in the setting of a dilated aorta in MFS. There is a clear need for prospective research in this field.

1. Introduction

The incidence of thoracic aortic disease (TAD) such as thoracic aortic aneurysms and dissections is estimated to be 9.1–16.3/100,000 per year [1]. However, thoracic aortic aneurysms are mostly asymptomatic and its prevalence is probably underestimated. About 20% of patients with thoracic aortic dilation have a positive family history of aortic disease [2], which can be an expression of an underlying disorder such as bicuspid aortic valve (BAV) or connective tissue disorders, such as Marfan Syndrome (MFS), Loeys-Dietz syndrome, Ehlers-Danlos syndrome, Turner Syndrome, and MFS patients. BAV patients are of particular interest because this condition is not uncommon with a prevalence of about 1% in the general population [3–5]. However, BAV patients seem to be at relatively low risk for aortic dissection [6]. On the contrary, Marfan Syndrome has a lower prevalence of 6.5/100,000, but these patients are at high risk of acute aortic dissection [7].

The hemodynamic changes associated with exercise, and specifically the increase in blood pressure, is potentially associated with an enhanced risk of aortic growth and acute aortic dissection in the context of a thoracic aortic disease (TAD). Current guidelines state that patients with TAD should avoid strenuous resistance or isometric exercise and competitive sports [8–10]. Due to the lack of data, however, these European, Canadian and American guidelines are characterized by low levels of evidence [8–10]. Recommendations for specific patient groups, such as patients with BAV, are in line with these guidelines. However, MFS patients are advised to only participate in low and moderate intensity sports with regular checks including echocardiography every 6 months, even if aortic root dilatation is absent [11–13].

The importance of daily exercise became clear in the 1950’s when an inverse relationship between physical activity and cardiovascular risk was discovered [14]. Ever since, it has become well understood that a sedentary lifestyle is an important modifiable risk factor for cardiovascular disease and mortality [15]. Furthermore, regular exercise is known to prevent and reduce hypertension [16]. For TAD patients it is even more important to not have a sedentary lifestyle, but also to prevent thoracic aortic growth and the occurrence of aortic dissection, creating a difficult paradox for clinicians. In this study, we sought to provide an up-to-date systematic review of the available evidence on exercise and sports participation in TAD patients including those with inherited aortopathies, and identify gaps in knowledge. We particularly aimed to find evidence on: (1) the aortic remodelling associated with regular exercise training and upper limits of dimensions in physically active individuals, (2) the risk of acute thoracic aortic dissection during exercise, and (3) the impact of exercise on the thoracic aorta in specific patient groups, especially in BAV and MFS patients.

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2. Methods

2.1. Literature search

A broad systematic search was performed in Medline, Embase and Web of Science on 2 August 2018. The following search terms (including synonyms) were used: exercise, sports, athletes, training and thoracic aortic aneurysm, thoracic aortic dissection. Additionally, search terms were included for various inheritable connective tissue disorders: Marfan syndrome, Loeys-Dietz syndrome (including aneurysm osteoarthritis syndrome e.g. SMAD3 mutation), Turner syndrome, Ehlers-Danlos syndrome and bicuspid aortic valve. The exact search details are shown in supplemental file 1. Additional publications were obtained by hand searching, and reference lists were cross-checked to identify possible relevant papers overlooked by the original search. Duplicates were identified and removed.

2.2. Study selection

Titles and abstracts were screened for eligibility by two independent researchers (CT and LB). Only articles in the English language were included. Solely original data was included, therefore reviews and meta-analysis were excluded. Furthermore, book chapters, double publications on the same subject and conference abstracts were excluded. Papers that could not be accessed in full text were also excluded. Only case reports on acute thoracic aortic dissection associated with exercise were included, while case reports on thoracic aortic dilatation and case reports on aortic dissections not related to exercise were excluded. Papers on thoracic aortic dilatation in athletes were included if aortic diameters were reported. Of all potentially eligible papers the full text was reviewed. In case of disagreement a third reviewer was asked for counsel (JR) and eligibility was assessed by reasoning.

3. Results

3.1. Search results

Figure 1 shows the flowchart of the study selection. Our search identified a total of 1652 unique publications. After reviewing the titles and abstracts 1530 papers were excluded, and 122 potentially eligible papers were reviewed in full text. Finally, 26 studies and 12 case reports were included. We grouped the selected papers based on the abovementioned subjects of interest. Sixteen studies were found on thoracic aortic diameters in athletes. Three studies and twelve case reports were identified on the occurrence of acute aortic dissections during exercise. Three studies reported on exercise in MFS and four evaluated exercise in patients with BAV. Unfortunately, no papers were identified addressing the association between exercise and thoracic aortic dilatation or risk of dissection in patients with Loeys-Dietz syndrome, aneurysm-osteoartithitis Syndrome (AOS e.g. SMAD3 mutation), vascular Ehlers-Danlos syndrome or Turner syndrome.

3.2. Thoracic aortic dimensions in athletes

We identified 16 papers published between 1981 and 2015 which evaluate aortic dimensions in athletes practicing a variety of sports disciplines, shown in Table 1. Almost all papers were cross-sectional cohort studies (15/16), and one was a longitudinal cohort study. The number of included patients differed greatly, ranging from 9 to 1929 participants. Eleven studies compared aortic diameters in athletes to a sedentary control group, shown in Figure 2 (17–27). Overall, outcomes of these studies show that athletes have significantly larger absolute aortic diameters than controls. However, the reported differences in absolute mean aortic root diameters are small: varying between 0.6 and 4 mm. Aortic diameter measurement was performed at the level of the aortic root in all studies, only two studies measured aortic diameter at multiple levels (23,28). One study reported aortic root diameters corrected for body surface area (BSA) and found no significant difference between athletes and controls, although the absolute aortic root diameters were significantly different between the groups [26]. Three papers only included female athletes [17,19,20], and five papers only included male athletes [18,21–24]. The 99th percentile of aortic root diameters in male athletes was found to be 40 mm and 34 mm for female athletes [29]. Five articles reported the prevalence of aortic root dilatation [27,29–32]. In these articles, different definitions of aortic dilatation were used, as shown in Table 1. The reported prevalence of aortic dilatation among athletes was low (0.26–1.3%), except in one cohort of athletes from the US national volleyball team, in which 6% of female athletes had an aortic root diameter ≥34 mm, and 8% of male athletes had an aortic root diameter ≥40 mm [32]. However, these volleyball players were very tall with an average body height of 198.2 ± 8.0 cm in males and 184.1 ± 7.4 cm in females.

Four studies evaluated differences in aortic diameter between strength trained and endurance trained athletes [21,27,28,31]. Three studies report a small but significant difference in absolute aortic root diameters, with slightly larger aortic root diameters in strength trained athletes than athletes who perform dynamic exercise. The mean differences reported ranged from 2.1–5 mm. However, mean aortic root measurements were all below 40 mm [27,28,31].

3.3. Exercise-related acute thoracic aortic dissections

Table 2 presents all case reports and case series reporting the occurrence of thoracic aortic dissections during exercise. The papers were published between 1987–2016 and each describe
1 to 31 cases of acute thoracic aortic dissection occurring during sports activities. A total of 49 patients were described, of whom 42 suffered Stanford type A thoracic aortic dissections and 7 patients had Stanford type B dissections. Remarkably, only 2 out of 49 patients (4%) were female. The age ranged from 12 to 76 years. However, many reports only included young patients, with half of the papers reporting on patients up to 20 years of age [33–38]. In the majority of cases (26/49) weightlifting was the type of sport associated with the occurrence of aortic dissection [34–37,39–41]. MFS was diagnosed after presentation in four patients and one patient was known to have a connective tissue disorder other than MFS, which was not specified. Notably, family history was not obtained or reported in 7 of the 12 papers [34,35,39,41–44].

Furthermore, three retrospective cohort studies on sports related acute aortic dissections type A (AD-A) were identified, shown in Table 3. Only one paper focussed on the different types of sports practised during AD-A [45]. This study described 650 patients with a mean age of 62.3 years in patients with sports-associated AD-A and 63.7 years in non-sports associated AD-A. Of all AD-A’s 4.1% was found to be associated with sports activities [45]. The type of sport most often reported was golf (32%), followed by swimming and cycling (each 16%), weight lifting (12%), and dancing (8%). Figure 3 illustrates the distribution of sports-related AD-A’s reported in this study over the different sports categories. These exercise related AD-A’s occurred in all age groups and there was no significant difference in sex distribution between sports related AD-A’s (60% males) and non-sports related AD-A’s (52% males) [45]. Two retrospective cohort studies were identified specifically studying the occurrence of AD-A during a specific exercise: sexual intercourse and alpine skiing [46,47]. The first reports exercise and sexual intercourse associated AD-A’s in a cohort of 365 patients and found a much higher percentage of 68% exercise associated AD-A’s, with no significant difference between males and females. In this study, evidence of MFS was present in only 0.9% of patients. AD-A associated with sexual intercourse occurred only in males (17/245) [46]. The other retrospective cohort study by Schachner et al [47] reported on AD-A’s occurring during winter season and they found that 22% of all AD-A’s were associated with alpine skiing, and the majority of these cases were unrelated to trauma (82%). There was no significant difference in sex distribution between skiing associated AD-A (88% males) and AD-A not associated with skiing (77% males).

### 3.4. Exercise in patients with BAV

We identified four papers reporting on the association between exercise and thoracic aortic diameters or thoracic aortic
<table>
<thead>
<tr>
<th>Ref. nr.</th>
<th>First author</th>
<th>Year</th>
<th>Journal</th>
<th>Study design</th>
<th>n (total)</th>
<th>Patient population</th>
<th>Control group</th>
<th>Outcome measures</th>
<th>Prevalence</th>
<th>Outcome</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>Rubal</td>
<td>1981</td>
<td>Medicine and Science in Sports and Exercise</td>
<td>Cross-sectional cohort study</td>
<td>9</td>
<td>Female softball athletes</td>
<td>100</td>
<td>10 age-and body size-matched sedentary controls</td>
<td>Left ventricular parameters, aortic root diameter at end-diastole</td>
<td>Not reported</td>
<td>Mean aortic root diameter in athletes was 22 mm ± 1 and 23 mm ± 1 in controls.</td>
</tr>
<tr>
<td>18</td>
<td>Wieling</td>
<td>1981</td>
<td>British Heart Journal</td>
<td>Longitudinal cohort study</td>
<td>23</td>
<td>Male oarsmen: seniors (n = 14) and freshmen (n = 9)</td>
<td>0</td>
<td>17 healthy age-matched controls</td>
<td>Right ventricular parameters, aortic root diameter</td>
<td>Not reported</td>
<td>At the beginning of the season aortic root diameter was 31.3 mm ± 1.5 in senior oarsmen, 28.8 mm ± 2.0 in freshmen, and 29.9 mm ± 2.8 in control subjects.</td>
</tr>
<tr>
<td>19</td>
<td>Crouse</td>
<td>1992</td>
<td>Research Quarterly for Exercise and Sport</td>
<td>Cross-sectional cohort study</td>
<td>15</td>
<td>Female basketball athletes</td>
<td>100</td>
<td>22 age-matched non-athletic controls</td>
<td>Left ventricular parameters and aortic root diameter</td>
<td>Not reported</td>
<td>Aortic root diameter was 25.7 mm ± 3.3 in athletes and 21.7 mm ± 2.4 in controls.</td>
</tr>
<tr>
<td>20</td>
<td>Pelliccia</td>
<td>1996</td>
<td>JAMA</td>
<td>Cross-sectional cohort study</td>
<td>600</td>
<td>Female athletes from Italian national teams</td>
<td>100</td>
<td>65 age-matched untrained females and 738 age, ethnicity, sports discipline and training intensity matched elite male athletes</td>
<td>Left ventricular parameters and aortic root diameter</td>
<td>Not reported</td>
<td>The aortic root was 27.6 mm ± 2.5 in athletes, 27.0 mm ± 1.8 in controls, and 30.3 mm ± 2.0 in male athletes.</td>
</tr>
<tr>
<td>21</td>
<td>Whyte</td>
<td>1999</td>
<td>International Journal of Sports Medicine</td>
<td>Cross-sectional cohort study</td>
<td>29</td>
<td>Elite modern pentathletes (n = 11) and triathletes (n = 18)</td>
<td>0</td>
<td>13 sedentary controls</td>
<td>Left ventricular parameters, aortic root diameter</td>
<td>Not reported</td>
<td>Aortic annulus diameter was 28.8 mm ± 5.1 in triathletes, 33.5 mm ± 2.1 in pentathletes and 31.1 mm ± 1.9 in controls.</td>
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<tr>
<td>30</td>
<td>Kinoshita</td>
<td>2000</td>
<td>American Heart Journal</td>
<td>Cross-sectional cohort study</td>
<td>1929</td>
<td>Athletes active in competitive sports</td>
<td>19</td>
<td>No control group</td>
<td>Aortic root diameter &gt;40 mm: 0.26%–0.36% and 0.96% in basketball and volleyball players</td>
<td>0.26%–0.36% of athletes had aortic root dilatation &gt;40 mm, 0.96% of basketball and volleyball players had aortic root dilatation &gt;40 mm.</td>
<td>A higher prevalence of aortic dilatation is to be anticipated among basketball and volleyball players, many of whom are very tall.</td>
</tr>
<tr>
<td>22</td>
<td>Dzudie</td>
<td>2006</td>
<td>European Journal of Echocardiography</td>
<td>Cross-sectional cohort study</td>
<td>21</td>
<td>Male handball players</td>
<td>0</td>
<td>21 age-, sex-, height- and weight-matched sedentary men</td>
<td>Left ventricular parameters and aortic root diameter</td>
<td>Not reported</td>
<td>Aortic root diameter was 29.6 mm ± 3.6 in control subjects and 30.3 mm ± 2.8 in handball players.</td>
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<tr>
<td>Ref. nr.</td>
<td>First author</td>
<td>Year</td>
<td>Journal</td>
<td>Study design</td>
<td>Study population</td>
<td>Outcome measures</td>
<td>Outcome</td>
<td>Prevalence</td>
<td>Conclusion</td>
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<td>23</td>
<td>Babaee Bigi</td>
<td>2007</td>
<td>American Journal of Cardiology</td>
<td>Cross-sectional cohort study</td>
<td>100 Male elite athletes</td>
<td>Aortic diameter, aortic regurgitation</td>
<td>Results</td>
<td>Not reported</td>
<td>Aortic diameters were measured at Ann 25.1 ± 2.9 in athletes and 21.8 ± 2.4 in controls, SoV 38.2 ± 4.1 in athletes and 31.6 ± 3.2 in controls, STJ 34.1 ± 2.8 and 29.5 ± 3.1 in controls, AA 36.1 ± 4.5 in athletes and 31.0 ± 2.9 in controls.</td>
<td>Aortic root diameters in all segments of the aortic root were significantly greater in elite strength-trained athletes compared with an age- and height-matched population.</td>
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<tr>
<td>29</td>
<td>Pelliccia</td>
<td>2010</td>
<td>Circulation</td>
<td>Cross-sectional cohort study</td>
<td>2317 Highly trained athletes</td>
<td>Aortic diameter</td>
<td>Results</td>
<td>Mean aortic root diameter was 32.2 mm ± 2.7 in male athletes with 99th percentile 40 mm, and 27.6 mm ± 2.6 in female athletes with 99th percentile 34 mm.</td>
<td>Aortic root enlargement (40 mm in males and 34 mm in females) is particularly uncommon in highly trained athletes.</td>
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<tr>
<td>31</td>
<td>D’Andrea</td>
<td>2010</td>
<td>American Journal of Cardiology</td>
<td>Cross-sectional cohort study</td>
<td>615 Elite athletes: endurance-trained athletes (n = 370) and strength-trained athletes (n = 245)</td>
<td>Aortic diameter</td>
<td>Results</td>
<td>The mean aortic root diameter at the SoV was 31 mm (2.8–3.6) in endurance trained athletes and 36 mm (3.2–4.2) in strength trained athletes.</td>
<td>The aortic root diameters at all levels were significantly greater in strength trained athletes. Significant ascending aortic dilatation and aortic regurgitation proved to be uncommon in strength trained athletes.</td>
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<tr>
<td>24</td>
<td>Carlsson</td>
<td>2010</td>
<td>European Journal of applied physiology</td>
<td>Cross-sectional cohort study</td>
<td>10 Male endurance athletes</td>
<td>Cardiac functional parameters, cardiac structural parameters (among which aortic root diameter)</td>
<td>Results</td>
<td>Not reported</td>
<td>Aortic root diameter was 30.4 mm ± 3.2 in athletes and 28.4 mm ± 4.4 in controls.</td>
<td>Aortic root diameter was not significantly larger in athletes than in controls.</td>
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<td>25</td>
<td>Caselli</td>
<td>2011</td>
<td>European Journal of Echocardiography</td>
<td>Cross-sectional cohort study</td>
<td>429 Athletes from Italian national teams</td>
<td>Left ventricular parameters and aortic root diameter</td>
<td>Results</td>
<td>Not reported</td>
<td>Aortic root diameter was 31.0 mm ± 3.6 in athletes and 28.7 mm ± 3.3 in controls.</td>
<td>Aortic root diameter was significantly larger in athletes than in controls.</td>
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<tr>
<td>26</td>
<td>Krol</td>
<td>2011</td>
<td>Echocardiography</td>
<td>Cross-sectional cohort study</td>
<td>38 Members of the Polish Olympic team (rowing, cycling, speed-skating)</td>
<td>Left ventricular parameters, right ventricular parameters, aortic diameter (level of measurement not specified)</td>
<td>Results</td>
<td>Not reported</td>
<td>Aortic diameters were 33 mm ± 4 in elite athletes and 29 mm ± 2 in controls. After indexing for BSA the mean aortic size index for athletes was 1.6 cm/m² ± 0.1 and 1.5 cm/m² ± 0.2 for controls.</td>
<td>Aortic diameters were significantly larger in elite athletes group than in controls. However after indexing for BSA there was no significant difference between the groups.</td>
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<tr>
<td>Ref. nr.</td>
<td>First author</td>
<td>Year</td>
<td>Journal</td>
<td>Study design</td>
<td>n (total)</td>
<td>Patient population</td>
<td>Sex (% female)</td>
<td>Control group</td>
<td>Outcome measures</td>
<td>Prevalence of aortic dilation</td>
<td>Results</td>
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<tr>
<td>27</td>
<td>D’Andrea</td>
<td>2012</td>
<td>Journal of the American Society of Echocardiography</td>
<td>Cross-sectional cohort study</td>
<td>410</td>
<td>Elite athletes: endurance-trained athletes (n = 220) and strength-trained athletes (n = 190)</td>
<td>38</td>
<td>240 healthy controls</td>
<td>Aortic root diameter, aortic root distensibility and elasticity</td>
<td>Aortic root diameter was 36 mm ± 5 in strength trained, 31 mm ± 6 in endurance trained athletes and 32 mm ± 3 in controls.</td>
<td>Aortic root diameters and stiffness were significantly greater in strength trained athletes than in endurance trained athletes and controls. While aortic distensibility was higher in endurance trained athletes compared to controls.</td>
</tr>
<tr>
<td>28</td>
<td>Aparci</td>
<td>2013</td>
<td>Experimental &amp; Clinical Cardiology</td>
<td>Cross-sectional cohort study</td>
<td>60</td>
<td>Personnel Etimesgut Military Hospital: strenuous activity trainers (n = 30) and ordinary activity trainers (n = 30)</td>
<td>Unknown</td>
<td>No control group</td>
<td>Aortic diameters, left ventricular parameters, left atrial diameters</td>
<td>Subjects with abnormally enlarged aortic diameter (≥40 mm) were excluded</td>
<td>In the strenuous activity training group mean aortic diameters were: 35.6 mm (Sv) and 36.8 mm (AA), in the ordinary activity training group the mean aortic diameter was 33.5 mm (Sv) and 34.4 mm (AA).</td>
</tr>
<tr>
<td>32</td>
<td>Davis</td>
<td>2015</td>
<td>Clinical Journal of Sport Medicine</td>
<td>Cross-sectional cohort study</td>
<td>70</td>
<td>Athletes from the US national volleyball team</td>
<td>47</td>
<td>No control group</td>
<td>Aortic diameter and Ghent criteria (signs of Marfan syndrome)</td>
<td>Aortic root diameter ≥40 mm: 8% of male athletes. Aortic root diameter ≥34 mm: 6% of female athletes</td>
<td>34% of the athletes had at least 1 characteristic of MFS (Ghent criteria) but none had more than 2 characteristics.</td>
</tr>
</tbody>
</table>

Ann: Aortic Annulus, SoV: Sinus of Valsalva, STJ: Sinotubular Junction, AA: Ascending Aorta
dilatation rate in BAV patients, which are shown in Table 4. Of these, three papers came from the same research group [48–50]. Two of which compared athletes with BAV to athletes with a normal tricuspid aortic valve (TAV) [48,49]. Both reported significantly larger aortic diameters at all measured levels in BAV athletes compared to TAV athletes. However, all reported mean diameters were below 36 mm. One cross-sectional study, which included 58 competitive athletes with BAV, showed no correlation between aortic dimensions and duration of training [48]. Two longitudinal studies presented by the same research group reported on mean aortic diameter growth rate in BAV athletes, presumably describing the same patients. The mean growth rates reported were: 0.78 mm/year at the aortic annulus (Ann), 0.61 mm/year at the Sinuses of Valsalva (SoV), 0.81 mm/year at the sinotubular junction (STJ) and 0.98 mm/year at the proximal ascending aorta (AA) [49,50]. The mean age of these two cohorts of BAV athletes were 19 ± 8.8 years and 25 ± 11 years. No significant increase of aortic diameter was reported in TAV athletes (mean age 25 ± 5 years) after five years of follow-up. Another longitudinal study by Spataro et al. found no clear association between sports participation and valve deterioration in BAV patients, with a mean follow-up duration 13 years [51]. Unfortunately, no aortic diameter measurements were reported and no conclusions can be drawn about the effect of exercise on the aortic diameter in this cohort of BAV athletes. Only one paper compared BAV athletes to sedentary BAV subjects. This article reported no difference in aortic growth rate between the two groups at all measured levels of the thoracic aorta: Ann, SoV, STJ and AA [50].

3.5. Exercise in marfan syndrome

Table 4 presents the three papers on exercise in MFS, all published in 2017. Two papers describe mouse model studies investigating the effects of mild-moderate dynamic exercise on the aortic wall in MFS mice [52,53]. Both were controlled trials with one or more dynamic exercise training groups and a sedentary group. The follow-up duration of both studies was five months. Both papers reported a reduction of aortic diameter growth rate in MFS mice. This was testified by the larger amount of mechanical stress on the aorta required to induce rupture of the aortic wall [52]. Exercise seemed to improve aortic wall elasticity in one study [52], but no significant improvement was found in the other [53]. Dynamic exercise was not found to increase lamina ruptures, indicating no additional structural damage in the tunica media [53]. An optimum of protective effects was found at a training intensity level of 55–65% of maximum oxygen uptake (VO2max), while higher intensity of dynamic exercise training seems to blunt the positive effects [52]. The third paper is a small prospective cohort study that evaluated the feasibility and effects of a three-week rehabilitation program in 19 MFS patients with a mean age of 46.7 ± 7.8 years [54]. During the one-year follow-up, no adverse medical events were reported, physical fitness improved, and psychological distress decreased. These effects were already present after three weeks of rehabilitation, and mostly remained persistent throughout the one-year follow-up [54]. Unfortunately, no information on aortic diameters was provided.

4. Discussion

To our knowledge, this is the first systematic review describing the effect of exercise and sports participation in TAD patients. We were not able to identify any controlled or randomized trials evaluating the longitudinal effect of exercise on survival or risk of aortic dissection in TAD patients. When focusing on the association between exercise and thoracic aortic growth rate very limited data can be found. In total, we identified 38 papers of interest, of which 9 were case reports, 3 case series, 8 longitudinal cohort studies and 16 cross-sectional cohort studies. Two were mouse-model studies: one non-randomized controlled trial and one randomized controlled trial. Assessment of methodological quality of the included papers was planned, but ultimately not performed quantitatively, since the large variety of study designs made consistent and comparable quality assessment impossible and meaningless. Eventually it can be concluded that most papers would reach low scores.

4.1. Are aortic dimensions different in athletes?

Screening before participating in competitive sports provides a lot of easily accessible data resulting in a large number of
| Ref. nr. | First author | Year | Journal | Study design | n (total) | Age years | Sex | Stanford Classification | Max. aortic diameter | Type of sport | Aortopathy | Family history | Conclusion |
|---------|--------------|------|---------|-------------|-----------|-----------|-----|------------------------|---------------------|--------------|------------|-------------|--------------|------------|
| 33      | Bain         | 1987 | The American Journal of Forensic Medicine and Pathology | Case report | 1 20 | M | Type A | 60 mm | Fitness | Marfan Syndrome | Positive for sudden death | This case demonstrates Marfan Syndrome presenting as sudden, unexpected death. |
| 39      | De Virgilio  | 1990 | The Annals of Thoracic Surgery | Case series | 4 22-57 | M | Type A | Unknown | Weightlifting | Not suspected | Unknown | Individuals who have evidence of cystic medial disease or family histories of this disease should avoid weight lifting. Weight lifting, with its profound cardiovascular effects, may be the major, if not sole cause of aortic dissection. |
| 34      | Schor        | 1993 | Journal of Vascular Surgery | Case report | 1 18 | M | Type B (periaortic hematoma) | Unknown | Weightlifting | Not suspected | Unknown | Individuals with Marfan Syndrome, cystic medial disease or family histories of the disorder should be strongly urged to refrain from weight-lifting activities. |
| 35      | Baumgartner  | 1997 | The Annals of Thoracic Surgery | Case report | 1 19 | M | Type A | Unknown | Weightlifting | Marfan Syndrome | Unknown | |
| 36      | Elefteriades | 2003 | Journal of the American Medical Association | Case series | 5 19-53 | Unknown | Type A | 40-52 mm | Weightlifting, push-ups, heavy lifting | Not suspected | Positive for aortic disease in 1 patient | The risk of weight lifting as a cause of aortic dissection has generally been underappreciated. Aortic dissection should be considered in symptomatic patients with a family history of early cardiac deaths, suspect of a connective tissue disorder, or who practice weightlifting. Increased blood pressure due to heavy weight lifting places aortic wall stress to a level that produces aortic dissection in individuals with pre-existing mild to moderate aortic enlargement. |
| 37      | Hatzaras     | 2007 | Cardiology | Case series | 31 19-76 | 30 M, 1 F | | | | | | |
| 38      | Uchida       | 2009 | Interactive CardioVascular and Thoracic Surgery | Case report | 1 12 | M | Type B | Unknown | Swimming | Not suspected | Negative | Swimming coaches and pediatricians should recognize that swimming exercises like the butterfly stroke are a risk factor for aortic dissection in children. |
| 42      | Westaby      | 2011 | Circulation | Case report | 1 28 | M | Type B | Unknown | Soccer | Bicuspid aortic valve, aortic coarctation | Unknown | Aortopathy associated with a bicuspid aortic valve and coarctation may contribute to aneurysmal transformation and rupture. Early diagnosis of Marfan Syndrome is crucial as it has a positive influence on the outcome. |
| 43      | Chattanukulchaiskun | 2013 | British Medical Journal Case Reports | Case report | 1 38 | M | Type A | 52 mm | Bowling | Marfan Syndrome | Unknown | Early diagnosis of Marfan Syndrome is crucial as it has a positive influence on the outcome. |
| 41      | Ozyildirim    | 2015 | The American Journal of Cardiology | Case report | 1 28 | M | Type A | Unknown | Weightlifting | Unknown | Unknown | Weight lifting creates significant stress along the aortic wall and this produces predisposition to acute aortic dissection. |
| 44      | Geeda        | 2016 | European Heart Journal | Case report | 1 25 | F | Type A | 100 mm | Volleyball | Marfan Syndrome | Unknown | Echocardiography has a potential role in preventing tragic sudden death in sport. |
The sport most frequently associated with type A dissections in this series was golf (n = 8; 32%), followed by swimming and cycling (each n = 4; 16%), then... (n = 3; 12%), dance (n = 2; 8%), and finally, long-distance running, fencing, table tennis, and archery (each n = 1; 4%).

Onset of symptoms during a sports activity. Non-sports exertion, such as lifting or moving a heavy load, defecation, or sexual activity, were classified into the non-sports group.

Onset of symptoms during recreational skiing without additional trauma. Only 1 patient (6%) had a skiing accident with consequent ascending aortic dissection.

Type A aortic dissections related to exercise: Itagaki et al. [45] reported a relation to exercise in 4.1% of all AD-A. We found a striking difference in the reported amount of acute thoracic aortic dissections related to exercise: Itagaki et al. [45] reported a relation to exercise in 4.1% of all AD-A. Thus, there has been much controversy about the link between exercise and acute thoracic aortic dissections. This has made clinicians cautious when counseling AD patients about exercise. We found a striking difference in the reported amount of acute thoracic aortic dissections related to exercise: Itagaki et al. [45].

It is caused by acute aortic dissections [46, 60]. Over the past decades, there has been a marked increase in the number of athletes reported in relation to exercise in 4.1% of all AD-A. The difference in aortic root diameter between athletes and controls was blunted [26]. This difference was caused by a pathological process, but presumably results from higher cardiac output and difference in body size between athletes and controls, which is known to be more pronounced in athletes than in non-athletic controls [55]. One study showed that after indexing aortic root diameter for BSA, the significant difference in aortic root diameter between athletes and controls was blunted [26]. Indicating the differences in aortic root diameter between athletes and controls is not necessarily applicable to less intensely trained and older individuals, and patients who already have TAD.

4.2. Is there an association between exercise and acute thoracic aortic dissections?

The incidence of sudden cardiac death among the young population (< 40 years) is approximately 1.3 to 8.5 per 100,000 person-years [57]. Approximately 1.5% of sudden death in young athletes is caused by acute aortic dissections [58, 60]. The larger aortic diameter in athletes compared to non-athletic controls is consistent with the finding of a larger recent meta-analysis [56]. One study showed that after indexing aortic root diameter for BSA, the significant difference in aortic root diameter between athletes and controls was blunted [26]. Indicating the differences in aortic root diameter between athletes and controls is not necessarily applicable to less intensely trained and older individuals, and patients who already have TAD.

The true amount of sports-related type A aortic dissections might be somewhere in between, such as the 22% of all winter season AD-A reported in-hospital mortality of up to 33% [45]. It is caused by acute aortic dissections [46, 60]. The difference in aortic root diameter between athletes and controls was blunted [26]. This difference was caused by a pathological process, but presumably results from higher cardiac output and difference in body size between athletes and controls, which is known to be more pronounced in athletes than in non-athletic controls [55]. One study showed that after indexing aortic root diameter for BSA, the significant difference in aortic root diameter between athletes and controls was blunted [26]. Indicating the differences in aortic root diameter between athletes and controls is not necessarily applicable to less intensely trained and older individuals, and patients who already have TAD.
population is crucial here. When a study includes all patients with dissection, the mean age will be relatively high, and golf will be a sport which is prevalently practised. In younger cohorts, a totally different sports involvement pattern is likely to be found. Furthermore, this study was conducted in Japan where golf is known to be a very popular form of exercise. Therefore, in the absence of reliable information on rates of sports participation, no conclusion can be drawn on the association between dissection and a specific sports activity. Concerning the impact of sex, it was striking that almost all case reports describe males with acute aortic dissections related to exercise. However, this does not seem representative since the larger series both from Itagaki and Gansera reported no significant differences in sex distribution [45, 46]. Population based studies might provide additional information, but data on the prevalence of participation in different types of sports, aortic diameters and long-term follow-up are scarce.

4.3. How does exercise influence the thoracic aorta in BAV and Marfan patients?

Although bicuspid aortic valve is the most prevalent congenital heart disease and an important underlying etiology of thoracic aortic dilatation, the association between exercise and aortic diameter and growth rate has been investigated to a limited extent in this patient group. In BAV patients, Galanti et al. and Stefani et al. state that the aortic growth rate they reported in BAV athletes does not differ from aortic growth rate reported in the general BAV population [49, 50]. Indeed, the reported dilatation rate of 0.98 mm/year found in the athletes with BAV seems comparable to the reported aortic dilatation rate in various studies reporting aortic growth rate in the general BAV population [62, 63]. Even though the BAV populations studied by Stefani et al and Galanti et al were relatively young (19 ± 8.8 years and 25 ± 11 years), and younger age is known to be associated with higher aortic growth rates [64]. These findings suggest that aortic growth rate is not significantly influenced by exercise in BAV patients.

Two recently published papers have investigated the effect of dynamic exercise on the thoracic aorta in mice with MFS. Both studies reported mild to moderate dynamic exercise had a positive effect on aortic growth rate and seemed to improve aortic wall structure. This suggests that exercise does not only have potential negative effects on the thoracic aorta in TAD patients, but might be actually beneficial [52, 53]. Further research is needed to evaluate these potential positive effects of exercise on the thoracic aorta in MFS patients and patients with other thoracic aortic diseases. Especially, since mouse model studies on the aorta might not always be reliable [65]. One randomized trial has been performed in patients with an abdominal aortic aneurysm (AAA) in 2014 [66]. In this trial 140 patients with AAA
Table 4. Papers on exercise in patients with Marfan Syndrome and bicuspid aortic valve.

<table>
<thead>
<tr>
<th>Ref. nr.</th>
<th>Group</th>
<th>First author</th>
<th>Year</th>
<th>Journal</th>
<th>Study design</th>
<th>n (total)</th>
<th>Patient population</th>
<th>Genetic mutation</th>
<th>Sex (% female)</th>
<th>Control group</th>
<th>Outcome measures</th>
<th>Follow-up</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>BAV</td>
<td>Spataro</td>
<td>2008</td>
<td>International Journal of Sports Medicine</td>
<td>Longitudinal cohort study</td>
<td>81</td>
<td>Competitive athletes with BAV from Italian national teams divided into 2 groups: the low-risk group (n = 51) and the high-risk group (n = 30)</td>
<td>NA</td>
<td>10</td>
<td>No control group</td>
<td>Aortic regurgitation, aortic stenosis and left ventricular parameters, aortic root diameters.</td>
<td>13 ± 4.9 years (range 5–19 years)</td>
<td>Over the follow-up period, six of the initially low-risk athletes (7%) and all of the high-risk patients showed significant worsening of morphologic features of bicuspid aortic valve and/or incidence of symptoms. In high-risk subjects the progression of valvular disease occurred independently from the former athletic activity. Continued sport participation is not responsible itself of BAV worsening. However, long-term athletic training may be associated with progressive worsening of the valvular lesion and the appearance of clinical symptoms. A short echocardiographic examination should be performed at least once during an athlete’s sporting life.</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>BAV</td>
<td>Stefani</td>
<td>2008</td>
<td>British Journal of Sports Medicine</td>
<td>Cross-sectional cohort study</td>
<td>58</td>
<td>Non-elite but competitive athletes with BAV</td>
<td>NA</td>
<td>0</td>
<td>75 non-elite but competitive athletes with TAV</td>
<td>Aortic regurgitation, aortic stenosis and aortic root diameters.</td>
<td>NA</td>
<td>Aortic root dimensions at all levels were significantly greater in athletes with BAV than in athletes with a normal TAV. No relation was found with age, body surface area, aortic regurgitation or years of training. A short echocardiographic examination should be performed at least once during an athlete’s sporting life.</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>BAV</td>
<td>Galanti</td>
<td>2010</td>
<td>British Journal of Sports Medicine</td>
<td>Longitudinal cohort study</td>
<td>88</td>
<td>Athletes with BAV and mild aortic regurgitation</td>
<td>NA</td>
<td>Unknown</td>
<td>56 athletes with TAV</td>
<td>Left ventricle parameters and aortic diameters</td>
<td>5 years (30/88 subjects)</td>
<td>There was a progressive increase at each measured aortic level (Ann: 0.78 mm/year; SoV: 0.81 mm/year; STJ: 0.83 mm/year; AA: 0.98 mm/year). The increase became significant from the last 2 years of the 5-year follow up. A short echocardiographic examination should be performed at least once during an athlete’s sporting life.</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>BAV</td>
<td>Stefani</td>
<td>2014</td>
<td>Cardiology Research and Practice</td>
<td>Longitudinal cohort study</td>
<td>292</td>
<td>Subjects with BAV who were evaluated at the Sports Medicine and Exercise Centre, divided into three different groups: athletes (n = 210), sedentary (n = 59), and ex-athletes (n = 23)</td>
<td>NA</td>
<td>Unknown</td>
<td>No control group</td>
<td>BAV morphology classification, left ventricular parameters and aortic diameters</td>
<td>5 years</td>
<td>Typical BAV morphology was most frequent in all three groups (68% athletes, 67% sedentaries, and 63% ex-athletes). The aortic dimensions showed a progressive enlargement during follow-up, with no difference between athletes and sedentary subjects. There was a progressive increase at each measured aortic level (Ann: 0.78 mm/year; SoV: 0.61 mm/year; STJ: 0.81 mm/year; AA: 0.98 mm/year).</td>
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<thead>
<tr>
<th>Ref. nr.</th>
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<th>Journal</th>
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<th>n (total)</th>
<th>Patient population</th>
<th>Genetic mutation</th>
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<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>54</td>
<td>MFS</td>
<td>Benninghoven</td>
<td>2017</td>
<td>Orphanet Journal of Rare Diseases</td>
<td>Longitudinal cohort study</td>
<td>19</td>
<td>Patients with MFS or similar syndrome in stable condition</td>
<td>Not specified</td>
<td>71</td>
<td>No control group</td>
<td>Adverse events, physical fitness and psychological assessment</td>
<td>1 year</td>
<td>No adverse medical events were reported. Physical fitness improved from admission to discharge. Psychological distress decreased. Admission to discharge effects mostly persisted through the one year follow-up but declined to smaller sizes.</td>
<td>The three week rehabilitation program improved physical fitness and psychological wellbeing. Medical assessments ruled out medical problems or adverse events caused by participation in the program.</td>
</tr>
<tr>
<td>52</td>
<td>MFS</td>
<td>Gibson*</td>
<td>2017</td>
<td>Journal of Applied Physiology</td>
<td>Non-randomised controlled trial (mouse-model study)</td>
<td>16</td>
<td>Male mice with MFS divided in a sedentary group (n = 10), voluntary exercise group (n = 3) and forced exercise group (n = 3)</td>
<td>Fbn1C1039G/+</td>
<td>0</td>
<td>19 mice without MFS, divided in a sedentary group (n = 4), voluntary exercise group (n = 7) and forced exercise group (n = 8)</td>
<td>Histological characteristics, isometric force, aortic wall elasticity and stiffness and combined benefit score for: elastin fiber length, elastin fragmentation, and elasticity</td>
<td>5 months</td>
<td>Both voluntary and forced exercise routines reduced aortic diameter, prevented aortic wall weakening, increased the breaking stress and improved aortic wall elasticity in MFS mice. There is an optimum of protective effects at training intensity levels between 55% and 65% (of VO2max) which significantly reduces elastin fragmentation and disorganization within the aortic wall.</td>
<td>The present study provides helpful insights into the potential protective effects of a mild exercise routine in MFS patients in the absence of pharmacological interventions.</td>
</tr>
<tr>
<td>53</td>
<td>MFS</td>
<td>Mas-Stachurska*</td>
<td>2017</td>
<td>Journal of the American Heart Association</td>
<td>Randomized controlled trial (mouse-model study)</td>
<td>19</td>
<td>Mice with MFS, randomized to a sedentary group n = 9 and exercise group n = 10</td>
<td>Fbn1C1039G/+</td>
<td>47</td>
<td>21 mice without MFS, randomized to a sedentary group n = 11 and exercise group n = 10</td>
<td>Left ventricular parameters, aortic root diameter, aortic pulsatility, aortic stiffness and histological characteristics of aortic wall tissue</td>
<td>5 months</td>
<td>In MFS mice subjected to exercise aortic root diameter was smaller than in their sedentary littermates and aortic dilatation rate was blunted, becoming comparable to the controls. Exercise training improved aortic stiffness in controls but not in MFS mice, but did not increase lamina ruptures in MFS mice, indicating no additional structural damage in the tunica media.</td>
<td>Moderate dynamic exercise prevented aortic root dilation and mitigates cardiac hypertrophy.</td>
</tr>
</tbody>
</table>

* Mouse-model study
MFS; Marfan Syndrome, BAV; Bicuspid Aortic Valve, TAV; Tricuspid Aortic Valve, Ann; Aortic Annulus, SoV; Sinus of Valsalva, STJ; Sino-tubular Junction, AA; Ascending Aorta
were randomized to either standard care or exercise training including dynamic as well as isometric exercise (rowing). No difference in abdominal aortic growth rate was reported between the groups. Although AAA has a different aetiology than thoracic aortic aneurysms and should therefore be seen as a different disease entity, the findings of this study are promising. A randomized study, such as the one illustrated above for AAA patients, would provide important additional information about the effect of exercise in TAD patients.

5. Conclusion

Although several case reports have described aortic dissection occurring during exercise, no high-quality studies have been performed to illuminate the association between exercise and acute aortic dissection. In athletes, aortic diameters are only slightly larger than in controls. Evenly, aortic diameter growth rate does not seem to be enhanced by exercise in BAV patients. In mice with MFS a positive effect of mild to moderate dynamic exercise on the thoracic aorta diameter was

![Figure 4. Hemodynamic response to exercise. (a) Response to dynamic exercise of progressively increasing workload. This causes a volume overload as a result of increased cardiac output (Q) and arterial blood pressure (ABP), with a decrease in total peripheral resistance (TPR). (b) Response to a static handgrip contraction. This causes a pressure overload as a result of increased blood pressure, but no decrease in total peripheral resistance. ABP (mm Hg): systolic, mean and diastolic arterial blood pressures; HR: heart rate (beats/min); Q: cardiac output (liters/min); SV: stroke volume (ml/beat); TPR: total peripheral resistance (PRU); VO2: oxygen uptake (ml/min/kg). Reprinted by permission from J.H. Mitchell and P.B. Raven, ‘Cardiovascular Adaptation to Physical Activity,’ in Physical Activity, Fitness, and Health: International Proceedings and Consensus Statement, edited by C. Bouchard, R.J. Shephard, and T. Stephens (Champaign, IL: Human Kinetics, 1994), 288.]

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**Panel A — Dynamic**

- VO2 (ml/min/kg)
- Q (l/min)
- HR (bpm)
- SV (ml/beat)
- ABP (mm Hg)
- TPR (PRU)

**Panel B — Static**

- VO2 (ml/min/kg)
- Q (l/min)
- HR (bpm)
- SV (ml/beat)
- ABP (mm Hg)
- TPR (PRU)

![Graphs showing hemodynamic response to exercise.](image-url)
found. There clearly is a gap in knowledge about the effects of exercise and sports participation in TAD patients. Currently there is no unequivocal evidence to support discouragement of exercise and sports participation in TAD patients. Hence, mild to moderate regular exercise should be encouraged, for its known positive effects on overall health. However, based on theoretical knowledge, participation in heavy static exercise should likely be avoided in TAD patients.

6. Expert opinion

When a patient is diagnosed with TAD, discussing lifestyle modification is mandatory. Next to cessation of smoking, controlling hypertension and prevention of obesity, discussing exercise and sports participation is important. However, there is not enough evidence to strongly discourage exercise or recommend any particular type of exercise or sport. Theoretically, high blood pressure is unfavourable. Therefore, it is important to distinguish between dynamic (also isotonic) and static (also isometric) exercise [61], since both initiate a different hemodynamic response (illustrated in Figure 4). On the other hand exercise and sports participation are also known to have many positive effects on cardiovascular and overall health. For the general population the Dutch and American health councils, as well as the World Health Organization recommend a target rate of 150 to 300 minutes per week of moderate to heavy intensity exercise [67–69], as participation in regular physical activity has shown to have many benefits [67,68].

Therefore, we believe it is mandatory to explain both the negative and positive effects of exercise to TAD patients. In order to create full understanding and ideally reach a shared decision, rather than imposing restrictions on sports participation. In order to prevent TAD patients becoming scared of physical activities and to minimize concerns, stress and anxiety further affecting TAD patient’s quality of life, which was shown to be reduced compared to healthy controls [70].

Ideally future research would be (randomized) controlled trials longitudinally evaluating the effect of exercise on thoracic aortic aneurysm dilatation rate, the risk of thoracic aortic dissections, quality of life and survival of TAD patients. Secondly, the effect of different types and intensities of exercise on thoracic aortic growth rate acceleration needs to be evaluated. More research is especially needed in patients with Loeys-Dietz syndrome, aneurysm-osteoarthropathy Syndrome (AOS e.g. SMAD3 mutation), vascular Ehlers-Danlos syndrome and Turner syndrome, on which we found no evidence at all.

7. Five-year view

In the upcoming five years we envision that more research will be carried out on the association between exercise and thoracic aortic growth and acute aortic dissection. Further exploring the potential beneficial effect of dynamic exercise on the aortic wall in humans is warranted. This knowledge will enable us to better understand and predict the risks of exercise and sports participation in TAD patients. This will hopefully enforce better counseling, with more detailed and well-founded advice to TAD patients.

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Declaration of interest

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References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.


This study reports no difference in aortic root diameter between athletes and controls after correction for Body Surface Area.


This study reports the amount of sports-related AD-A and focussed on the different types of sports practised during AD-A.


This study reports aortic diameter growth rates in athletes with bicuspid and tricuspid aortic valve.


This study reports a positive effect of mild-moderate dynamic exercise in mice with MFS.


