ELEVATED PEAK EXERCISE SYSTOLIC BLOOD PRESSURE IS NOT ASSOCIATED WITH REDUCED EXERCISE CAPACITY IN SUBJECTS WITH TYPE 2 DIABETES

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Running head: Blood pressure and exercise capacity in type 2 diabetes

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ABSTRACT

BACKGROUND: Subjects with type 2 diabetes without cardiovascular disease have a reduced exercise capacity compared to non diabetic subjects. However, the mechanisms responsible for this phenomenon are unknown. PURPOSE: To evaluate the impact of exercise systolic blood pressure (SBP) response on diverse exercise tolerance parameters in type 2 diabetic subjects. METHODS: Twenty-eight sedentary men with type 2 diabetes were recruited for this study. Subjects were treated with oral hypoglycemic agents and/or diet. Evaluation of glycemic control and peak exercise capacity were performed for each subject. The subjects were divided into two groups according to the median value of peak SBP (210 mmHg) measured in each subject. RESULTS: We observed a 13%, 13% and 16% reduction in the relative peak oxygen uptake ($\dot{V}$O$_2$ peak), absolute $\dot{V}$O$_2$ peak and peak work rate in the low compared to the high peak SBP group [26.95±5.35 vs 30.96±3.61 ml·kg$^{-1}$·min$^{-1}$; 2.5±0.4 vs 2.8±0.6 L·min$^{-1}$ and 169±34 vs 202±32 watts (all p<0.05)]. After adjusting for age, relative $\dot{V}$O$_2$ peak was still significantly different (p<0.05). There were similar peak respiratory exchange ratio (RER) (1.20±0.08 vs 1.16±0.07; p=0.24) and peak heart rate (160±20 vs 169±15 beat per min; p=0.18) between the low compared to the high SBP group. No difference in glycemic control was observed between the 2 groups. CONCLUSION: The results reported in this study suggest that in subjects with type 2 diabetes without cardiovascular disease, an elevated
exercise SBP is not associated with reduced exercise capacity and its modulation is probably not related to glycemic control.

**Keywords:** $\dot{V}O_2$ peak, type 2 diabetic patients, high blood pressure response
INTRODUCTION

The study of oxygen uptake (\(\dot{VO}_2\)) during an incremental exercise protocol reflects the integration of numerous body functions in response to an imposed work stimulus (28). The \(\dot{VO}_2\) measured at maximal exercise, i.e. maximal or peak \(\dot{VO}_2\) (\(\dot{VO}_2\)max or \(\dot{VO}_2\)peak), is very important in clinical practice since it is related to survival (19). In subjects with type 2 diabetes, a reduced \(\dot{VO}_2\)max has been reported compared to non diabetic subjects (23; 24). However, the mechanisms responsible for this phenomenon remain unclear. Presence of endothelial dysfunction (10; 27) and abnormalities of cardiac function such as diastolic dysfunction (21) may be related to this reduced exercise capacity. Furthermore, subtle hemodynamic changes in response to exercise appearing early in the time course of diabetes might also have a negative influence on exercise capacity.

Type 2 diabetes is related to arterial stiffness (6) which in turn is associated with increased afterload (6), leading to an elevated systolic blood pressure (SBP) (4). An exaggerated SBP response to exercise is associated with a lower cardio-respiratory fitness level in women (12). In contrast, athletes are known to develop an elevated blood pressure (BP) response in association with a higher exercise capacity compared to non athletes (9). In fact, a positive relationship between the exercise BP response and left ventricular mass (LVM) has been documented in this population (20). However, the influence of early
Blood pressure and exercise capacity in type 2 diabetes

hemodynamic changes induced by diabetes such as the presence of an elevated exercise SBP response on exercise capacity in subjects with type 2 diabetes without cardiovascular disease is unknown.

The aim of the present study was to evaluate the impact of an elevated SBP in response to peak exercise on different parameters related to exercise capacity in sedentary subjects with type 2 diabetes without cardiovascular disease. We hypothesized that subjects with higher exercise SBP would have a reduced exercise capacity.

MATERIALS AND METHODS

Study population

Twenty-eight sedentary men with type 2 diabetes were recruited for this study. All subjects were type 2 diabetics treated with oral hypoglycemic agents (metformin, glyburide and/or glyclazide) and/or diet. No subject was on insulin. Exclusion criteria were a documented presence of cardiovascular disease and hypertension, all forms of complications related to diabetes and cardiovascular related medication. No subject presented macroalbuminuria. The study was approved by the local hospital ethics committee in accordance with the Declaration of Helsinki and all subject gave signed informed consent.
Evaluations

Blood sampling

At subjects’ arrival at the laboratory, a 18-gauge polyethylene catheter was inserted into a forearm vein for blood sampling. Blood samples were drawn at rest from subjects 30 minutes before the exercise protocol for the measurement of fasting blood glucose (FBG) and glycated hemoglobin (HbA1c), following an 8-hour overnight fast. FBG was assayed using the hexokinase method (Roche Diagnosis, Indianapolis, IN). HbA1c was assayed using the ion-exchange high-performance liquid chromatography (HPLC) method (Bio-Rad, Hercules, CA).

Exercise protocol

Exercise capacity was evaluated for each subject using an incremental protocol of 15 watts/min following a warm-up period of 1 minute at 15 watts and 2 minutes at 30 watts, performed on an electromagnetically braked cycle ergometer (Corival, Lode, Netherlands) at a pedalling rate of 50 to 70 rpm. Expired air was continuously collected for the determination of $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$), pulmonary ventilation ($\dot{V}_E$) and the respiratory exchange ratio (RER) ($\dot{V}CO_2/\dot{V}O_2$) on a breath-by-breath basis (Medgraphics, CPX Ultima, St Paul, MN). Heart rate (HR) was obtained using electrocardiographic monitoring during the test. Subjects exercised until volitional exhaustion. Peak exercise ($\dot{V}O_2$ peak) was defined as the mean $\dot{V}O_2$ recorded in the last 15 seconds of the incremental exercise protocol concurrent with a RER $\geq$ 1.15. The exercise
protocol was always performed in the fasting state at the same time of the day at 20 °C room temperature.

**Blood pressure**

Following 15 minutes of quiet rest in a supine position, resting BP was then measured with the subject seated using an automated sphygmanometer with headphone circuit option (Model 412, Quinton Instrument Co., Bothell, WA, USA). BP during exercise was measured every 2 minutes throughout the maximal exercise protocol using the same automated sphygmanometer as for the evaluation of resting BP. The subjects were divided into two groups according to the median value of peak SBP measured in each subject.

**Statistical analysis**

A Student unpaired t-test and an one-way ANCOVA were used to evaluate the peak exercise parameters differences between the groups. The Mann-Whitney test was used for data not normally distributed. The hypoglycemic regimen in the two groups were compared using the Fisher’s exact test. The Pearson’s correlation was used to assess associations between variables. All data are presented as mean±standard deviation unless otherwise specified. A p value < 0.05 was considered statistically significant.
RESULTS

Baseline characteristics of each group separated on the basis of the median peak exercise SBP are presented in Table 1. There was no statistical difference in all baseline characteristics between groups. Also, there was no statistical difference in the proportions of subjects on hypoglycemic agents. However, the subjects in the high peak SBP group tended to be younger (50 ± 10 vs 56 ± 8 y; p=0.08) whereas a trend for a lower resting SBP was observed in the low peak SBP group (< 210 mmHg) compared to the high peak SBP group (> 210 mmHg) (130 ± 11 vs 139 ± 14 mmHg; p=0.06).

Table 2 presents results from the peak exercise capacity evaluation (\(\dot{VO}_2\) peak). Per study design, there was a difference between the peak SBP between groups (p<0.001). A reduced increment in SBP (peak SBP minus resting SBP) during exercise was observed in the low peak SBP group compared to the high peak SBP group (63±21 vs 98±17 mmHg; p<0.001). We observed a 13% reduction in the relative and absolute \(\dot{VO}_2\) peak and a 16% reduction in the peak work rate in the low compared to the high peak SBP (all p<0.05). An elevated rate-pressure product (SBP x heart rate) was also observed in subjects with higher peak SBP (p<0.001). After adjusting for age, relative \(\dot{VO}_2\) peak was still significantly higher in subjects with higher peak SBP (p<0.05).
Significant relationships were observed between the resting SBP ($r=0.422$), absolute $\dot{V}O_2$ peak ($r=0.405$), exercise duration ($r=0.414$), peak work rate ($r=0.454$) and peak exercise SBP (all $p<0.05$) (Figure 1). While there was a significant inverse relation between age and absolute values of $\dot{V}O_2$ peak ($r=-0.612; p<0.001$) and a trend between age and relative values of $\dot{V}O_2$ peak ($r=-0.332; p=0.08$), there was no significant relation between age and peak SBP. No difference in the glycemic control (FBG and HbA1c) was observed between the 2 groups.

**DISCUSSION**

These results suggest that, in subjects with type 2 diabetes without cardiovascular disease, an elevated exercise SBP is not associated with reduced exercise capacity. Furthermore, SBP modulation during exercise is not related to glycemic control in our sample. To our knowledge, the present study is the first to evaluate the impact of diverse exercise SBP responses on parameters related to exercise capacity in subjects with type 2 diabetes.

The presence of an elevated SBP response during exercise may be a predictor of future hypertension (17; 18; 26). In contrast, an elevated SBP response to exercise has been also observed in endurance and strength-trained athletes as well as in subjects with prehypertension and seems to be positively associated with exercise capacity (7; 25). In the present study, important parameters related
Blood pressure and exercise capacity in type 2 diabetes

to exercise capacity, namely absolute $\dot{V}O_2$ peak, exercise duration and peak work rate, were positively related to peak exercise SBP. In addition, subjects with an elevated SBP (> 210 mmHg) in response to peak exercise presented higher $\dot{V}O_2$ peak compared to subjects with lower SBP (< 210 mmHg) even after adjustment for age. The literature regarding the BP response to exercise in subjects with diabetes is sparse. A greater diastolic BP (DBP) in response to submaximal exercise has been reported in type 2 diabetes (2) while an exaggerated SBP has also been documented in normoalbuminuric type 1 (3) as well as in type 2 diabetic patients (13).

Type 2 diabetes is related to reduced left ventricular (LV) systolic volume, altered myocardial and diastolic functions and increased arterial stiffness (6; 11; 22). These are all important parameters related to BP regulation and potential contributors to the reduced exercise capacity documented in diabetics. The elevated peak exercise SBP observed in our subjects is probably partly associated with the arterial stiffness observed in subjects with diabetes (4; 6). In theory, a cascade of events will take place following the appearance of arterial stiffness: 1) increased afterload, 2) reduced stroke volume, 3) LV remodelling, 4) increased SBP, 5) diastolic dysfunction, 6) reduced exercise performance and, 7) systolic dysfunction (6; 8). So, how can we reconcile the positive results related to elevated peak SBP observed in our subjects with the reported harmful impacts of diabetes on the cardiovascular function that should normally lead to a reduced exercise performance?
A plausible explanation could be that a relatively more important LV remodelling, induced by diabetes and triggered more specifically by arterial stiffness (6), might be present and induce a transitory adaptive beneficial impact, i.e. a higher cardiac output compared to subjects with lower exercise SBP, before the appearance of diastolic dysfunction. This might override the deleterious impact induced by diabetes on LV function. In athletes, a positive relationship has been reported between a non-pathologic LV hypertrophy with a preserved diastolic function (15), elevated exercise SBP and exercise capacity (9). On the other hand, Poirier et al. demonstrated that diastolic dysfunction influences negatively exercise capacity in subjects with type 2 diabetes (21). In other words, the impact of a relatively more important increased LV mass in subjects with higher exercise SBP, potentially induced by arterial stiffness to compensate for an increase in afterload, could have a transitory positive and relatively more important adaptive impact on exercise SBP and exercise capacity than arterial stiffness *per se* compared to subjects with lower exercise SBP. This positive influence on exercise capacity is probably lost with the appearance of diastolic dysfunction (21). Figure 2 illustrates a hypothetic schematic representation regarding this enhanced, or preserved, exercise capacity observed in subjects with higher peak exercise SBP.

BP response appears to be related to blood glucose control (16). Indeed in the resting state, the presence of hyperglycemia led to an increase in SBP and DBP.
Blood pressure and exercise capacity in type 2 diabetes independently of endogenous insulin in 20 patients with type 2 diabetes (16). A reduced availability of nitric oxide has been suggested as a potential explanation (16). However, in our 2 groups with a marked difference in peak exercise SBP, there was no significant difference between short term (FBG) as well as long term (HbA1c) blood glucose control, suggesting that the BP modulation observed during exercise in these subjects may not have been influence by blood glucose exposure per se.

The principal limitation of the present study is the absence of a control group of non diabetic subjects. Consequently, we used the terms elevated and high SBP instead of exaggerated SBP since we did not compare our results with a “normal” exercise response obtained from a control group. Nevertheless, the goal of this study was to investigate the impact of an elevated exercise SBP on exercise capacity in subjects with type 2 diabetes. Therefore, the group with peak exercise SBP below 210 mmHg could be considered as control subjects since 210 mmHg is a clinically relevant cut-off regarding the exercise-induced hypertensive response (14). Of note, age might have influenced at some point our results but the higher exercise capacity observed in our subjects with higher exercise SBP is still present compared to subjects with lower exercise SBP after adjustment for age. Also, even if all the subjects were carefully screened in light of our inclusion and exclusion criteria, we cannot rule out the possibility that the differences observed in our groups were related to the insulin resistance state and/or the presence of left ventricular diastolic dysfunction. Furthermore, it is already known
that the resting SBP represents an independent predictor of exercise SBP, which explains over 40% of the inter-individual variability (1). In this study, the resting SBP was also related to peak SBP but it explained only 17% of the variance. Since there was no significant difference in terms of resting nor peak exercise HR, it seems unlikely that sympathetic overactivity might have accounted for our results. However, we cannot exclude the possibility that a subtle change in sympatho-vagal activity, i.e. sympathetic predominance, might have influenced our findings (22). Finally, we cannot ignore that these differences might be related to whether the maximal effort was attained or not since we used $\dot{V}O_2$ peak instead of $\dot{V}O_2$ max. However, this is unlikely since our 2 groups reached similar RER both above 1.15 and it was recently shown that $\dot{V}O_2$ peak is likely to be a valid index of $\dot{V}O_2$ max (5).

Further research is needed to evaluate if; 1) these results represent an increase or a preservation of exercise performance, 2) LV remodelling is related to increased peak SBP and exercise capacity in these subjects and, 3) these results will be influenced in subjects with LV diastolic function.

CONCLUSION

Our results suggest that, in subjects with type 2 diabetes without cardiovascular disease, an elevated exercise SBP is not associated with reduced exercise capacity and its modulation is probably not related to glycemic control.
GRANTS

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REFERENCES


Blood pressure and exercise capacity in type 2 diabetes


FIGURE LEGENDS

Figure 1a Relationship between $\dot{V}O_2$ peak and peak exercise systolic blood pressure

SBP: Systolic blood pressure

Figure 1b Relationship between exercise duration and peak exercise systolic blood pressure

SBP: Systolic blood pressure

Figure 1c Relationship between total work rate and peak exercise systolic blood pressure

SBP: Systolic blood pressure

Figure 2 Schematic representation of the parameters influencing the evaluation of exercise capacity in patients with higher peak exercise systolic blood pressure
Table 1  **Baseline characteristics of the groups according to median peak systolic blood pressure**

<table>
<thead>
<tr>
<th></th>
<th>&lt; 210 mmHg</th>
<th>&gt; 210 mmHg</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>14</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>56±8</td>
<td>50±10</td>
<td>0.08</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172±4</td>
<td>173±8</td>
<td>0.84</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>93±14</td>
<td>92±13</td>
<td>0.76</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31±5</td>
<td>31±4</td>
<td>0.66</td>
</tr>
<tr>
<td>FBG (mmol/L)</td>
<td>6.8±1.5</td>
<td>7.1±1.6</td>
<td>0.62</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.5±1.1</td>
<td>6.5±1.2</td>
<td>0.82</td>
</tr>
<tr>
<td>Resting HR (bpm)</td>
<td>74±12</td>
<td>80±11</td>
<td>0.24</td>
</tr>
<tr>
<td>Resting SBP (mmHg)</td>
<td>130±11</td>
<td>139±14</td>
<td>0.06</td>
</tr>
<tr>
<td>Resting DPB (mmHg)</td>
<td>84±9</td>
<td>86±6</td>
<td>0.49</td>
</tr>
<tr>
<td>Duration of diabetes (months; range)</td>
<td>26±35 (0-113)</td>
<td>17±25 (0-74)</td>
<td>0.5</td>
</tr>
<tr>
<td>Therapeutic regimen (n)</td>
<td>Diet only</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Oral hypoglycemic agents</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

Values are mean ± SD

BMI: Body mass index; FBG: Fasting blood glucose; HbA1c: Glycated hemoglobin; HR: Heart rate; SBP: Systolic blood pressure; DPB: Diastolic blood pressure.

HbA1c normal range: 4.3-6.2%
### Table 2  Exercise capacity parameters observed in the groups according to median peak systolic blood pressure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>&lt; 210 mmHg</th>
<th>&gt; 210 mmHg</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total work (W)</td>
<td>169±34</td>
<td>202±32</td>
<td>0.01</td>
</tr>
<tr>
<td>Exercise duration (sec)</td>
<td>725±122</td>
<td>823±131</td>
<td>0.09</td>
</tr>
<tr>
<td>( \dot{V}_{O_2} ) peak (ml·kg(^{-1})·min(^{-1}))</td>
<td>27.0±5.4</td>
<td>31.0±3.6</td>
<td>0.03</td>
</tr>
<tr>
<td>( \dot{V}_{O_2} ) peak (L·min(^{-1}))</td>
<td>2.47±0.39</td>
<td>2.84±0.55</td>
<td>0.046</td>
</tr>
<tr>
<td>Peak HR (bpm)</td>
<td>160±20</td>
<td>169±15</td>
<td>0.18</td>
</tr>
<tr>
<td>Delta HR (bpm)</td>
<td>85±22</td>
<td>89±20</td>
<td>0.64</td>
</tr>
<tr>
<td>( \dot{V}_E ) max</td>
<td>103±26</td>
<td>120±26</td>
<td>0.09</td>
</tr>
<tr>
<td>RER</td>
<td>1.20±0.08</td>
<td>1.16±0.07</td>
<td>0.24</td>
</tr>
<tr>
<td>Peak exercise SBP (mmHg)</td>
<td>193±16</td>
<td>235±19</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Delta SBP (mmHg)</td>
<td>63±21</td>
<td>96±17</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Peak exercise DPB (mmHg)</td>
<td>94±11</td>
<td>97±17</td>
<td>0.60</td>
</tr>
<tr>
<td>Delta DBP (mmHg)</td>
<td>11±13</td>
<td>11±17</td>
<td>0.88</td>
</tr>
<tr>
<td>Peak RPP (mmHg beat min(^{-1}))</td>
<td>30822±4406</td>
<td>39676±5515</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Peak RR (Breath · min(^{-1}))</td>
<td>42±7</td>
<td>43±7</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Values are mean ± SD

\( \dot{V}_{O_2} \) peak: peak oxygen consumption; HR: Heart rate; \( \dot{V}_E \) max: Maximal pulmonary ventilation; RER: Respiratory exchange ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; RPP: Rate pressure product; RR: Respiratory rate
Figure 1a

![Graph showing the relationship between VO\textsubscript{2} peak (L min\textsuperscript{-1}) and peak exercise SBP (mmHg). The Pearson correlation coefficient (r) is 0.405, and the p-value is less than 0.05.]
Figure 1b

![Graph showing the relationship between exercise duration and peak exercise SBP. The graph includes a linear regression line with an r value of 0.414 and a p value less than 0.05.](image)
Figure 1c

![Graph showing the relationship between peak exercise SBP (mmHg) and total work rate (Watts). The graph includes a linear regression line with the equation: $r=0.454$, $p<0.05$.](image-url)
Figure 2

Arterial stiffness

Increased afterload

Reduced stroke volume

Left ventricular remodelling

Increased exercise systolic blood pressure

Increased or preserved exercise performance

Diastolic dysfunction

Reduced exercise performance

Systolic dysfunction