HIGHLIGHTED TOPIC | Mechanisms of Sympathetic Regulation in Cardiovascular Disease

Altered hemodynamics during muscle metaboreflex in young type 1 diabetes patients

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Robert S, Marongiu E, Pinna M, Angius L, Olla S, Bassareo P, Tocco F, Concu A, Milia R, Crisafulli A. Altered hemodynamics during muscle metaboreflex in young type 1 diabetes patients. J Appl Physiol 113: 1323–1331, 2012. First published June 14, 2012; doi:10.1152/japplphysiol.00280.2012.—A reduction in catecholamine levels during exercise has been described in young subjects with type 1 diabetes mellitus (DM1). It has been suggested that type 1 diabetes per se is associated with the loss of sympathetic response before any clinical evidence. Considering that an increase in sympathetic drive is required for normal cardiovascular response to muscle metaboreflex, the aim of this study was to assess the hemodynamics during metaboreflex in DM1 patients. Impedance cardiography and wave contour analysis were used to measure hemodynamics during metaboreflex activation, obtained through postexercise ischemia in 14 DM1 patients and in 11 healthy controls (CTL). Principal results were: 1) blunted blood pressure response during metaboreflex was observed in DM1 patients compared with the CTL; 2) reduced capacity to increase systemic vascular resistance was also witnessed in DM1 subjects; 3) DM1 subjects reported higher stroke volumes as a consequence of reduced cardiac afterload compared with the CTL, which led to a more evident cardiac output response, which partially compensated for the lack of vasoconstriction. These facts suggest that cardiovascular regulation was altered in DM1 patients and that there was a reduced capacity to increase sympathetic tone, even in the absence of any overt clinical sign. The metaboreflex test appears to be a valid tool to detect early signs of this cardiovascular dysregulation.

Circulatory response to muscle metaboreflex is attracting growing interest in the scientific community, since it is thought to contribute significantly to cardiovascular regulation during exercise by providing continuous feedback to the cardiovascular control areas on the metabolic status of contracting muscles (7, 43). The afferent arm of this cardiovascular reflex is activated whenever group III and IV free nerve endings in the musculature sense the accumulation of exercise-derived metabolic by-products (2, 35), and this activation, in turn, induces an increment in sympathetic tone. It is widely ascertained that group III and IV nerve endings project to the dorsal horn of the spinal cord. However, less is known about the central pathways of the metaboreflex, even though it appears that the medulla is essential for its expression. Putative metabolites involved in this reflex are lactic acid, adenosine, potassium, diprotonated phosphate, hydrogen ion, and arachidonic acid products (35, 39, 42).

The hemodynamic adjustments in response to this reflex are complex and involve interplay among cardiac performance, cardiac preload, systemic vascular resistance (SVR), and heart rate (HR) changes (13, 13a, 13c, 21, 27). The result is that blood pressure (BP) increases, but the leading phenomenon responsible for this increment could be a flow-mediated or a vasoconstriction-mediated mechanism or both (2, 12, 13a, 20, 30, 36, 40). This reflex has been demonstrated to be involved in the genesis of exercise intolerance in patients with heart failure, since it has been associated with the elevated sympathetic outflow that takes place in this disease (13b, 28b, 33, 34). Recently, the metaboreflex has also been found to be overactive in other conditions, such as hypertension and postmenopause (8, 14, 37).

In young subjects with type 1 diabetes mellitus (DM1), a reduction in catecholamine levels during exercise has been described frequently (5, 18). This fact has been associated with reduced sensitivity to catecholamine of tissues, such as the medulla glans, myocardium, and others (18). Moreover, in type 1 diabetes without clinically overt autonomic neuropathy, the response of adrenaline to hypoglycemia is blunted, thus suggesting that type 1 diabetes per se is associated with loss of sympathetic response to various stimuli before any clinical evidence (5, 6, 38). Although this condition seems to be well compensated and does not cause any clinical symptoms, the situation could deteriorate progressively and lead to symptomatic manifestations of sympathetic deficit.

Taking into account that elevated sympathetic drive is the key characteristic of metaboreflex (2, 7, 43), we wondered whether DM1 patients without any sign of autonomic neuropathy would show sympathetic impairment in response to metaboreflex. In particular, we wondered whether a test eliciting metaboreflex would help to identify early dysfunction in sympathetic activation. Such information would allow cardiovascular regulation of these patients to be monitored well before they become symptomatic. Thus the aim of this study was to assess the hemodynamic responses to metaboreflex recruitment in DM1 patients. To the best of our knowledge, no other investigation on this topic has been carried out.
METHODS

Study Population

Two groups of subjects were studied.

1. DMI group. Fourteen subjects (three females/11 males) affected by DMI were enrolled. Patients’ anthropometric characteristics are shown in Table 1. Study inclusion criteria were 1) 18–40 years; 2) DMI diagnosis reached at least 18 mo previously; 3) a stable insulin regimen involving either insulin pump or insulin long- and short-acting insulin; 4) body mass index (BMI) of 20–25; 5) no severe episodes of hypoglycemia within previous 2 wk; and 6) no sign of autonomic neuropathy at neurological examination nor of orthostatic hypotension. At the time of the study, their mean level ± SE of hemoglobin A1c was 7.1 ± 0.26%.

2. Control group. Eleven healthy controls (CTL; two females/nine males) similar in age to the DMI group were enrolled. The absence of cardiac or metabolic disease was confirmed by anamnesis and physical examination. Subjects’ demographic characteristics are reported in Table 1.

Written consent was obtained from all participants. The study was approved by the University of Cagliari local ethical committee and conforms to the principles of the Helsinki Declaration.

Experimental Design

All experiments were carried out in a temperature-controlled, air-conditioned room (22°C; relative humidity 50%). A preliminary incremental exercise test on an electromagnetic braked cycle ergometer (Tunturi EL 400, Finland) was performed by all individuals, prior to entering the study, to characterize subjects’ physical capacity. The test consisted of a linear increase of workload (10 W/min or 30 W/min, depending on sex and subject fitness status), starting at 10 W at a pedaling frequency of 60 rpm until exhaustion, which was taken as the point at which the subject experienced muscle fatigue (i.e., was unable to maintain a pedaling rate of at least 50 rpm). Achievement of maximum oxygen uptake (VO2max) was considered as the attainment of at least two of the following criteria: 1) a plateau in VO2 despite increasing speed (<80 ml/min); 2) a respiratory exchange ratio >1.10; and 3) a HR >10 beats/min of predicted HRmax, calculated as 220 – age (19). VO2, carbon dioxide output (VCO2), and pulmonary ventilation (Ve) were measured by breath throughout the preliminary test by means of a metabolic measurement cart (Breeze; Medical Graphics, St. Paul, MN), calibrated immediately before each exercise test. The mean ± SE values of Wmax, HRmax, VO2max, VCO2max, and Ve max reached by subjects in both groups are reported in Table 1. After this preliminary test (the interval was at least 3 days), each subject underwent the following study protocol, randomly assigned to eliminate any order effect. A. Postexercise muscle ischemia session. The postexercise muscle ischemia (PEMI) session involved 3 min of resting, followed by 3 min of exercise consisting of a rhythmic (30 compressions/min) dynamic handgrip at 30% of the maximum assessed as the peak reached during five previous maximal compressions on a hydraulic dynamometer (MAP 1.1; Kern & Sohn, Balingen, Germany). Exercise was followed by 3 min of PEMI on the exercised arm, induced by rapidly (<3 s) inflating an upper-arm biceps tourniquet to 50 mmHg above peak exercise systolic pressure. The cuff was kept inflated for 3 min. A further 3 min of recovery were allowed after the cuff was deflated for a total of 6 min of recovery. This protocol has been shown to trap the muscle metabolites in the exercising limb and to maintain stimulation of the metaboreceptors (13b, 13c, 28, 39).

B. Control exercise recovery session. The control exercise recovery (CER) session included the same rest-exercise protocol performed for PEMI, followed by a CER of 6 min without tourniquet inflation.

C. Cold pressor test session. We used the cold pressor test (CPT) session as a second model of sympathetic neural activation, as it has been shown to be capable of activating central vasomotor processes and their efferent pathways thereby increasing sympathetic tone (22, 44). After 3-min resting periods, the subjects performed CPT, which consisted of immersing the dominant hand in cold water (5–10°C) for 2 min. Afterward, 3 min of recovery were allowed.

Sessions A, B, and C were distanced from each other by at least 1 day (interval, 1–7 days). Throughout all phases of the study, hemodynamic parameters were measured by means of impedance cardiography (NCCOM 3; BoMed Medical Manufacturing, Irvine, CA), which allows continuous, noninvasive cardiodynamic measuring and has been used in similar experimental settings (12, 13, 13a–c).

The data acquisition method is described in detail in our previous work (12, 13, 13a–c). Briefly, NCCOM 3-derived analog traces of electrocardiogram, thorax impedance (Zt), and Zt first derivative (Zti) and their efferent pathways thereby increasing sympathetic tone (13c) were inspected for ectopic beats and analyzed using power spectral analysis based on the fast Fourier transform (Kubios HRV analysis software 2.0; Biosignal Analysis and Medical Imaging Group, University of Kuopio, Finland). Two main components were considered: that in the frequency band from 0.04 to 0.15 Hz [low frequency (LF)] and that in the range from 0.15 to 0.4 Hz [high frequency (HF)]. It is widely accepted that HF power reflects vagal modulation of HR and

Table 1. Demographic characteristics of the study population

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<th>DMI</th>
<th>CTL</th>
<th>P value</th>
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<tr>
<td>Age (y)</td>
<td>29.18 ± 1.29</td>
<td>29.1 ± 1.61</td>
<td>P &gt; 0.05</td>
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<tr>
<td>Weight (kg)</td>
<td>64.55 ± 10.08</td>
<td>63.27 ± 2.70</td>
<td>P &gt; 0.05</td>
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<tr>
<td>Height (cm)</td>
<td>170.52 ± 10.61</td>
<td>168.27 ± 2.83</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>BMI</td>
<td>22.22 ± 0.45</td>
<td>22.24 ± 1.18</td>
<td>P &gt; 0.05</td>
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<tr>
<td>Wmax (W)</td>
<td>222.14 ± 15.63</td>
<td>178.58 ± 22.13</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>HRmax (beats/min)</td>
<td>167.25 ± 5.85</td>
<td>172.5 ± 6.61</td>
<td>P &gt; 0.05</td>
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<tr>
<td>VO2max (ml · kg·min⁻¹)</td>
<td>33.23 ± 1.79</td>
<td>27.95 ± 2.53</td>
<td>P &gt; 0.05</td>
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<tr>
<td>VCO2max (ml · kg·min⁻¹)</td>
<td>42.13 ± 2.55</td>
<td>37.86 ± 3.48</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Ve max (l/min)</td>
<td>68.73 ± 4.85</td>
<td>67.9 ± 6.43</td>
<td>P &gt; 0.05</td>
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Values are means ± SE. The table also shows maximum values of work rate (Wmax), heart rate (HRmax), oxygen uptake (VO2max), carbon dioxide production (VCO2max), and ventilation (Ve max) reached during the preliminary incremental test. DMI, type 1 diabetes mellitus; CTL, control; BMI, body mass index.
that the LF power reflects complex interplay between sympathetic and vagal modulation. The very low component (<0.03 Hz) was not taken into account because of its uncertain physiological meaning (32). The ratio LF/HF was also calculated and used as an index of sympatho-vagal balance.

In DM1 patients, blood-glucose levels at rest and at the end of the metaboreflex were also measured to detect whether any episode of hypoglycemia had occurred. To that end, a portable blood-glucose monitor system for blood-glucose self-monitoring was used (Accu-Chek Aviva, Roche Diagnostics, Indianapolis, IN) (16).

**Data Analysis**

Beat-to-beat hemodynamic and breath-by-breath ventilatory collected data were averaged for 3 min. Differences between groups in means ± SE of variables’ absolute values during rest periods preceding handgrip runs were studied by means of the two-way ANOVA for repeated measures with group (DM1 or CTL) and condition (rest before CER or before PEMI test) as main factors, followed by Bonferroni post hoc when appropriate. Responses during exercise and recovery are reported as means ± SE percent changes from corresponding rest values, and comparisons were performed using the two-way ANOVA for repeated measures (factors: condition and group), followed by Bonferroni post hoc when appropriate. Statistical analysis was carried out by using commercially available software (GraphPad Prism; GraphPad Software, La Jolla, CA). Statistical significance was established as P values of <0.05 in all cases.

**RESULTS**

The protocol was completed by all subjects, and no complaints of unbearable pain or discomfort during the periods of arm circulatory occlusion or during CPT were reported. No sign of hypoglycemia, before or after tests were conducted, was observed in the DM1 patients, as their means ± SE of blood-glucose level were 121.12 ± 14.05 and 135.25 ± 12.3 mg/dl, respectively, at rest and at the 1st min after metaboreflex. Table 1 shows group similarity in terms of age, height, mass, and BMI. Moreover, Table 1 reports that the VO2max, VCO2max, Ve max, and HRmax values during the incremental test were achieved by the groups. Table 2 shows absolute values of data recorded during rest periods preceding handgrip strains. Statistics revealed that groups started with similar levels of circulatory and ventilatory parameters.

Cardiovascular and ventilatory time courses during the PEMI and the CER test are shown (see Figs. 1–3). HR (Fig. 1) increased during all exercise sessions compared with rest and promptly returned to rest level during recovery. No difference in the HR time course between the groups was observed. Furthermore, the HR response was not affected by PEMI maneuvers. SV (Fig. 1) increased during the metaboreflex period of both the DM1 and the CTL group compared with rest. In the DM1 group, SV increased with respect to the corresponding time point of the CTL group. In both groups, CO rose in response to handgrip efforts (Fig. 1). In the DM1 group, CO maintained higher levels than rest during the first part of recovery from both the PEMI and the CER test. Subsequently, CO returned to baseline. Differently, during the CER test of the CTL group, CO returned to baseline once exercise ceased, whereas during the first part of recovery from the PEMI test, CO maintained higher levels compared with rest.

Concerning PEP/VET (inversely related to contractility; Fig. 2), a decrease was observed (i.e., contractility increased) during the exercise runs of both groups compared with rest. This parameter also maintained lower values during the circulatory occlusion of the PEMI test compared with rest. There was no difference between groups in the PEP/VET time course. Figure 2 shows the MBP time course, which exhibited similar behavior in the two groups: it increased in response to exercise and remained elevated with respect to rest in the PEMI sessions. However, MBP response was lower in the DM1 than in the CTL group. Thus in the CTL group, the PEMI maneuver induced a more pronounced MBP response than in the DM1 group. A noteworthy difference between the groups was seen in the SVR response (Fig. 2). In fact, this parameter increased during the PEMI session in the CTL group, whereas it remained stable throughout the test in the DM1 group.

Figure 3 highlights time courses of ventilatory data. VO2 increased from the rest level in response to handgrip exercise in both groups. In all tests, this variable also remained higher compared with rest during the first recovery period to return to baseline during the remaining recovery. This behavior was not affected by metaboreflex activation nor by group. An almost identical time course was shown by VCO2 and Ve.

Figure 4 shows changes in the power of LF and HF. Values are displayed in both absolute and normalized units. There was no main effect detected for LF and HF power, whereas the LF/HF ratio was increased by the PEMI maneuver compared with the CER condition in both groups.

Finally, Table 3 demonstrates that the hemodynamic response to the CPT was not different between groups, although

![Table 2. Absolute values of hemodynamic data during the rest periods preceding PEMI and CER tests in both groups under study](https://www.jappl.org)
it should be noted that the HR response was close to reaching statistical significance ($P = 0.084$) since HR tended to decrease rather than to increase during the CPT in the DM1 group. Moreover, MBP tended to be lower in DM1 subjects, even though in this case as well, statistical significance was not reached.

**DISCUSSION**

To the best of our knowledge, this is the first study to focus on the hemodynamic response to the muscle metaboreflex in DM1 patients. The principal, new findings from the present investigation are that 1) DM1 patients had a blunted MBP response during the metaboreflex recruitment compared with controls; 2) DM1 subjects also exhibited a reduced capacity to increase SVR in response to the metaboreflex; and 3) SV was higher during the metaboreflex in DM1 patients than in controls. Taken together, these facts suggested that cardiovascular regulation was altered in DM1 patients.

It is well ascertained that cardiovascular response to the muscle metaboreflex elicited by PEMI involves an increase in sympathetic tone, which is responsible for the increase in BP that takes place in this setting (13b, 13c, 15, 29, 42). The rise in BP is the consequence of a combination of SVR and CO increments. That is, BP can rise because of arteriolar constriction and/or a flow-mediated mechanism. Both of these phenomena are under the control of the autonomic nervous system, which operates to increase arteriolar tone and/or HR and cardiac performance (7, 13, 13b, 13c, 40).

The blunted MBP response to metaboreflex found in the present study suggests that the capacity to elevate the sympathetic tone is impaired in DM1 patients. This finding is consistent with the concept that some form of autonomic failure is present in DM1 patients, even in the absence of an overt, autonomic neuropathy (5, 6, 38). Catecholamine levels were reported to be lower in type 1 diabetic subjects than in controls, both at rest and during exercise (1, 18, 38). It was speculated that one explanation for this phenomenon is that repeated episodes of overt or subclinical hypoglycemia may reduce the capacity to activate the sympathetic tone, thus progressively leading to autonomic failure (17, 25). This reduced sympathetic activity seems to be well tolerated at an early age, since the exercise capacity of young DM1 subjects was found to be...
normal (17). However, although this condition does not appear to induce any clinical manifestation, it could deteriorate progressively and lead to symptomatic manifestations of sympathetic deficit.

Together with the blunted MBP response, the present investigation also shows that the capacity to increase SVR (i.e., to induce arteriolar vasoconstriction) was impaired in DM1 patients, and this fact further supports the concept that an autonomic deficit was present in DM1 subjects. It is, however, noteworthy that these patients partially compensated for the lack of vasoconstriction by increasing SV with respect to controls. This phenomenon led to a more evident CO response in the DM1 group compared with the CTL group during the metaboreflex. In our opinion, the higher SV observed in DM1 patients was the consequence of a reduced cardiac afterload, which probably caused a more efficient cardiac emptying in these subjects. Indeed, cardiac performance was very similar between groups, as testified by the PEP/VET behavior (inversely related to myocardial performance), and consequently, it could not be responsible for the phenomenon.

Despite the fact that the blunted SVR response would suggest that there was a reduced sympathetic response in DM1 subjects, the very similar HR behavior seen between groups should be considered, and this fact seems to speak against the occurrence of a reduced sympathetic tone in the DM1 group during the metaboreflex. This phenomenon could be explained by taking into account that the baroreflex stimulation was also reduced in this setting, since the MBP response was blunted compared with controls. It is well known that the baroreflex buffers the metaboreflex-induced increase in sympathetic tone.
by increasing the parasympathetic tone at the sinus node. Hence, it is possible that during the metaboreflex of the DM1 subjects, a reduction in both sympathetic and parasympathetic tone took place, thus explaining the similar HR response between groups. As a consequence, it appears that it is not possible to detect any sympathetic impairment during the metaboreflex, looking at HR behavior alone. Rather, the integrate cardiovascular response, including BP, SVR, and CO, should be investigated to discover early signs of sympathetic dysfunction. In good accordance with this assertion was the finding that the LF and HF components of the HR power spectrum and the LF/HF ratio were not different between groups, thus indicating that at the sinus node, the metaboreflex activation led to a similar sympatho-vagal balance in both groups of subjects.

Collectively, the cardiovascular data of the present study seem to indicate that the cardiovascular regulation to the muscle metaboreflex is impaired in DM1 subjects. It should be emphasized that our study population did not show any sign of autonomic neuropathy and that its exercise capacity was similar to that of the CTL group. A practical implication of the present investigation is that the metaboreflex test appears to be useful in detecting early signs of dysfunction in sympathetic regulation. Therefore, the metaboreflex may become a routinely used test to monitor the cardiovascular status of DM1 patients. Moreover, it should be underlined that the CPT did not find any difference in terms of HR and MBP between the DM1 and the CTL groups, even though diabetics showed the tendency to have a blunted response in both parameters. Thus the CPT probably does not offer the same sensitivity as the
metaboreflex in detecting early impairments in circulatory regulation, although this outcome was probably due to the fact that we did not enroll enough patients to reach statistical significance.

It should be underlined that in our study, only subjects with DM1 were enrolled. Thus we cannot know whether the sympathetic impairment shown by DM1 patients is also present in patients with type 2 diabetes mellitus. Our hypothesis is that individuals with type 2 diabetes would show a rather different hemodynamic response to metaboreflex compared with DM1 subjects, since they often have insulin resistance and hyperinsulinemia, which normally causes a sympathetic overactivation, as reported by previous research (24, 41). Hence, it is possible to hypothesize that in the absence of neuropathy, type 2 diabetic patients would experience a greater sympathetic tone compared with DM1 subjects. However, this hypothesis remains speculative, and further study is needed to clarify the point.

Data of the present study support the concept that the metaboreflex-induced increase in BP is the consequence of both SVR and CO increments. In contrast to what we found in the present work, some previous experiments reported no significant changes in CO during PEMI, whereas substantial peripheral vasoconstriction took place (3, 28). These studies concluded that the pressor response during PEMI was the consequence of peripheral vasoconstriction. However, other studies in the human and in the animal setting support our findings that the metaboreflex-induced increase in BP also relies on a flow-mediated mechanism (28b). Moreover, very recently, it was found in dogs that the mechanisms involved in the muscle metaboreflex response are continuously dependent on whether a rise in CO occurs; i.e., whether vasoconstriction

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<th>DM1</th>
<th>CTL</th>
<th>P value</th>
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<tr>
<td>HR</td>
<td>95.46 ± 3.08</td>
<td>102.05 ± 1.22</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>SBP</td>
<td>104.65 ± 2.37</td>
<td>109.35 ± 2.99</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>DBP</td>
<td>109.45 ± 4.3</td>
<td>116.23 ± 2.52</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>MBP</td>
<td>106.67 ± 3.25</td>
<td>113.31 ± 3.46</td>
<td>&gt; 0.05</td>
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Values are means ± SE. SBP, systolic blood pressure; DBP, diastolic blood pressure.
occurs depends on whether CO rises (20). Thus our findings seem to be in line with the concept that the rise in BP during the metaboreflex may not be solely the consequence of a neurally induced increase in peripheral vascular resistance, rather that it also depends on the possibility to increase CO.

Limitations of the Present Study

A possible limitation of the present investigation is the use of impedance cardiography to measure hemodynamic. It should be considered that the “gold standard” for hemodynamic assessment includes the Fick and the dye-dilution methods, which, however, are invasive and not advisable in subjects who do not require invasive procedures for clinical purposes. Among noninvasive techniques, the choices are restricted to rebreathing, Doppler echocardiography, and impedance cardiography. The impedance method—likewise, rebreathing and Doppler echocardiography—suffers from some limitations (45). Probably the major source of errors with this technique is that hard efforts affect impedance traces by generating artefacts due to legs’ and chest’s movements. To overcome this potential source of error, a postacquisition analysis procedure, selected from stored signal impedance traces not affected by artefacts, was used. We used the same method previously in similar studies dealing with metaboreflex (12, 13, 13a–c). This method, although time consuming, has been demonstrated to be reliable and reproducible. Moreover, the mild exercise protocol chosen in the present investigation did not generate either great enhancement in ventilation or marked chest movements. So, although the impedance method suffers from difficulties, we think that it is suitable for studies such as the present one.

In conclusion, present data indicate that DM1 patients had a blunted BP response during the metaboreflex because of a reduced capacity to increase SVR. However, as a consequence of a reduced cardiac afterload, their SV response was higher than that of controls, and this phenomenon led to a more evident CO response that partially compensated for the lack of vasoconstriction. All of these facts suggest that the cardiovascular regulation is altered in DM1 patients and that there is a reduced capacity to increase sympathetic tone, even in the absence of any overt clinical sign. The metaboreflex test appears to be able to detect early signs of this cardiovascular dysregulation.

GRANTS

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DISCLOSURES

The authors have no conflicts of interest that are directly relevant to the content of this manuscript.

AUTHOR CONTRIBUTIONS


REFERENCES


