REVIEW ARTICLE

Consequences of Type 1 and 2 Diabetes Mellitus on the Cardiovascular Regulation During Exercise: A Brief Review

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Abstract: *Introduction*: One challenging problem in patients suffering from Diabetes Mellitus (DM) is the elevate incidence of cardiovascular events. Exercise has been proved useful in reducing cardiovascular risks in these patients. However, both type 1 and 2 DM significantly affect the cardiovascular response during exercise. Therefore, on one side exercise is considered to be a valid therapeutic tool for DM, whereas on the other side during exercise these patients may experience troubles in the cardiovascular regulation.

Background: Several impairments at central and at peripheral level have been reported during exercise in both types of DM. For example, sympathetic dysfunctions have been demonstrated in type 1 and 2 DM. Furthermore, impairments in hemodynamics have been often reported. The purpose of the present paper is to briefly review the latest data on the role played by type 1 and 2 DM in the cardiovascular regulation during dynamic exercise.

Conclusion: Hemodynamic dysfunctions may develop in both type 1 and 2 DM during exercise. However, these cardiovascular dys-regulations are different between the two kinds of diabetes.

1. INTRODUCTION

Type 1 and 2 *Diabetes Mellitus* (DM) are increasing their prevalence worldwide. Especially type 2 DM is a concerning medical problem since it is linked to obesity and metabolic syndrome, which are growing by alarming proportions. One of the challenges is the elevate incidence of cardiovascular events in these two pathologies, which are significantly higher in DM patients as compared to normal individuals.

Although both type 1 and 2 DM are characterised by chronic hyperglycaemia, the physiopathology is very different between the two states. The key difference between type 1 and 2 DM is the insulin production. Type 1 DM is caused by the deterioration of the pancreatic ß cells because of an auto-immune process. This results in a progressive reduction of insulin production until its total abolition [1]. Differently, type 2 DM is a metabolic disease characterised by chronic hyperglycaemia due to both resistance to insulin action at tissue level (especially at the striated muscle and at the adipose cells) and to a defect in insulin secretion of ß cells, which prevents insulin resistance to be compensated for by enhanced insulin production [2]. Thus, while insulin is virtually absent in type 1 DM, type 2 DM is characterised by a reduced capacity of peripheral tissues to regulate glucose homeostasis in response to insulin.

Exercise has been demonstrated useful in reducing cardiovascular risk in both type of diabetic patients. However, type 1 and 2 DM significantly affect the cardiovascular response during exercise because of potential dysregulation at various cardiovascular levels.

Therefore, on one side exercise is considered a valid therapeutic tool for DM, whereas on the other side these patients may experience troubles in regulating the cardiovascular apparatus during exercise. For example, in type 1 DM a reduction in catecholamine levels during exercise has been frequently described and this fact has been associated with a reduced sensitivity to catecholamine of tissues such as the medulla glands and myocardium. Even though this condition seems to be well compensated and does not cause any clinical symptoms, this situation may progressively deteriorate and lead to symptomatic manifestations of sympathetic deficit during effort [3-5]. Differently, type 2 DM and insulin resistance have been frequently reported to increase sympathetic tone both at rest and during exercise [6-8]. This fact may in turn induce increments in systemic vascular resistance and elevated blood pressure response to effort. Moreover, other hemodynamic deficits at central and peripheral level may develop in the two types of diabetes.

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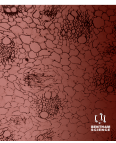
The purpose of the present paper is to review the latest data on the role played by type 1 and 2 DM in the cardiovascular regulation during dynamic exercise.

2. THE CARDIOVASCULAR REGULATION DURING EXERCISE IN HEALTHY SUBJECTS

It is well known that arterial blood pressure (ABP) can be expressed by the following equation:

$$ABP = CO*SVR,$$

where CO is cardiac output and SVR is systemic vascular resistance.

When dynamic exercise is performed with large muscle mass, such as during running, cycling, swimming etc., an intense metabolic vasodilation occurs in the contracting muscles due to functional sympatholysis, thereby causing a reduction in SVR in proportion with the intensity of the effort and the muscle mass being activated [9-15]. This is a challenge for the cardiovascular apparatus since it potentially leads to a drop in ABP, with cerebral hypoperfusion and fainting. However, most of times cardiovascular control mechanisms successfully counteract exercise-induced muscle vasodilation so that exercise is performed daily by billions people without any complication. This because CO is contemporary increased and compensates for the reduced SVR [16-18]. Actually, in normal individuals dynamic exercise is characterized only by a small to moderate increment in mean arterial pressure (MAP) [10, 13, 14].

Beyond the described cardiovascular adjustments there is a fine hemodynamic tuning which is determined by the activity of neural mechanisms in the cardiovascular control centres [18]. There are at least three neural mechanisms participating in this cardiovascular regulation: 1) the "exercise pressor reflex", 2) the "central command", and 3) the "arterial baroreflex". The *Medulla Oblongata* is considered to be the major centre of control and integration of these reflexes [19].

In the "central command" the cardiovascular control areas located in the medulla are activated by regions of the brain responsible for motor unit recruitment. This establishes a basal level of sympathetic activity and vagal withdrawal arising from the motor cortex and related to the intensity of the strain and to motor drive [20-22].

The exercise pressor reflex originates from peripheral signals coming from mechano- and metabo-receptors in the muscle, which are type III and IV nerve endings. These thin nerve endings convey information about the mechanical and metabolic conditions of the working muscle [18]. The information is in turn integrated with those arising from the central command by the medullary cardiovascular centres.

The resulting autonomic modulation is characterised by an increase in sympathetic tone and a reduction in parasympathetic activity that produce heart rate (HR) elevation and myocardial contractility enhancement, which together concur in sustaining CO.

Finally, this autonomic activity is modulated by baroreflexes, which collect ABP level and, coherently, buffer any excessive increase in sympathetic tone and oppose any mismatch between SVR and CO by controlling arteriolar vasodilatation and cardiac chronotropism [23].

In short, in normal individuals dynamic exercise is characterised by autonomic adjustments which include an increase in sympathetic and a decrease in parasympathetic tone proportional to the drive from motor cortex, the metabolic and mechanical status of the contracting muscle, and the blood pressure level. This fine regulation can be disrupted in type 1 and 2 DM, since both pathologies affect autonomic tone and cardiovascular functions.

Moreover, it is to be considered that insulin itself modulates the cardiovascular system. In normal subjects insulin induces a net vasodilatory effect by affecting central and peripheral mechanisms. Briefly, insulin stimulates the production of nitric oxide (NO), thereby causing vasodilation. However, insulin also causes vasoconstriction by promoting synthesis of endothelin-1 (ET-1). Furthermore, insulin increases sympathetic tone by exerting centrally-mediated sympathetic stimulation [24, 25]. However, in healthiness the net effect is vasodilation.

3. CONSEQUENCES OF TYPE 1 DM ON THE CARDIOVASCULAR REGULATION DURING EXERCISE

In type 1 DM impairment in both central and peripheral hemodynamics during exercise have been reported. In detail, in these patients reductions in maximum HR (HR_{max}), ventricular diastolic functions and stroke volume (SV) have all been observed in response to exercise [3-5, 26-28]. Moreover, peripheral vascular responsiveness deficit, together with a reduction in circulating blood volume, have been reported [4, 29-32]. All these phenomena may affect SV and SVR regulation, thereby leading to a reduced capacity to properly adjust CO, ABP, and muscle blood flow during effort.

Of interest, in subjects with type 1 DM a reduction in catecholamine levels during exercise has been several times described [3, 33, 34]. Moreover, in patients without symptoms of autonomic neuropathy, the response of adrenaline to hypoglycemia has been found to be blunted. This fact indicates that type 1 DM *per se* is associated with a reduced response to sympathetic activation before any clinical evidence [5, 34, 35], although this condition seems to be well tolerated and usually does not cause any clinical symptoms. However, this situation may progressively deteriorate and lead to symptomatic manifestations of sympathetic deficit.

More recently a blunted ABP response during metaboreflex stimulation (*i.e.* the metabolic arm of the exercise pressor reflex) has been found in young type 1 DM patients [4]. Together with the blunted ABP response, this study also showed that the capacity to induce arteriolar vasoconstriction (*i.e.* to increase SVR) was impaired, and these findings were interpreted by authors through a reduction in the capacity to properly elevate the sympathetic tone in these patients [4]. This result is consistent with the concept that some form of autonomic failure is present in patients with type 1 DM even in the absence of an overt autonomic neuropathy.

A possible explanation for the reported reduced sympathetic activity during exercise is that repeated episodes of sub-clinical or overt hypoglycemia reduce the capacity to

activate the sympathetic tone, thus leading to autonomic failure [36, 37]. This reduced sympathetic activity seems to be well tolerated, at least at early age. Actually, the exercise capacity of young type 1 DM subjects was found to be normal even in the presence of autonomic failure [4, 36].

The autonomic failure often described in these patients can explain why their maximum HR_{max} has been often found reduced as compared to that of normal subjects [26, 27, 38, 39]. The blunted sympathetic response may also explain, at least in part, the reduced capacity to increase SV during exercise in these patients, as a reduced sympathetic activity causes inotropic impairments. However, to the best of our knowledge this possibility has never been tested. Moreover, as previously described, a reduction in circulating blood volume has been reported in type 1 DM [30], and this fact may potentially affect cardiac pre-load and SV response to effort.

Therefore, even in the absence of overt sympathetic neuropathy at rest, patients with type 1 DM may experience troubles in the cardiovascular regulation to exercise as the response of all the four hemodynamic modulators (*i.e.* chronotropism, inotropism, cardiac pre-load, and after-load) may be impaired by a deficit in the sympathetic tone as well as by a reduction in the circulating blood volume. In the long term, when the sympathetic deficit becomes more evident, symptoms related to the incapacity to properly adjust ABP to exercise may become clinically evident, with low blood pressure and early fatigue during exercise.

As concerns physical capacity in type 1 DM, findings are contradictory. Available data reported both reduced or similar maximum oxygen uptake (VO_{2max}) in these patients in comparison with healthy individuals [26, 27, 30, 31, 38, 40-43]. The conflicting results can be explained through the different time since diagnosis in the various studies, as with disease progression there is a progressive impairment in the response to sympathetic activation and in the cardiovascular regulation. Moreover, with age the incidence of diabetic neuropathy becomes higher and symptoms of sympathetic deficit are more frequent. Of note, some investigations reported that poor glycaemic control is associated with reduction in VO_{2max} [26, 27, 38-40, 42]. Therefore, the possibility arises that with time tissues sensitivity to sympathoadrenergic activation reduces and that symptoms related to this condition progressively increase.

In summary, in patients suffering from type 1 DM a dysregulation in central and peripheral hemodynamic response to exercise has often been observed, with reductions in maximum HR_{max}, SV, and CO and with impairments in the capacity to vasoconstrict the arteriolar bed in comparison to healthy subjects. Moreover, physical capacity expressed as VO_{2max} has often been reported to be lower than in normal individuals. The reduction in catecholamine levels and in the response to sympathetic activation may at least in part explain these facts. Furthermore, a reduction in circulating blood volume has been demonstrated in these patients, thereby explaining why they can not properly enhance cardiac pre-load during effort. With the progression of the disease, symptoms related to diabetic neuropathy become more evident, with progressive deterioration of the cardiovascular regulation in response to exercise.

4. CONSEQUENCES OF TYPE 2 DM ON THE CARDIOVASCULAR REGULATION DURING EXERCISE

In type 2 DM hyperglycaemia is the result of both resistance to insulin action at tissue level and to a defect in insulin secretion of ß cells [2]. Hence, type 2 DM is characterised by a reduced capacity of peripheral tissues to regulate glucose homeostasis in response to insulin. Frequently, type 2 DM is accompanied by comorbidities such as hypertension, lipid metabolism disorders, and overweight or obesity in a combination called metabolic syndrome.

It is well known that in healthiness, increments in glucose blood concentration induce a parasympathetic-mediated insulin production. Conversely, sympathetic activation blunts the pancreatic secretion of insulin. These antagonistic actions provide a precise control over energy regulation since it makes more energy available when energy is needed by the body, such as during exercise. Opposite, it leads to energy storage when energetic requirement is low. If these controlling mechanisms do not properly work, then glucose homeostasis may be disrupted.

There is a strong evidence that acute increments in plasma insulin concentration stimulate sympathetic activity and that chronic hyperinsulinaemia induces a re-setting in cardiac autonomic control with secondary increase in sympathetic tone [8, 44-46]. These findings indicate that hyperinsulinaemia and insulin resistance is directly implicated in the pathogenesis of cardiovascular mortality associated with type 2DM because of sympathetic overactivation [7, 44].

Moreover, other observations demonstrate that sympathetic activity is exaggerated in obesity and that this phenomenon can be counteracted by weight lost. Furthermore, convincing evidence supports the concept that sympathetic system plays a critical role in the development of obesity. Indeed, central fat (in particular visceral) has been demonstrated to be strongly associated with sympathetic nervous system tone. Yet, a decreased parasympathetic activity has been observed in obese individuals [6]. These findings are consistent with the concept that autonomic dysfunction is present in obesity in absence of overt diabetes and indicate that there is a common link among obesity, sympathetic overactivation, hyperinsulinaemia and type 2 DM.

Other research has reported that during exercise exaggerated sympathetic-mediated vasoconstriction and blunted vasodilator responsiveness are present in the muscle of patients suffering from type 2 DM [47-49]. Additionally, cerebral auto-regulation has been found impaired during isometric exercise in these patients [49]. Although the exact mechanism(s) responsible for this vascular dysfunction is not exactly known, several evidences suggest that autonomic abnormalities may play a key role [6].

In support of this concept there is the recent observation revealing that patients with obesity complicated by metabolic syndrome have a hemodynamic response to the activation of the exercise pressor reflex characterized by a pronounced increase in arteriolar vasoconstriction without significant CO participation. This is in contrast to what found in healthy individuals. Moreover, obese subjects without metabolic complications did not show this hemodynamic

scenario, *i.e.* they did not show an exaggerated vasoconstriction during the exercise pressor reflex [50]. Results from the quoted study also suggest that in obesity with metabolic syndrome the exaggerated SVR increment is due to the presence of hyperinsulinaemia, since the SVR response was significantly related to fasting glucose levels. Authors speculated that this phenomenon was in accordance with the concept that insulin may augment sympathetic outflow and may contribute to sympathetic overdrive in metabolic syndrome [51]. Also, there are reports demonstrating that patients with type 2 DM have decreased levels of heart rate variability [44, 52], thereby reinforcing the presence of augmented sympathetic activity in these patients.

However, apart from sympathetic hyper-activation, other possible mechanisms might explain the described impairment in exercise-induced vasodilation in type 2 DM. As previously stated, in normal individuals the net effect of insulin release is vasodilation. This effect is achieved through multiple different mechanisms which exert opposite hemodynamic actions [25]. Briefly, insulin promotes NO production, which exerts a vasodilating effect. On the other hand, insulin contemporary stimulates ET-1 synthesis, which exerts vasoconstriction. Moreover, it is to be highlighted that activation of ET-1 pathway has been linked to inflammatory and atherogenic processes [53]. In normal subjects the effects of NO release prevails over those exerted by ET-1 and a overall dilatory action of insulin is evident. It has been reported that in the presence of insulin resistance there is a reduction in NO-induced vasodilation [54-56]. In reality, in isolated arteries from insulin-resistant animals, insulin has been demonstrated to induce vasoconstriction instead of vasodilation. Thus, it was proposed that insulin resistance leads to an imbalance between NO and ET-1 production, with the effects of ET-1 prevailing over NO-induced vasodilation. This phenomenon may be an important factor in the pathogenesis of cardiovascular disease in patients with insulin resistance and type 2 DM [57].

Finally, likewise reported for type 1 DM, a reduction in blood volume has been reported also for type 2 DM [58]. This fact is likely to affect the diastolic function and impairs SV response in these patients.

In summary, in patients suffering from insulin resistance and type 2 DM there is an evident tendency towards vasoconstriction, exaggerated increments in SVR and elevated blood pressure at rest. These phenomena are also present in response to effort and may be ascribed to several factors: increased sympathetic tone, reduced NO availability, imbalance between NO and ET-1 production, and possibly others which are still to be discovered. An impaired diastolic function and SV response to exertion have also been reported.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

While exercise is a well established tool to manage both type 1 and 2 DM and to prevent their cardiovascular complications [6, 59, 60], some aspects related to the cardiovascular regulation in these patients still need to be fully elucidated. Poor fitness level represents an important barrier to exercise regularly. Consequently, factors involved in the possible impairment of cardiovascular response to exercise should be investigated.

It is still unclear whether or not a deficit in autonomic response, which is present in type 1 DM even in the absence of an overt autonomic neuropathy, exerts any negative effect on the hemodynamic response to effort. For example, it should be clarified whether this sympathetic impairment is related to the reduced SV response in these patients. Moreover, it is still to be elucidated the role played by the reduced circulating blood volume in the diastolic function of these patients. This phenomenon is to be considered also for type 2 DM.

Contrary to what found in type 1 DM, in type 2 DM sympathetic overactivation has often been reported and it has been linked to hyperinsulinaemia. However, the precise origin of this sympathetic dys-regulation is still unclear. Furthermore, the origin of the impairment in endothelium-induced vasodilation is still to be fully explained. While the reduction in NO production appears to be well ascertained, other metabolites are probably involved in the phenomenon. One is probably NO-ET-1 imbalance, but very likely others are still to be discovered.

Other important points to be addressed are which type of exercise should be recommended for these patients. Recent observations suggest a protective effect of moderate and vigorous-intensity but not mild-intensity physical activity on the incidence of cardiovascular events and microvascular complications [61]. It was also suggested that combined training (*i.e.* a combination of both aerobic and resistance training) is the most efficacious exercise intervention to prevent the metabolic and cardiovascular complications of DM, at least in type 2 DM. Actually, combined training appeared the most effective in improving HbA_{1c}, fasting glucose, HDL, Triacylglycerols, body weight, and diastolic blood pressure [60].

In conclusion, patients suffering from type 1 and 2 DM experience different troubles in the hemodynamic regulation during exercise. This fact possibly leads to a dys-regulated cardiovascular response which in turn induces limitations in the tolerance to effort. Further research is warranted to fully understand the origin of this hemodynamic dys-regulation in order to limit its consequences on the capacity to exercise and its impact on the quality of life of diabetic patients.

On the basis of the reported literature, clinicians should promote exercise as a valid strategy to counteract adverse metabolic and cardiovascular effects of both type 1 and 2 DM. However, they should also consider that hemodynamic complications may possibly develop. For this reason attention should be paid and patients should be carefully and regularly checked, insulin therapy periodically re-evaluated, and training optimally planned.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise

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