Reduced exercise arteriovenous O₂ difference in Type 2 diabetes

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Bagdi, James C., James L. Aoina, Helen C. Oxenham, Warwick Bagg, and Robert N. Doughty. Reduced exercise arteriovenous O₂ difference in Type 2 diabetes. J Appl Physiol 94: 1033–1038, 2003. —Maximal O₂ consumption (VO₂ max) is lower in individuals with Type 2 diabetes than in sedentary nondiabetic individuals. This study aimed to determine whether the lower VO₂ max in diabetic patients was due to a reduction in maximal cardiac output (Q̇max) and/or peripheral O₂ extraction. After 11 Type 2 diabetic patients and 12 nondiabetic subjects, matched for age and body composition, who had not exercised for 2 yr, performed a bicycle ergometer exercise test to determine VO₂ max, submaximal cardiac output, Q̇max, and arterial-mixed venous O₂ (a-v O₂) difference were assessed. Maximal workload, VO₂ max and maximal a-v O₂ difference were lower in Type 2 diabetic patients (P < 0.05); Q̇max was low in both groups but not significantly different: 11.2 and 10.0 l/min for controls and diabetic patients, respectively (P > 0.05). Submaximal O₂ uptake and heart rate were lower at several workloads in diabetic patients; respiratory exchange ratio was similar between groups at all workloads. Peripheral O₂ delivery and extraction may also be reduced in Type 2 diabetic patients. Reduced arteriovenous O₂ difference contributes to a decreased VO₂ max in Type 2 diabetic patients.

Maximal aerobic capacity; cardiac output

Type 2 diabetes is associated with obesity and sedentary living (17); however, maximal and submaximal O₂ consumption (VO₂) are lower in patients with Type 2 diabetes than in similarly fit individuals of similar age, gender, body composition, and self-reported physical activity (7, 8, 10, 19, 20, 27). These findings suggest that some characteristic of diabetes other than fitness or body composition contributes to decreases in maximal VO₂ (VO₂ max). With the exception of aerobically fit, healthy individuals who can be limited by pulmonary gas exchange (4), VO₂ max is affected by limitations in cardiac output (Q̇), redistribution of blood flow to working muscle, and skeletal muscle O₂ extraction in healthy individuals (21). However, little is known about the mechanism responsible for the lower VO₂ max in Type 2 diabetic patients than in similarly unfit nondiabetic subjects.

There is indirect evidence suggesting that exercise Q̇ may be impaired by Type 2 diabetes. Up to 60% of individuals with Type 2 diabetes have impaired diastolic function (18), which is associated with reduced VO₂ max in healthy subjects (32). Roy et al. (22) showed a lower resting and exercising Q̇ in a combined group of Type 1 and 2 diabetic patients than in nondiabetic controls; however, it is not clear from their findings whether this difference was the result of diabetes or differences in fitness level.

Peripheral O₂ delivery and extraction may also be affected by Type 2 diabetes. Type 2 diabetic patients have impaired nitric oxide-induced vascular function (16, 34), which can result in impaired muscle blood flow during exercise (15). Moreover, Type 2 diabetic patients have reduced oxidative enzyme activity (26), increased percentage of type IIb fibers, and decreased percentage of type I fibers (13). However, these characteristics are similar to those in obese nondiabetic controls (13, 29) and may reflect a lack of fitness, rather than a specific effect of diabetes.

To clarify whether Q̇ and peripheral mechanisms are responsible for the decreased VO₂ max in individuals with Type 2 diabetes, this study compared VO₂, Q̇, and calculated arterial-mixed venous (a-v) O₂ difference in Type 2 diabetic patients with age-, weight-, and fitness-matched controls at maximal and submaximal exercise intensities.

Methods

Subjects and screening. Eleven individuals with Type 2 diabetes and 12 nondiabetic individuals, aged 40–60 yr, completed the study. Only individuals with body mass index between 25 and 40 kg/m² who had performed fewer than three 20-min sessions per week of moderate-intensity physical activity for ≥2 yr were recruited for the study. After providing informed, written consent, all subjects underwent a medical screening protocol. Screening included a medical examination, resting transthoracic echocardiogram, 12-lead exercise electrocardiogram test (Bruce protocol), blood anal-

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yses of fasting glucose, glycosylated hemoglobin, serum lipids, and creatinine, and spot urine analysis for albumin-to-creatinine ratio. Subjects were excluded if they showed clinical or symptomatic evidence of cardiovascular or pulmonary disease, impaired systolic function, or valvular abnormalities on echocardiogram, had uncontrolled hypertension (i.e., had resting blood pressure >160/90 mmHg or were taking >1 antihypertensive medication), showed evidence of impaired renal function (urinary albumin-to-creatinine ratio > 2.5), or were taking insulin. Eight diabetic patients were taking diabetic medications (metformin-glipizide), and two diabetic patients were taking angiotensin-converting enzyme inhibitors for hypertension. No control subject was taking prescribed medication. For the diabetic group, the average duration of diagnosis of diabetes was 5.4 ± 3.1 yr. Subject characteristics are summarized in Table 1.

Experimental measurements and study design. At 1–2 wk after medical screening, subjects performed an incremental workload VO2max test on a cycle ergometer (model ERG 900, Schiller) that maintains constant power output at different pedaling velocities. All testing was performed in the same laboratory at 22–23°C. Initial workloads were set at 25 or 50 W, depending on subject ability. Workload was increased by 25 W each 1-min stage, unless the subject did not believe he or she could perform a full-stage increase, in which case workload increased by 15 W. With use of this individualized protocol, all tests lasted 6–12 min. Breath-by-breath data were collected and analyzed on O2 and CO2 analyzers (models S-3A and CD-3A, respectively, Ametek), which were calibrated with room air and standardized gas containing 6% CO2 before each test. It was assumed that VO2max had been achieved when two of the following three criteria had been met: 1) <2 ml·kg−1·min−1 increase in VO2 with increase in workload, 2) respiratory exchange ratio (RER) > 1.10, and 3) achievement of age-predicted heart rate (31). Failure to meet two of these criteria resulted in a retest or exclusion from further analysis.

Maximal Q (CO2 rebreathing). After ~1 wk, maximal Q (Qmax) and submaximal Q were estimated noninvasively during cycling exercise by the CO2 rebreathing equilibration method using the Fick equation, as originally performed by Collier (3) and described by Jones (9). Gas analyzers were calibrated with room air and standardized gas consisting of 13% CO2 before each test. Q was measured during two 5-min bouts of exercise at 60 and 70% VO2max as established during the VO2max test. To achieve steady state, subjects cycled at a predetermined constant workload equaling 60% or 70% VO2max until a plateau in VO2 occurred and heart rate (as measured by a Polar monitor) fluctuated by less than five beats in successive minutes. Once this happened, the subject briefly held his or her breath while inspired gas was switched to a 3-liter anesthetic bag that contained 12% CO2-88% O2 at 60% VO2max and 13% CO2-87% O2 at 70% VO2max, as recommended by Jones. End-tidal Pco2 was measured and displayed using Chart version 4.0 software on a MacLab computer. Rebreathing continued until Pco2 had reached a plateau or for 15 s. Stroke volume was calculated as Q/heart rate, and a-vo2 difference was calculated as VO2/Q. Because stroke volume is thought to plateau at ~40% VO2max in nonelite athletes (1, 6), maximum stroke volume was estimated as the average of the two submaximal values. Qmax was determined by multiplying the maximal stroke volume by the heart rate obtained at VO2max. With use of this method, a coefficient of variation (SD/mean × 100) of 4.5% has been established for three repeated estimates of Qmax in nondiabetic subjects in this laboratory.

Statistical comparisons. Unpaired Student’s t-tests (2-tailed) were used to compare means between Type 2 diabetic and control groups. Univariate linear regression was performed to identify the relationship between continuous variables. P < 0.05 was considered statistically significant. Values are means ± SD.

RESULTS

Age, body composition, and blood and urinary markers were similar between groups with the exception of high-density lipoprotein cholesterol, which was lower in Type 2 diabetic patients, and glycosylated Hb, fasting glucose, and triglycerides, which were higher in Type 2 diabetic patients (P < 0.05). Seven subjects were excluded by medical screening or failure to achieve VO2max. The resulting groups were 36% (diabetic group) and 58% (control group) female. The data are summarized in Table 1.

Maximal and relative hemodynamic results. Group comparisons at VO2max and 60 and 70% VO2max are summarized in Table 2. The control group achieved higher workloads at 60, 70, and 100% VO2max than the diabetic group. Peak and submaximal VO2 were higher in the control group. RER was similar between groups at each intensity. Heart rate was similar between groups at peak exercise but was significantly lower in the diabetic group at 60 and 70% VO2max. Q and stroke volume were similar between groups at each relative intensity. a-VO2 difference was similar between groups at 60% VO2max (P = 0.12), tended to be higher in the control group at 70% VO2max (P = 0.07), and was significantly higher in the control group at 100% VO2max (P < 0.05).

Hemodynamic results at identical absolute submaximal workloads. The number of subjects in the control and diabetic groups completing incremental exercise stages at 50, 75, 100, 125, and 150 W was 12 and 11, 12 and 12 and 9, 10 and 5, and 8 and 3, respectively. Figure 1A shows that VO2 (l/min) was higher in the
control group at 75 and 125 W (1.03 ± 0.20 vs. 0.80 ± 0.20 and 1.52 ± 0.30 vs. 1.20 ± 0.20, P < 0.05) and tended to be higher at 50 W (0.80 ± 0.20 vs. 0.63 ± 0.20, P = 0.064), 100 W (1.24 ± 0.30 vs. 1.03 ± 0.20, P = 0.058), and 150 W (1.73 ± 0.40 vs. 1.42 ± 0.00, P = 0.061). RER was not significantly different (P > 0.05) at any workload (Fig. 1B). Heart rate was similar at lower workloads but was higher in the control group at 125 and 150 W (Fig. 1C).

In the control group, VO_{2\text{max}} was correlated with Q_{\text{max}} (r = 0.82, P < 0.001) and a-\text{v} O_{2} difference (r = 0.78, P < 0.05). In the diabetic group, VO_{2\text{max}} was not correlated with Q_{\text{max}} (r = 0.14, P > 0.05; Fig. 2A) but was correlated with a-\text{v} O_{2} difference (r = 0.60, P < 0.05; Fig. 2B).

**DISCUSSION**

Q is generally thought to limit VO_{2\text{max}} because of the gross potential imbalance between skeletal muscle capacitance and Q_{\text{max}} (24). Thus, on the basis of VO_{2\text{max}} values, it is not surprising that both groups of subjects had low Q_{\text{max}}. However, the findings of this study provide indirect evidence that VO_{2\text{max}} is further reduced in sedentary Type 2 diabetic patients by an impairment in peripheral O_{2} extraction. VO_{2\text{max}} was 30% lower, Q_{\text{max}} was similar, and maximal a-\text{v} O_{2} difference was 19% lower in diabetic patients than in control subjects matched for physical activity, body composition, and age. Furthermore, VO_{2\text{max}} was correlated with a-\text{v} O_{2} difference, but not with Q_{\text{max}} in Type 2 diabetic patients, suggesting that impaired maximal total body O_{2} extraction contributed to lower VO_{2\text{max}} in Type 2 diabetic patients.

Some methodological factors should be considered when these results are interpreted. The data shown above are dependent on accurate determination of VO_{2\text{max}}. To the best of our ability, these data represented a “true” maximal value based on the fact that only subjects who achieved a plateau in VO_{2} and RER > 1.10 were included. Nonetheless, only two subjects achieved their age-predicted maximal heart rate, and this may have contributed to the low VO_{2\text{max}} in both groups. Because maximal heart rate is used to calculate Q_{\text{max}}, it is conceivable that Q_{\text{max}} values reported here are underestimated; however, the Q_{\text{max}} values obtained at 126 W (in diabetic patients) and 173 W (in controls) are consistent with previously reported submaximal Q measured by the CO_{2} rebreathing method during steady-state exercise at 133 and 200 W in trained nondiabetic subjects (30), suggesting that the values reported here are typical of these exercise intensities.

Medications taken by the diabetic group may have affected peripheral blood flow during exercise. Five patients took “low doses” of sulfonylurea drugs, which may reduce peripheral vascular function (2), and four patients took a biguanidine drug, which may improve endothelial function (14). However, it is impossible to estimate the effect, if any, of these two medications in the diabetic group, particularly during exercise.

Although the results of the present study are similar to results of previous studies that have reported VO_{2\text{max}} to be 20–30% lower in Type 2 diabetic patients than in age-, fitness-, and weight-matched nondiabetic controls (7, 8, 10, 19, 20, 27), the VO_{2\text{max}} values reported here are lower than those reported previously, with one exception (19), in which only female subjects were studied. Although 58% of our control subjects were women, we believe that our control subjects may represent a less fit sample than has been previously reported. This contention is supported by the fact that Q_{\text{max}}, which is lower in less fit individuals (1), was comparable to that in a group of Type 1 and Type 2 diabetic patients (22) but significantly lower than in healthy, nontrained subjects with Q_{\text{max}} of 17–22 l/min (1, 22, 23).

Maximal heart rate was lower than age-predicted norms (31), which likely contributed to low Q_{\text{max}} in the present study; however, an attenuated increase in exercise stroke volume may also have contributed. Maximum stroke volume in both groups was ~70 ml/beat, which is considerably lower than previously reported

| Table 2. Maximal and relative submaximal hemodynamic responses to exercise |
|-------------------------|-------------------------|-------------------------|-------------------------|
|                         | 60% VO_{2\text{max}}    | 70% VO_{2\text{max}}    | 100% VO_{2\text{max}}   |
|                         | Con                     | Diab                    | Con                     | Diab                    | Con                     | Diab                    |
| Power, W                | 90.4 ± 29.3             | 58.2 ± 27.4*            | 111.7 ± 34.1            | 75.0 ± 28.5*            | 172.5 ± 45.3            | 125.9 ± 33.9*            |
| VO_{2}                  | l/min                   |                         |                         |                         |                         |                         |
|                         | 1.17 ± 0.35             | 0.85 ± 0.20             | 1.34 ± 0.39             | 0.96 ± 0.19             | 1.90 ± 0.54             | 1.33 ± 0.21*             |
| ml·kg^{-1}·min^{-1}     | 14.61 ± 3.93            | 11.20 ± 2.19            | 16.82 ± 4.51            | 12.74 ± 2.05*           | 23.77 ± 6.41            | 17.57 ± 2.26*            |
| VO_{CO2}                | l/min                   |                         |                         |                         |                         |                         |
|                         | 1.11 ± 0.29             | 0.84 ± 0.28             | 1.39 ± 0.35             | 1.04 ± 0.30             | 2.22 ± 0.56             | 1.58 ± 0.25*             |
| ml·kg^{-1}·min^{-1}     | 14.16 ± 4.58            | 11.04 ± 2.84            | 17.63 ± 5.36            | 13.62 ± 3.05*           | 27.84 ± 6.85            | 20.93 ± 2.66*            |
| Heart rate, beats/min   | 120 ± 12                | 110 ± 71                | 143 ± 13                | 127 ± 11*               | 160 ± 13                | 149 ± 22                 |
| Stroke volume, ml       | 66.7 ± 13.9             | 66.5 ± 13.1             | 71.6 ± 14.3             | 70.1 ± 14.9             | 69.15 ± 13.65           | 68.3 ± 13.5              |
| a-\text{v} O_{2} difference, ml/l000 | 13.67 ± 2.61           | 11.86 ± 2.76            | 13.10 ± 2.63            | 11.11 ± 2.34            | 16.75 ± 2.96            | 13.54 ± 2.73*            |

Values are means ± SD. VO_{2}, O_{2} uptake; VO_{2\text{max}}, maximal VO_{2}; VO_{CO2}, CO_{2} output; RER, respiratory exchange ratio; Q, cardiac output; a-\text{v} O_{2} difference, arterial-mixed venous O_{2} difference. *P < 0.05; †P < 0.01 vs. control.
values in sedentary controls (8, 23). In healthy young control subjects examined in this laboratory, average maximal stroke volume was 112 ml (unpublished findings). Had the control subjects in this study achieved similar stroke volumes, their $Q_{\text{max}}$ would be comparable with those reported in previous studies in healthy controls. Instead, their stroke volumes were comparable to those reported after deconditioning by prolonged bed rest (8, 25), reaffirming our contention that these subjects represented a less aerobically fit population than previous investigations. We can only assume that resting values were normal on the basis of normal resting left ventricular end-diastolic and end-systolic dimensions and fractional shortening, which were similar in both groups.

The reasons for the difference in $a-\bar{v} O_2$ difference between groups can only be speculated from these data. The $a-\bar{v} O_2$ difference values in our ~50-yr-old diabetic group were only slightly higher than those reported in 60- to 69-yr-old men (28), suggesting that such low values may be normal for this age group; however, values in the age-matched control group were comparable to previous values in young subjects (1), suggesting that some characteristic of diabetes, independent of age and fitness, resulted in a lower $a-\bar{v} O_2$ difference.

Increases in mixed venous $O_2$ content, caused by a maldistribution of blood flow and/or reduced oxidative capacity of skeletal muscle, may explain this difference. Type 2 diabetic patients have impaired nitric oxide-mediated vascular function (34), which inhibits peripheral vasodilation (16). Maxwell and colleagues (15) showed that inhibition of endothelium-derived nitric oxide reduced the distribution of fluorescent microspheres to limb skeletal muscle after exercise. Furthermore, microvascular complications such as retinopathy and nephropathy, which are associated with impaired

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**Fig. 1.** Submaximal workload vs. $O_2$ consumption (A), respiratory exchange ratio (B), and heart rate (C) in control and Type 2 diabetic patients during an incremental bicycle ergometer test. Values are means ± SD. *Significantly different from Type 2 diabetes group ($P < 0.05$).

**Fig. 2.** Linear relationship between individual values for maximal $O_2$ consumption vs. maximal cardiac output (A) and maximal arterial mixed venous ($a-\bar{v}$) $O_2$ difference (B) in Type 2 diabetic patients.
vascular function, have been associated with reduced exercise capacity in Type 2 diabetic patients (5). Thus the diabetic patients in this study may have had increased mixed venous O₂ content resulting from decreased blood flow to working muscles during cycling exercise. This contention is supported by recent findings that have shown that exercise training improves peak V₀₂ (12) and peripheral vascular function (11) in Type 2 diabetic patients.

It is difficult to understand why submaximal V₀₂ is lower in Type 2 diabetic patients. a-ν O₂ difference was reduced at 100% V₀₂ max and tended to be lower at 70% V₀₂ max (P = 0.07) in diabetic patients. According to the Fick equation, this suggests that diabetic patients should have required higher Q to meet the O₂ demand of submaximal activities. However, heart rate was lower in diabetic patients than in controls, and stroke volume at submaximal workloads was similar to that in controls. Although difficult to explain, these findings are similar to those of Regensteiner et al. (20), who reported that V₀₂ was lower during identical submaximal workloads in Type 2 diabetic patients. They showed that this resulted from slower V₀₂ and heart rate kinetic responses to increased submaximal workload (19).

Alterations in cellular properties of skeletal muscle may have affected submaximal V₀₂. Type 2 diabetic individuals have increased type IIb-to-type I fiber ratio (13) and lower oxidative enzyme activity (26, 29, 33) than non diabetic subjects. These reductions in the oxidative capacity of skeletal muscle may have resulted in less O₂ being consumed by working muscles in diabetic patients during submaximal exercise. Theoretically, increases in RER would be expected because of the resultant increase in anaerobic metabolism to meet the energy demand of work. Although not significant, it is noteworthy that RER was higher in diabetic patients at every workload.

In summary, the results of this study confirm previous findings that sedentary individuals (diabetic and nondiabetic) have low V₀₂ max and Qₑ max. However, Type 2 diabetic patients also had lower maximal a-ν O₂ difference than nondiabetic individuals of similarly low fitness, which may have further reduced their V₀₂ max. The reasons for this are not known; however, impairment in peripheral vascular function and/or skeletal muscle O₂ extraction are areas for further investigation.

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