Blood pressure response to isometric exercise in patients with peripheral atherosclerotic disease

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Summary

Background The purpose of this study was to compare the circulatory responses to isometric exercise in patients with peripheral atherosclerotic disease (PAD) with healthy controls.

Methods Eleven patients with diagnosed PAD, a control group of eleven healthy young adults, and a control group of eleven healthy age-matched adults participated. Blood pressure, heart rate, stroke volume, cardiac output, blood velocity in the brachial artery, acral skin perfusion was continuously recorded and total peripheral resistance calculated before, during and after 2 min of 40% maximum voluntary contraction of the forearm.

Results At rest we found a consistently higher level of mean arterial pressure (MAP) and systolic pressure (SP) in the elderly, both PAD patients and elderly controls, compared with the young controls. We found no significant difference in diastolic blood pressure. Two minutes isometric handgrip exercise induced a similar increase in MAP in all three groups (patients 32±6 (17–9) mm Hg [mean (SD)], young control group 25±3 (8–9) mm Hg, age-matched control group 36±1 (10–6) mm Hg). No significant differences were found in the other measured cardiovascular variables during isometric handgrip. Increased TPR is the main factor contributing to the increase in blood pressure in all three groups.

Conclusion Our study indicates that the pressor response continues to be well regulated with age, also when the cardiovascular system is altered by marked atherosclerosis. The consequence is that both PAD patients and elderly controls reach higher SP values during isometric exercise due to higher SP baseline values.

Introduction

Isometric (static) exercise produces a characteristic increase in blood pressure, as first described by Lindhard (Lindhard, 1920). He observed a far greater increment in arterial blood pressure during isometric than during dynamic exercise. This increase was first explained as a mechanical consequence of contracting muscles blocking their own blood supply. The current view is that the cardiovascular response to both dynamic and isometric exercise is the outcome of an interaction between several influencing factors. Some degree of central command, and also afferent input from skeletal muscle receptors and from arterial and cardiopulmonary baroreceptors seems to play a role (Duprez et al., 1989; Potts et al., 1993). Isometric exercise is a normal part of everyday activities and many occupational tasks.

The cardiovascular response to isometric exercise has been examined in many studies, but the majority of subjects tested have been young males. With ageing, the vascular wall changes, becoming less elastic and stiffer (Nichols et al., 1985; O’Rourke, 1990; Cheitlin, 2003). In the limited number of studies that have compared the isometric exercise response in older and younger individuals, there have been discrepancies between the findings. With regard to blood pressure, some studies have found that older individuals exhibit a greater blood pressure response to handgrip exercise than younger individuals (Petrofsky & Lind, 1975; Ordway & Wekstein, 1979; Van Loan et al., 1989; Smolander et al., 1998), whereas others have found the opposite (Seals et al., 1985; Matthews & Stoney, 1988).

However, most studies show that the pressor response is not affected by age (Sagiv et al., 1988; Taylor et al., 1991; Tonkin & Wing, 1994; Taylor et al., 1995; Boutcher & Stocker, 1999)

Peripheral atherosclerotic disease (PAD) is common, with a prevalence of 10–20% in the population older than 65 years (McDermott et al., 2002; Diehm et al., 2004). About 1.5% of
men under 49 and 5% of men over 50 will also develop symptoms of intermittent claudication. For women the incidence is slightly less (Dormandy et al., 1989). An overall annual mortality of 4·3% has been reported in patients with intermittent claudication (Dormandy & Murray, 1991). Physical activity has been found to have a positive effect in the prevention and treatment of PAD, and isometric exercise is also sometimes part of the training recommended for patients with cardiovascular disease (Aronow, 2001; Thompson et al., 2003).

Pathological changes in the vascular system associated with PAD are related to lipid deposition and calcification, and result in more rigid vascular walls. In PAD patients, the changes in the vascular wall and high blood pressure are associated with a higher risk of cardiovascular events such as myocardial infarction, stroke or rupture of an aneurysm (Palatini, 1998; Fornes & Lecomte, 2003; Thompson et al., 2003). Knowledge of blood pressure regulation in PAD patients is therefore needed in order to be able to give patients suitable guidelines, and to design appropriate training programmes. The aim of this study was to examine the pressor response to isometric exercise in patients with PAD, and to compare it with the response in healthy individuals. Exercise pressor response is very well regulated in young, healthy individuals (Hisdal et al., 2004). Several studies suggest that the blood pressure response in patients with PAD is different from healthy individuals, and that this may be related to altered vascular compliance (Oka et al., 2005; Bakke et al., 2006; Jae et al., 2006a,b). Our hypothesis was therefore that patients with PAD would show a different blood pressure response to healthy controls during isometric exercise. The results of the present study may make a contribution to better information and guidelines for the treatment of PAD patients.

Methods
Subjects
Eleven patients participated, six females and five males [age 66.8 (9-3) years, [mean (SD)], height 168.9 (9.8) cm, weight 71.8 (13.1) kg, BMI 25.0 (2.7)]. All patients had been diagnosed with PAD at the Department of Vascular Surgery. They all had symptoms of intermittent claudication, and had an ankle-brachial index (ABI) < 0.8 [0.6 (0.1)] at rest. All were active smokers or had recently stopped smoking. No one participated in any supervised exercise programmes. Subjects undergoing anti-hypertensive medical treatment and patients with heart disease or orthostatic hypotension were not included in the study.

We used two control groups, differing in age. The young control group consisted of eleven healthy subjects, seven females and four males [age 24.2 (5-1) years, height 169.8 (8.3) cm, weight 66.6 (10.0) kg, BMI 23.3 (2.0)]. The age-matched control group consisted of eleven healthy subjects, four females and seven males [age 62.7 (3-3) years, height 175.9 (11-4) cm, weight 77.4 (9-9) kg, BMI 25.0 (2.2)]. All control subjects were non-medicated and normotensive (blood pressure < 140/90 mm Hg), and had an ABI ≥ 1.0. All were non-smokers, although four of the age-matched controls had previously smoked. Before participating in the study, all subjects underwent a medical examination. The subjects were instructed not to drink coffee or tea, and not to exercise, smoke or eat for at least 2 h before the start of the experiment. Written informed consent was obtained from all participants, and the study was approved by the local ethics committee.

Handgrip
A custom-made handgrip unit (developed by E. Stranden) was used to measure and display the force exerted by the test subjects when squeezing the handle with their right hand. A digital display gave the test subject continuous information, making it possible to maintain the intended force. The test subjects were asked to exert a force corresponding to 40% of their individual and previously measured maximum voluntary contraction force (MVC). They were instructed to avoid the Valsalva manoeuvre and to relax all the muscles not primarily involved in contraction, in order to avoid recruitment of accessory muscle mass. MVC was determined approximately 10 min prior to the experimental session by asking the test subjects to press using maximum force around the handgrip transducer for a 3 s period. The contractions were held for two minutes. The mean force (arbitrary units) exerted in three such sessions was calculated and used as MVC.

Measurements
Instantaneous and continuous heart rate (HR) was obtained from the duration of each R-R interval of the ECG signal. Finger arterial pressure was continuously acquired by a photoplethysmographic pressure recording device (Finometer; FMS Finapres Medical Systems BV, Amsterdam, the Netherlands) measured from the left arm. Care was taken to adjust the arm so that the measured finger was at heart level. The instantaneous pressure output was transferred online to the recording computer where beat-to-beat mean arterial pressure (MAP) was calculated by numerical integration. The Finometer device has been shown to satisfy the validation criteria of the Association for the Advancement of Medical Instrumentation, and it has therefore been recommended for measurements in the clinical set-up and for research purposes (Guelen et al., 2003; Schutte et al., 2004). Beat-to-beat stroke volume (SV) was recorded by an ultrasound Doppler velocimeter (SD-50; GE Vingmed Ultrasound, Horten, Norway), operated in pulsed mode at 2 MHz with a hand-held transducer. The ultrasound beam was directed from the suprasternal notch toward the aortic root, and the sample volume range was adjusted so that measurements were made 1–2 cm above the aortic valve. We positioned the sample volume range centrally in the aorta by searching for the highest obtainable velocity signal. An angle of 20° between the direction of the sound beam and the bloodstream was assumed in the
calculations. Beat-to-beat cardiac output (CO) was calculated from the corresponding HR and SV values. Blood velocity in the left brachial artery (BBV) was measured using the ultrasound Doppler technique (Multi Dop T2; TNO TPD Biomedical Instrumentation, Amsterdam, the Netherlands). The operating frequency was 10 MHz. The transducer was placed over the cubital fossa with the ultrasound beam directed at the brachial artery. The instantaneous cross-sectional mean velocity was calculated by the Multi Dop T2 and transferred online to the computer. In a separate session, we used echo Doppler technique with a 10 MHz ultrasound probe (System Five; Vingmed GE Horten) to measure the diameter of the brachial artery in six young healthy subjects at rest and at the end of a period of isometric exercise. Despite a marked increase in blood pressure in all six subjects, we did not observe any changes in brachial artery diameter during isometric exercise. We therefore assumed that the changes we observed in blood velocity in the brachial artery were directly proportional to changes in blood flow in the artery. Laser Doppler technique (Periflux PF 4000; Perimed AB, Järfälla, Sweden) was used to measure acral skin blood perfusion (ASBP) in the pulp of the left second finger. The laser Doppler probes were attached to the skin with double-sided adhesive tape. The sampling frequency was 2 Hz. Total peripheral resistance (TPR) was calculated as [(MAP-CVP)/CO]. CO was used as an estimate for averaged flow through the resistance vessels. For ethical reasons, central venous pressure (CVP) was not measured. For the calculations of TPR we assumed CVP to be equal to zero. When comparing relative data, average values at rest (T = 0–60 s) were set equal to 100%.

Data analysis

For data storage and analysis we used the Regist3 software (developed by M. Eriksen, Norway). HR was acquired beat to beat from the ECG R waves. MAP was calculated for every heartbeat. For analyses, the recorded variables were converted into a 2-Hz sampled signal by interpolation. Throughout the recording period, there was considerable beat-to-beat variation in the recorded variables. This variation has been reported by other authors (Guz et al., 1987; Eriksen et al., 1990) and is partly due to the influence of respiration (Guz et al., 1987; Toska & Eriksen, 1993). Variations in the recorded variables not related to the pressor response were partly eliminated by calculating the average response from four identical runs for every test subject, synchronized by the onset of isometric exercise. Finally, the individual average curves from all subjects in each group were pooled and used to calculate the mean value in each set of synchronous samples for each 2-Hz time step. This process is known as coherent averaging, and it is used in order to emphasize waveshapes that are common to a series of recordings, and de-emphasizes those components that are not common (Toska et al., 1994). If the noise is random, the amplitude of the signal-to-noise ratio after n averages will improve by the square root of n (Rompelman & Ros, 1986; Challis & Kitney, 1990). All calculations were performed in Microsoft Excel 2000. Slope-rates were calculated using the linear trendline function for the time period between T = 71 (after the startle response) and T = 180 s (end of exercise).

Statistical analysis

Repeated measures ANOVA test was used to test for significant differences between the patients and the two control groups, and the Bonferroni correction to correct for multiple comparisons. Differences were considered significant at P<0.05. There was no interaction of groups. The statistical analyses were performed using the statistical program SPSS 12.0 (SPSS Inc., Chicago, IL, USA). The calculations were performed in MS Excel 2000.

Results

Figure 1 illustrates the development of all recorded cardiovascular variables throughout the period of isometric exercise. In Table 1 we present average resting values and maximal values at end of isometric exercise, as well as the differences between average resting values and average maximal values.

Mean arterial pressure at rest was higher in the PAD patient group and elderly controls, compared with young controls. This difference was due to higher SP baseline values. MAP increased steadily throughout the exercise period with a slope of about 0.19 (0.07) mm Hg s⁻¹ in the young controls, 0.28 (0.08) mm Hg s⁻¹ in the age-matched controls, and 0.25 (0.12) mm Hg s⁻¹ in the PAD patient group. There were no significant differences between the PAD patient group and the two control groups in the increase in MAP or in the slope rate at which MAP increased during isometric exercise. The consequence was that both PAD patients and elderly controls, compared to young controls, reached higher SP values during isometric exercise due to higher SP baseline values. We found no significant differences in DP between the three groups. HR increased steadily during the exercise period with a slope of 0.09 (0.08) beats s⁻¹ in the young control group, 0.06 (0.05) beats s⁻¹ in the age-matched control group, and 0.08 (0.06) beats s⁻¹ in the PAD patient group. There were no significant differences between the three groups in the total increase or in the slope rate for HR. Nor were there any significant differences between the PAD patient group and the two control groups in TPR, SV, CO, BBV or ASBP, neither in slope rate nor in total increase during the exercise period.

Discussion

It has been recognized for a long time that there is a marked increase in blood pressure during isometric muscle activity. The main finding in the present study was that PAD patients, age-matched controls and young healthy controls all showed similar cardiovascular responses during isometric handgrip workload.

Mean arterial pressure starts to increase immediately after the onset of isometric exercise. After the initial ‘startle’ response,
observed in the first few seconds after the onset of isometric exercise, MAP increased steadily throughout the rest of the exercise period in all three groups. At rest we found no significant differences between the groups in diastolic blood pressure. There was a consistently higher level of systolic pressure, and thereby also a higher level of MAP, in the older groups, both PAD patients and age-matched controls, than in the young controls. The difference in resting blood pressure is
observed a gradual increase in blood velocity in the brachial artery during isometric exercise, we measured the diameter of the brachial artery in six young healthy subjects at rest and at the end of a period of isometric exercise. Despite a marked increase in blood pressure in all six subjects, we did not observe any changes in brachial artery diameter during isometric exercise. We therefore assumed that the changes we observed in blood velocity in the brachial artery during exercise were directly proportional to changes in blood flow in the artery. Studies indicate there are changes in the brachial artery diameter during reactive hyperaemia and postexercise hyperaemia (Aldo et al., 2006; Ozcan et al., 2006), but the changes in conduit artery diameter do not significantly contribute to blood flow increase during exercise. Studies also show that PAD patients might have a different diameter response to reactive hyperaemia (Celerma-jer et al., 1992; Akopov et al., 1997), with a reduced ability to flow mediated vasodilatation in PAD patients compared to young, healthy subjects. In our study, a postexercise vasodilation in the young control group could be a possible bias, and this could explain the marked fall in postexercise brachial artery blood velocity (Fig. 1), which we otherwise contribute to a distal sympathetic vasoconstriction.

As blood flow increases and the diameter do not change in the brachial artery during isometric exercise, the tissues supplied with blood from this artery probably do not make a major contribution to the observed increase in TPR. We used ASBF as an index of cutaneous flow, and the fact that we also observed a similar pattern in the measurements of ASB in patients with PAD indicates that it is not a major participant to the increase in TPR. On the basis of previous observations during dynamic exercise, it seems reasonable to believe that the part of the vascular bed supporting the splanchnic and renal circulation plays an important role in the observed increase in TPR.

Unfortunately we had no techniques for measuring the circulation in these organ systems in this study.

In our research, we are studying the effect of a transient increase in blood pressure induced by isometric physical activity. There is an association between exercise blood pressure probably explained by increased arterial stiffness in two elderly groups (Nichols et al., 1985; O’Rourke, 1990; Cheitlin, 2003; Weber et al., 2003). As the slope of MAP increase during the exercise period was similar in the three groups, the maximum exercise blood pressure depends largely on the resting blood pressure. Subjects whose resting blood pressure is high will reach higher maximum values during isometric exercise. The duration of the exercise period and the strength of the contraction will also affect how much the blood pressure increases during isometric exercise (Williams, 1991). These findings also support the importance of a monitored treadmill exercise test before initiation of an exercise program to ensure safe and accurate exercise recommendations, and to identify individuals that require more intensive pharmacotherapy to prevent exercise-induced hypertension and tachycardia (Oka et al., 2005).

The HR increased by about 20%, and we also observed a gradual decline in SV during the exercise period. The drop in SV is probably caused by increased afterload due to the elevated MAP, and reduced filling time because of an increase in HR. Preload is probably not, or only to a small degree, affected by isometric exercise involving one arm only. As a consequence we only observed a small increase in cardiac output during isometric exercise. Increased vascular resistance or TPR is therefore the main factor contributing to the increase in blood pressure during isometric exercise in all three groups. This is in accordance to what has been reported in a previous study (Hisdal et al., 2004).

For ethical reasons we did not in this study measure CVP, which is therefore omitted from the calculation of TPR. We expect CVP to be very low compared with MAP and probably not much affected by the isometric exercise in this experiment. We therefore believe that the relative changes we observed in TPR represented real changes in vascular resistance. We also observed a gradual increase in blood velocity in the brachial artery during the period of isometric exercise. To ensure that the increased velocity could not be explained by constriction in the arterial.
and potential risk of stroke, cardiovascular events and mortality (Mittleman et al., 1993; Palatini, 1998; Kurl et al., 2001; Fornes & Lecomte, 2003). Despite the excessive blood pressure elevation associated with isometric strain in young athletes, stroke almost never occurs. According to guidelines, athletes who have severe hypertension should be restricted from high static sports until hypertension is controlled with medications and lifestyle modification (Kaplan et al., 1994, 2005). Patients suffering from aneurysm are advised to avoid activity resulting in marked rise in blood pressure, e.g. heavy lifting (Hatzaras et al., 2006). Since physical activity has beneficial effects, exercise is nevertheless strongly recommended in the prevention and treatment of cardiovascular disease (Hanson & Nagle, 1987; McCartney & McKelvie, 1996; Aronow, 2001; Carre, 2002; Franklin et al., 2003; Thompson et al., 2003). Resistance training is considered to be safe and effective for clinically stable coronary patients (McCartney & McKelvie, 1996; Franklin et al., 2003). In supervised cardiac rehabilitation programmes, gradual exposure to submaximum isometric training has been recommended for cardiac patients (Hanson & Nagle, 1987). Supervised rehabilitation programmes for patients with PAD also may include a certain amount of isometric exercise, both as a specific isometric exercise, or as part of other exercise activities. Our group has shown that patients with PAD have a significant and continuing increase in blood pressure when walking to maximum claudication distance (Bakke et al., 2006), and the level of increase in blood pressure is similar to the increase observed during isometric exercise found in the present study. Both strength-training and dynamic exercise have shown to be beneficial to PAD patients (Hiatt et al., 1994), as well as for patients with coronary disease, but patients and physicians should be aware of the marked increase in blood pressure that occurs during isometric muscular activity.

We conclude that moderate isometric effort in PAD patients results in a marked increase in blood pressure, but that the changes are no larger than those found in a normal population. The pressor response to isometric exercise has been shown to be well regulated and steady, even during induced alterations in preload (Hisdal et al., 2004), and in patients who lack the capacity to increase heart rate or stroke volume by nervous control after heart transplantation (Haskell et al., 1981). Our study indicates that the well-regulated pressor response is maintained with age, and when the cardiovascular system is altered by marked atherosclerosis. Compared to the findings in our previous study on blood pressure in patients with intermittent claudication during walking (Bakke et al., 2006), the results from the present study indicate that cardiovascular control is maintained during static but not dynamic exercise.

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