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Aerobic capacity in adolescence is associated with time to intervention in adult men with atrial septal defects

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ABSTRACT

Background: Atrial septal defect (ASD) is a congenital heart lesion that often remains undiagnosed until adulthood. The reasons for this may be multifactorial. It is, however, known that closure of a hemodynamically significant ASD improves exercise capacity. This study aimed to explore whether the aerobic capacity in late adolescence is associated with time to diagnosis and intervention in adult men with late diagnosis of an atrial shunt.
Methods: The Swedish Military Conscription Service Register contains data on exercise tests performed in late adolescence. By linking these data with the National Patient Register, 254 men with a later intervention for an ASD were identified.
Results: Interventions were performed at a mean of 26.5 ± 7.9 years after the initial exercise tests. The mean absolute workload among those with a later diagnosed ASD was similar to those without a later diagnosed ASD (274 ± 51 W vs. 276 ± 52 W, $p = 0.49$). Men with a higher exercise capacity (≥1 SD) had their intervention earlier (21.9 ± 8.6 years vs. 27.5 ± 7.4 years, $p < 0.001$).
Conclusions: The aerobic exercise capacity was similar in adolescent men with later interventions for ASD compared to the reference population. Furthermore, those with high exercise capacity appeared to be diagnosed earlier. Thus, low exercise capacity may not be a feature of ASD during adolescence, but rather develop later in life as a natural progression of the disease.

1. Introduction

Most patients with congenital heart disease are diagnosed and have their first intervention in childhood. Some remain undiagnosed until adult age, and among these atrial septal defects (ASDs) and coarctation of the aorta are the most common diagnoses with predominance of the ASDs.

The majority of patients with ASDs are diagnosed in childhood [1]. In adults, ASDs may be asymptomatic for decades and diagnosis is usually triggered either by symptoms or as a coincidental finding of a murmur during routine physical examination [1]. Furthermore, in native ASDs, exercise capacity is commonly reduced [2] up to 35–39% [3,4] even in those regarded as asymptomatic [5–7]. Post intervention, peak oxygen uptake improves in most patients [6,7]. Therefore, it is reasonable to assume that adults with "late" diagnosis of ASDs have reduced exercise capacity but have adapted over the years and thus remain asymptomatic. Data on exercise capacity many years prior to ASD intervention in adults are scarce, most probably related to the difficulties to perform such studies. In this context, it is important to note that most adults with an ASD had their intervention within 3 years after diagnosis [1].

In the present study, we used the Swedish Military Conscription Service Register (MCSR) that contains data on standardized exercise tests performed in nearly 1.5 million men, and identified those with a later intervention of ASD via the National Patient Register (NPR). Our hypothesis was that their exercise capacity was reduced already in late adolescence. The main purpose of the study was to establish the exercise capacity in late adolescence in those requiring ASD closure later in life.

2. Methods

2.1. Databases

This study was based on data from the MCSR and the Swedish National Patient Register (NPR). The study was approved by the regional ethics review board (Dnr 2010–113-31).

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2.2. The Military Conscription Service Register

The MCSR comprises data for males who participated in Swedish military conscription at the age of 18 years during 1969 to 1996 (n = 1,426,579). Two to 3% of all men were excluded from conscription due to severe medical illness or incarceration. During conscription, participants were examined using a battery of standardized tests including anthropometric measurements (height and body weight), blood pressure, aerobic fitness and isometric muscle strength for grip, elbow flexion and knee extension. Further details regarding the MCSR tests have been published previously [8].

In the present study, unrealistic test values were considered incorrect data entry and classed as missing data; i.e. height < 100 and > 220 cm, body weight < 30 and > 250 kg, systolic blood pressure < 70 and > 250 mm Hg, diastolic blood pressure < 20 and > 115 mm Hg, peak work load (Wmax) at exercise test <1 and >600 W, and isometric muscle strength for grip, elbow flexion and knee extension = 0 N.

2.3. The Swedish National Patient Register

The NPR, administered by the Swedish National Board of Health and Welfare, contains information on inpatient and outpatient care in Sweden [9]. Diagnoses are reported by physicians and coded according to the International Classification of Disease (ICD) codes, with the 10th edition (ICD-10) [10] used from 1997 until present. Interventions performed between January 1, 1997 and December 31, 2012 were analyzed.

Patients intervened for ASD were identified in the NPR by using procedure codes relevant for ASD interventions: FFC00, FFC10, FFC22, FFC32, FFC50, FFC60 and FFD20. The NPR data regarding ASD interventions were linked with the MCSR through the Swedish ten digit personal identity number [11]. Cases with a stroke diagnosis prior to or in connection to the ASD intervention were considered as possible patent foramen ovale, which has the same ICD-10 code as ASD, with cryptogenic stroke and therefore excluded from further study (n = 53). Two hundred ninety-seven persons were thereby identified both in the NPR and in the MCSR. Those with missing data regarding aerobic fitness were also excluded (n = 43). Two hundred fifty-four later patients (Table 1) and 1,426,282 referents (those without an intervention for an ASD) fulfilled the inclusion criteria, and none of the exclusion criteria, and were finally included in the study.

2.4. Statistics

All calculations were performed using Statistical Package for Social Sciences version 23 (IBM SPSS Statistics, IBM, Armonk, NY, USA). Data were assessed for normality. Individuals with an ASD intervention were divided into two groups – those with exercise capacity ≥1 standard deviation (SD) above mean (high exercise capacity) and those <1 SD above mean (low to moderate exercise capacity). Corresponding analyses were performed with individuals divided into those with isometric muscle strength ≥1 SD above mean (high muscle strength) and those <1 SD above mean (low to average muscle strength). Comparisons were also made between patients with an ASD intervention and the presumably healthy reference population. For all continuous variables, differences in means were analyzed using Student's *t*-test. Survival curves to illustrate time from baseline tests at military conscription to intervention for ASD were constructed with the Kaplan–Meier method, and differences between the curves were evaluated with the log-rank statistic. The null hypothesis was rejected for *p*-values < 0.05.

3. Results

Out of 1,426,536 individuals in the MCSR, 254 men with later intervention for ASD were identified. The intervention was performed 26.5 ± 7.9 years after conscription with a range from 6.3 to 41.1 years. Men with ASD were slightly taller (181.1 ± 6.9 cm vs. 179.1 ± 6.6 cm, $p < 0.001$), had higher body weight (71.1 ± 11.9 kg vs. 69.8 ± 10.5 kg, $p = 0.035$) and lower systolic blood pressure (126.3 ± 9.4 mm Hg vs. 128.4 ± 10.9 mm Hg, $p = 0.001$) than referents. The groups did not differ with respect to diastolic blood pressure (68.3 ± 10.1 mm Hg vs. 67.4 ± 10.0 mm Hg, $p = 0.12$), isometric muscle strength (grip strength; 615.4 ± 96.9 N vs. 614.9 ± 98.5 N, $p = 0.93$, elbow flexion; 386.7 ± 82.0 N vs. 387.0 ± 84.8 N, $p = 0.95$, knee extension; 575.3 ± 114.0 N vs. 569.2 ± 118.3 N, $p = 0.42$), or absolute aerobic exercise capacity (273.5 ± 50.5 W vs. 275.8 ± 52.5 W, $p = 0.49$). The relative aerobic exercise capacity (3.9 ± 0.7 W/kg vs. 4.0 ± 0.7 W/kg), was borderline lower ($p = 0.048$) than in the reference population (Table 2).

Table 1
Distribution of interventions among patients with ASD included in the study.

Type of intervention	n (%)
Suture of ASD secundum	19 (7.5)
Percutaneous transluminal closure of ASD secundum	205 (80.7)
Patch closure of ASD secundum	22 (8.7)
Total ASD secundum	246 (96.9)
Suture of ASD sinus venosus	1 (0.4)
Patch closure of ASD sinus venosus	7 (2.8)
Total ASD sinus venosus	8 (3.1)

ASD, atrial septal defect; n, number.

Table 2
Descriptive data on patients with ASD and referents.

	Patients with ASD		Reference population		*p*
	n	Mean ± SD	n	Mean ± SD	
Height cm	254	181.1 ± 6.9	1,396,470	179.1 ± 6.6	**<0.001**
Weight kg	254	71.1 ± 11.9	1,396,306	69.8 ± 10.5	**0.035**
Systolic BP mm Hg	254	126.3 ± 9.4	1,384,637	128.4 ± 10.9	**0.001**
Diastolic BP mm Hg	254	68.3 ± 10.1	1,384,306	67.4 ± 10.0	0.121
Grip strength N	246	615.4 ± 96.9	1,295,138	614.9 ± 98.5	0.931
Elbow flexion N	246	386.7 ± 82.0	1,295,107	387.0 ± 84.8	0.950
Knee extension N	246	575.3 ± 114.0	1,295,042	569.2 ± 118.3	0.420
Grip strength N/kg	246	8.8 ± 1.4	1,293,611	8.9 ± 1.4	0.056
Elbow flexion N/kg	246	5.5 ± 1.1	1,293,585	5.6 ± 1.1	0.118
Knee extension N/kg	246	8.2 ± 1.6	1,293,522	8.2 ± 1.6	0.535
Wmax W	254	273.5 ± 50.5	1,222,673	275.8 ± 52.5	0.490
Wmax index W/kg	254	3.9 ± 0.7	1,222,271	4.0 ± 0.7	**0.048**

p-values represent differences in mean values between patients with ASD and the reference population. ASD, atrial septal defect; BP, blood pressure; N, Newton; n, number, Wmax, peak work load. Bold numbers indicate $p < 0.05$.

Men with high exercise capacity had their intervention earlier than those with low to moderate exercise capacity (21.9 ± 8.6 years vs. 27.5 ± 7.4 years, $p < 0.001$). In survival analysis, the interventions occurred evenly distributed over time, but earlier for those with high exercise capacity (log-rank $p < 0.001$) (Fig. 1). Men with high exercise capacity had higher absolute isometric grip strength (620.2 ± 101.3 N vs. 592.1 ± 67.3 N, $p = 0.028$) and absolute isometric knee extension strength (568.4 ± 115.9 N vs. 608.5 ± 99.0 N, $p = 0.038$) compared with those who had low to moderate exercise capacity. The groups did not differ with respect to absolute isometric elbow flexion strength (387.0 ± 83.2 N vs. 385.1 ± 76.7 N, $p = 0.89$). When indexed to body

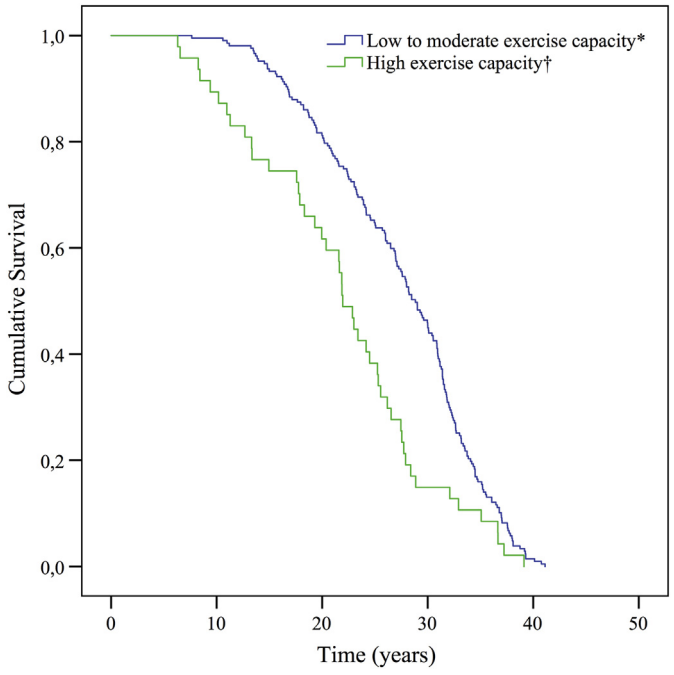

Fig. 1. Kaplan–Meier curves illustrating time from military conscription to intervention for ASD among patients with low to moderate exercise capacity and high exercise capacity ASD, atrial septal defect; Wmax, peak work load. Differences between the curves were assessed using log-rank statistics; $p < 0.001$. *Wmax/kg < 1 SD above mean. †Wmax/kg ≥ 1 SD above mean.

weight, men with high exercise capacity had higher relative isometric knee extension strength (9.0 ± 1.5 N/kg vs. 8.0 ± 1.5 N/kg, $p < 0.001$) than those with low to moderate exercise capacity. No difference in relative isometric grip strength (8.8 ± 1.0 vs. 8.7 ± 1.4 N/kg, $p = 0.783$) or relative isometric elbow flexion strength (5.7 ± 0.8 N/kg vs. 5.4 ± 1.1 N/kg, $p = 0.193$) was found between the groups (Table 3). Regarding isometric muscle strength, no difference in the time point for intervention was detected between the groups in survival analysis (data not shown).

4. Discussion

In the present study, by combining two large national registers, we have performed a prospective follow-up of standardized exercise tests performed in military conscription and identified those with later intervention for an ASD. We showed, in contradiction to the working hypothesis, that these individuals had a normal exercise capacity in late adolescence, in the study population two to three decades prior to ASD intervention. In addition, men with ASD had similar isometric muscle strength as the reference population. Furthermore, it was clear that those with higher exercise capacity had their intervention earlier. Since it is known that patients with an indication for ASD closure later in life generally have reduced exercise capacity [2], our findings may suggest that impaired exercise capacity develops over the years and might thus not be present in late adolescence. Consequently, on a group level, low exercise capacity is not a feature of adolescents that later need an intervention for ASD.

Previous studies show that most patients with ASD have reduced exercise capacity [2–7]. These reports are, however, based on exercise tests performed relatively close to intervention. The recovery of exercise capacity after an intervention [6,7] clearly shows that exercise capacity indeed is reduced due to the atrial shunt. Our data showed that exercise capacity in late adolescence, on a group level, was normal in absolute numbers, but borderline low - albeit clinically insignificant - when indexed to body weight. Therefore, it could be concluded that the functional effect of the cardiac lesion develops during adulthood despite the presence of a structural defect since birth. Due to aging, the left ventricular myocardium normally becomes less compliant, which tends to increase the left-right component of an atrial shunt [12]. This can partly explain the mechanism why patients with an ASD who are asymptomatic in childhood and early adulthood become symptomatic later in life [13]. During dobutamine stress, the left to right shunt volume remains constant as the systemic cardiac output increases [14]. This may also be an explanation for a relative lower effect on exercise capacity in a younger age but occurrence of limitations and symptoms as the magnitude of the shunt increases with aging and a less compliant left ventricle.

Somewhat surprisingly, men with higher exercise capacity at conscription were intervened earlier. To the best of our knowledge this has not been reported previously. Intuitively, reduction of the exercise capacity from an already low level is expected to cause symptoms. Here we showed that this may be true. However, it occurred later than in those with lower exercise capacity. The reasons for this are not clear. It might be that those with high exercise capacity are more attentive to impairment and therefore seek medical advice earlier.

We also noted that men with ASD had lower systolic blood pressure than the reference population. A possible explanation for this might be that the atrial shunt reduces the end-diastolic volume in the left ventricle and thus also the cardiac output, thereby lowering the systolic blood pressure, but with a difference that probably only appears with statistical significance in quite large populations as in the present study.

It has been reported that most interventions for ASDs are performed in childhood, and that patients present in screening programs identified by symptoms or by physical examination. The proportion of children versus adults with catheter interventions for ASDs is almost equal in Swedish healthcare [15], challenging the statement that most interventions are performed in children. In any case, late diagnosis of ASD might reflect a discreet pattern of the disease's natural progression. The reasons for a varying natural course probably reflect different pathophysiologies. Based on the present data, we cannot present a plausible mechanism for these differences without being speculative.

4.1. Limitations

Due to the nature of the MCSR our study included only men. In the NPR, about 40% of ASDs were found in men as expected [16]. However, we cannot rule out that the pathophysiology and natural course differ between men and women. We did not have access to data on individual structural (anatomical shunt size), functional (e.g. Qp/Qs ratios) or detailed surgical data. The study endpoints, i.e. intervention, were based on a national register that has proven validity [9]. Only interventions performed between January 1, 1997 and December 31, 2012 were analyzed. It may also be speculated the threshold for performing an echocardiogram and the diagnostic performance of echocardiograms have changed during the observed period, however, this could not be confirmed by plotting age against year of intervention.

4.2. Conclusions

On a group level, men intervened for ASD in adulthood had, from a clinical view, similar exercise capacity at late adolescence as peer referents. However, those with high exercise capacity appeared to be diagnosed and treated earlier. Thus, low exercise capacity is not a feature of adolescents that later needs an intervention for ASD.

Table 3
Descriptive data on ASD patients with low to moderate exercise capacity and high exercise capacity.

	Patients with low to moderate exercise capacity[a]		Patients with high exercise capacity[b]		*p*
	n	Mean ± SD	n	Mean ± SD	
Height cm	207	181.4 ± 7.2	47	179.4 ± 5.4	0.077
Weight kg	207	71.9 ± 12.7	47	67.7 ± 6.3	**0.001**
Systolic BP mm Hg	207	126.2 ± 9.5	47	126.9 ± 9.1	0.634
Diastolic BP mm Hg	207	68.4 ± 10.0	47	67.9 ± 10.4	0.761
Grip strength N	204	620.2 ± 101.3	42	592.1 ± 67.3	**0.028**
Elbow flexion N	204	387.0 ± 83.2	42	385.1 ± 76.7	0.893
Knee extension N	204	568.4 ± 115.9	42	608.5 ± 99.0	**0.038**
Grip strength N/kg	204	8.7 ± 1.4	42	8.8 ± 1.0	0.783
Elbow flexion N/kg	204	5.4 ± 1.1	42	5.7 ± 0.8	0.193
Knee extension N/kg	204	8.0 ± 1.5	42	9.0 ± 1.5	<**0.001**
Wmax W	207	260.0 ± 44.2	47	333.0 ± 29.1	<**0.001**
Wmax index W/kg	207	3.7 ± 0.6	47	4.9 ± 0.3	<**0.001**

p-values represent differences in mean between patients with low to moderate exercise capacity and high exercise capacity. BP, blood pressure; N, Newton; n, number; Wmax, peak work load. Bold numbers indicate $p < 0.05$.
[a] Wmax < 1 SD above mean.
[b] Wmax ≥ 1 SD above mean.

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