Is exercise blood pressure a marker of vascular endothelial function?

N. TZEMOS, P.O. LIM and T.M. MACDONALD

From the Hypertension Research Centre, Department of Clinical Pharmacology and Therapeutics, Ninewells Hospital and Medical School, Dundee, and 1Department of Cardiology, Wales Heart Research Institute, University of Wales College of Medicine, Heath Park, Cardiff, UK

Introduction

Blood pressure (BP) during exercise is routinely measured during treadmill testing of individuals with chest pain. An abnormal response, whereby the BP falls or fails to rise during exercise, is universally accepted to be a sign of more severe cardiac ischaemia. Similarly, such responses in patients with hypertrophic cardiomyopathy indicate a high risk for cardiac death, hence exercise BP assessment is now included in the routine work-up of these patients. The converse, i.e. an exaggerated BP response (ExBPR) during exercise is more controversial, especially when seen in apparently healthy individuals. There are, however, accumulating data to suggest that ExBPR is an early sign of cardiovascular disease. In particular, ExBPR seems to relate to the future development of hypertension, left ventricular hypertrophy (LVH) and is also a potent predictor of future cardiac events. The origin of ExBPR is incompletely understood at present. In this brief review we examine the available literature on the link between cardiovascular disease and ExBPR, and speculate on the nature of this relationship.

The prognostic value of exercise BP response

Despite being the standard to guide treatment of hypertension, resting ‘office’ BP may not be the best measure of cardiac risk.1,2 For example, it relates poorly to LVH, an important cardiac prognostic factor.1-3 There are alternative ways of assessing BP such as ambulatory BP monitoring (ABPM), home BP and exercise BP. For each of these measures studies have shown that BP correlates better with LVH than the office BP.1

In normotensive middle-aged men, ExBPR has been reported to be an independent predictor of future cardiovascular morbidity and mortality.4,5 Exercise BP also correlates better with LVH than the office BP6,7 (Table 1). Gottdiener and colleagues found a significant relationship between maximal exercise SBP (>210 mmHg) and LVH in normotensive volunteers.8 Similarly, Mahoney and colleagues have shown in 274 children aged 6–15 years that the exercise diastolic BP and the rise in systolic BP (∆SBP) correlated better with LVH than did resting BP measures.9 These findings are intriguing, because echocardiographic LVH is a powerful and independent risk factor for future cardiovascular disease.3,10

ExBPR has also been shown to be a powerful predictor of future sustained hypertension in adolescence and young adults.11,12,4 In these studies, normotensive healthy volunteers with an exercise SBP >195 mmHg had a 2–3-fold increased risk of future sustained hypertension.4,2,13

It is possible that the exercise BP provides an index that would reflect daily fluctuations of BP and
indeed, we have previously found a significant relationship between exercise BP and the ambulatory BP.\textsuperscript{14} We believe that intermittent BP rises during daily (non-accustomed) physical exercises and/or stresses might be sufficient to produce target organ damage in susceptible individuals. An interesting category of patients that might reflect this hypothesis are those with ‘white coat’ hypertension. These patients develop higher exercise BP and they also have a higher incidence of impaired NO bioactivity and LVH, compared to the normal population.\textsuperscript{2}

Despite the above data that support exercise BP as a valuable non-invasive cardiovascular marker, it is also much criticized. It is unclear which exercise intensity BP should be measured as to provide the best measure of cardiovascular risk. Most studies have used arbitrary cut-off values, usually at the extreme of a response that is normally (Gaussian) distributed. The thresholds for cardiac risk used have varied between studies, although a SBP > 190 mmHg during exercise is commonly used.\textsuperscript{2} There are a number of negative studies that have attempted to correlate the maximal exercise BP with cardiovascular disease. One example is the CARDIA study, which used a threshold of ExSBP > 210 mmHg on treadmill testing.\textsuperscript{15} This study found 23% of participants with ExSBP > 210 mmHg, but after 5 years of follow-up, only 3.5% of these normal subjects developed hypertension, an incidence no higher than that found in normal responders.\textsuperscript{15} This inconsistent finding may be methodological. A high maximal BP can (paradoxically) be a marker of fitness since athletes, especially those specializing in isometric exercises, such as weight lifters, can develop very high BP during exercise.\textsuperscript{16} Similarly, any athlete can exercise to a high level of BP; what is more important is the rate by which the BP rises during exercise. In fit individuals, BP rises relatively slowly in comparison to individuals with lower cardiovascular fitness, in whom BP rises precipitously immediately on, or even before, commencing exercise.\textsuperscript{16}

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Age</th>
<th>Index</th>
<th>Office SBP</th>
<th>Exercise SBP</th>
<th>24 h systolic ABP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osse 1986</td>
<td>61 (24 f)</td>
<td>42</td>
<td>LVMI</td>
<td>0.40*</td>
<td>C (30w or 20w/3 min) Max</td>
<td>0.49**</td>
</tr>
<tr>
<td>Ardillo 1996</td>
<td>63 (19 f)</td>
<td>47</td>
<td>LVMI</td>
<td>0.20</td>
<td>C (50w/5 min) Max</td>
<td>0.41**</td>
</tr>
<tr>
<td>Rossman 1994</td>
<td>60 (13 f)</td>
<td>40</td>
<td>LVMI</td>
<td>0.17</td>
<td>T</td>
<td>0.38**</td>
</tr>
</tbody>
</table>

*\(p<0.05; **p<0.01; T, treadmill; C, cycle; Max, maximal.\)

Another issue is with the measure of BP during exercise. The maximal BP cannot be accurately measured with non-invasive auscultatory methods because BP falls rapidly on stopping exercise (Figure 1). The exercise modality also has implications, whether it is treadmill or bicycle. The cycle ergometer has been shown to exert greater work strain at a comparable work intensity than with the treadmill ergometer. With the above in mind, submaximal exercise might be more advantageous than maximal exercise, because it is less effort-dependent and perhaps better reflects daily life activities.\textsuperscript{16,17} Interestingly, we have previously shown that an exaggerated blood pressure response during those ‘daily life activities’ assessed as submaximal exercise predicted target organ damage in a cohort of hypertensive patients more closely than office blood pressure did (Figure 2). Finally, the baseline BP should be taken into account, since subjects with high exercise BP tended to have higher baseline BP, hence the prognostic value of exercise BP could be due to a tracking effect.\textsuperscript{18,4} Alternatively, the rise in BP per se during exercise or ΔExSBP between rest and exercise can be separately examined. This might be of particular value in hypertensive patients with higher resting BP but with an absolute increase in exercise BP
similar to that in normotensive subjects. It is possible that ΔExSBP is a marker of the exercise peripheral vasodilatory capacity, as discussed below.

Other risk factors, such as obesity (body mass index), smoking, family history, or rapid heart rate (index of physical fitness), may also play an important role in determining not only the exercise BP but also the overall cardiovascular risk. A few reports have implied contributions from family history and cigarette smoking in determining the exaggerated BP response, hence we need to control for these factors when the exercise is being assessed as an independent risk factor. However, it is likely that any factor that influences the state of the vasculature (e.g., hypercholesterolaemia, diabetes, smoking) will also influence the exercise BP, since this response is dependent on the state of the peripheral vasculature.

A brief physiology of exercise BP

Skeletal muscle constitutes approximately 40% of the total body mass, and at rest receives approximately 15–20% of cardiac output. During exercise, this rises to 80–90% of cardiac output, and in addition there is increased peripheral O₂ extraction. Dynamic exercise has a significant impact on the muscular vascular bed homeostasis via an incompletely understood phenomenon known as exercise hyperaemia, which is a net result of the interlinkage between neural, metabolic, and hydrostatic processes. Of these, local metabolic factors are considered to be the more important determinants of exercise-induced increase in muscular blood flow. Potassium ions (which act both directly on smooth muscle, and indirectly via a reduction of norepinephrine release), a rise in plasma osmolality, an increase in pH and CO with consequent metabolic acidosis (which also reduces norepinephrine release), histamine and hypoxaemia are all local factors that can cause vascular smooth muscle vasodilation. Interestingly, all these factors also stimulate nitric oxide (NO) release from the vascular endothelium. In comparison, exercise-induced vasodilation occurs to a much lesser extent, mediated by neuronal reflex regulation. Sympathetic vasoconstriction occurs through α-adrenergic receptor system and also through cholinergic nerve endings that mediate vasoconstriction in resistance arteries. During exercise, the rhythmic action of muscular contractions help to pump blood to and fro the capillary beds by compressing the vasculature at regular intervals and creating a pressure-gradient between the arteries and veins. In non-exercising muscles however, vasoconstriction occurs. This is probably mediated by increased endothelin 1 (ET-1) and norepinephrine release, aiding venous return and increasing cardiac output.

Normal exercise physiology and NO

The discovery by Furchgott and Zawadski of endothelial-derived relaxing factor (EDRF), later identified as vascular NO, has revolutionized vascular biology over the last two decades. The endothelium, previously thought to function solely as an inert anatomical barrier, is now known to have diverse functions, including anti-atherogenic and anti-atherosclerotic properties. The endothelium also releases vasoconstrictive and vasodilating agents, of which NO is arguably the most important. The endothelial cells are placed between the circulating blood and the vascular smooth muscle, and hence are exposed to physical forces such as shear stress, hydrostatic pressure and pulsatile stretch by the dynamics of arterial circulation. This non-stop interaction between the endothelium and the blood flow leads to mechanical deformation of the endothelial cells that releases the ‘basal’ NO. Basal NO release is responsible for a vasodilated state of the peripheral (including coronary) vasculature. Experimental studies have shown that acute changes in local blood flow increase NO release in vitro and cause flow-dependent vasodilatation in vivo. In addition to basal NO, the endothelial cells release further NO in response to various endogenous and exogenous substances, including acetylcholine (ACh), substance P, and bradykinin.
Based on the above, exercise-induced haemodynamic changes (including an increase in shear stress) in theory would enhance NO release, although this has not been consistently demonstrated. Endo and colleagues reported that the role of NO was minimal in hyperaemic vasodilation to static handgrip, and suggested that metabolic factors were probably more important. Others, however, have found a significant contribution of NO in hyperaemic vasodilation. Recently, Gilligan and colleagues found that basal NO release, as assessed pharmacologically by L-NMMA (a specific antagonist of nitric oxide synthase), was partly responsible for the increased flow after isometric exercise (handgrip). Interestingly, the same group also suggested that the increased availability of the NO substrate L-arginine did not significantly affect vascular tone during exercise, suggesting that substrate delivery is not a limiting factor in exercise NO release.

Muscular blood flow during exercise is not uniform, which may explain the difficulty in identifying the precise mechanism of exercise hyperaemia. Blood flow to exercising limbs in fact can be divided into four consecutive but overlapping phases: (i) rapid early vasodilatation; (ii) beginning of active exercise; (iii) steady-state; and (iv) recovery. The almost immediate increase and decrease in skeletal muscle blood flow at the onset and on stopping exercise would favour a neural mechanism. Shoemaker and colleagues have shown that NO release at the onset of exercise does not appear to be essential with regard to rapid vasodilation. Later, metabolic factors such hypoxaemia, reduced pH and histamine produced concomitantly during this early phase of exercise play a part in increasing muscle blood flow, in conjunction with the muscle pump. The possibility of mechanically induced hyperaemia has been recently discussed. Tschakovsky and colleagues showed that repeated cuff inflation and deflation (to simulate rhythmic muscle contraction) around the human forearm increased blood flow only when the arm was positioned below heart level, arguing against a significant NO contribution. During the steady-state phase of exercise, rhythmic muscle contractions and metabolic factors along with endothelial NO ensure a constant blood supply. Dyke and colleagues found that L-NMMA infusion significantly reduced forearm blood flow during this exercise stage, suggesting a significant contribution of NO. Finally, during recovery a combined action of acetylcholine and non-cholinergically produced NO substantially affects the blood flow. The role of NO in exercise-induced vasodilation remains far from clear. It is, however, indisputable that NO plays an important role in modulating the peripheral vascular tone at rest.

**Indirect evidence of NO involvement during exercise**

Physical exercise increases skeletal and coronary blood flow, resulting in increased shear stress on the surface of the vascular endothelium. Endothelial cells respond to short-term increases in shear stress by producing vasodilator compounds such as prostacyclin and NO. Predictably, endothelial function in animals that perform regular exercises is improved as a result of increased coronary endothelial NO production (probably mediated by an increase in eNOS expression) and/or increased angiogenesis. Indeed, higher basal NO production is observed in well-trained human athletes, an observation that may help to explain the beneficial effects of exercise in cardiovascular diseases. Hambrecht and colleagues reported that 4 weeks of structured exercise in humans improved coronary endothelial dysfunction in those with coronary artery disease. Taddei and colleagues have shown that regular physical training protects the vascular endothelium from ageing-related decline in NO bioactivity. They speculated that this might be due to altering the underlying oxidative stress. Hence many cardiovascular diseases have characteristic endothelial dysfunction with deficient basal NO release, thereby influencing platelet activity that can lead to thrombus formation, and subsequent events such as myocardial infarction. Thus, restoring normal endothelial function with exercise training could be protective. There is also evidence suggesting that exercise increases vascular endothelial growth factor (VEGF) expression which promotes angiogenesis with obvious clinical implications.

**Link between abnormal exercise BP response and NO bioactivity**

There are many reasons why arterial hypertension is characterized by an abnormal BP response to exercise. Progressive structural and functional changes occur during the hypertensive disease process that would modify the vascular calibre, hence increasing the peripheral vascular resistances (PVR). Increased PVR is the hallmark of arterial hypertension, which may itself perpetuate the hypertensive process. It is likely that functional and structural changes occur hand in hand, but the former are probably more important in the early phase of hypertension, with structural changes...
superseding later in accounting for the high PVR in hypertension. It is well accepted that high BP affects the intima, causing structural and biochemical changes, with the endothelial cells changing in shape and morphology. Subsequently, vascular smooth muscle cell hypertrophy/hyperplasia occurs, and this can produce an abnormal wall-to-lumen ratio and increasing flow resistance. Essential and secondary hypertension are associated with a varying degrees of endothelial dysfunction involving the NO pathway. Other factors such as endothelin (ET-1) and/or increased responsiveness to circulating catecholamines may also play a role. We recently showed that an abnormal systolic BP response (absolute ExSBP > 200 mmHg) in hypertensive patients accurately predicted endothelial dysfunction compared to normo-reators (ExSBP < 180 mmHg) (Figure 3). This suggests that even within the hypertensive population, endothelial dysfunction is not uniformly present, and that the exercise BP reflects the exercise-induced peripheral vasodilatory capacity. This is likely to be at least in part due to NO release in response to increased vascular wall shear stress. Failure of NO release during exercise would blunt the normal fall in PVR, resulting in an abnormal rise in exercise BP. Such hypertensive patients are likely to be more at risk of a future cardiac events. It has recently been shown that plethysmographic assessment of forearm endothelial function in hypertensive patients strongly predicts future cardiovascular events. We might therefore surmise that non-invasive methods for predicting endothelial dysfunction will be much more important in cardiovascular risk stratification in the future.

Conclusions

Exercise BP assessment may aid risk stratification both in hypertensive and normotensive subjects. There is evidence suggesting that NO makes an important contribution to regulating exercise BP, although this relationship is not fully understood. Exercise BP may thus be a useful marker of NO bioactivity, and hence an important cardiac prognostic factor.

References


49. Panza JA, Casino PR, Kilcoyne CM, Quyyumi AA. Impaired endothelium-dependent vasodilation in patients with essential hypertension: evidence that the abnormality is not at the muscarinic receptor level. *J Am Coll Cardiol* 1994; 23:1610–16.


