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Original article

Haemodynamic changes during a squat test, pulsatile stress and indices of cardiovascular autonomic neuropathy in patients with long-duration type 1 diabetes

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Abstract

Aim. – Cardiovascular autonomic neuropathy (CAN) and pulsatile stress are considered to be independent cardiovascular risk factors. This study compared haemodynamic changes during an active orthostatic test in adult patients with type 1 diabetes (T1DM), using low versus high RR E/I ratios as a marker of CAN.

Methods. – A total of 20 T1DM patients with low RR E/I ratios were compared with 20 T1DM patients with normal RR E/I ratios, matched for gender (1/1 ratio), age (mean: 46 years) and diabetes duration (22–26 years); 40 matched healthy subjects served as controls. All subjects were evaluated by continuous monitoring of arterial blood pressure (Finapres®) and heart rate using a standardized posture test (1-min standing, 1-min squatting, 1-min standing), thus allowing calculation of baroreflex gain.

Results. – Compared with controls, T1DM patients showed lower RR E/I ratios, reduced baroreflex gains, higher pulsatile stress (pulse pressure × heart rate), greater squatting-induced pulse pressure rises, orthostatic hypotension and reduced reflex tachycardia. Compared with T1DM patients with preserved RR E/I ratios, T1DM patients with low RR E/I ratios showed reduced post-standing reflex tachycardia and baroreflex gain, and delayed blood pressure recovery, but no markers of increased pulsatile stress. Interestingly, decreased baroreflex gain was significantly associated with both pulsatile stress and microalbuminuria.

Conclusion. – The use of RR E/I ratios to separate T1DM patients allows the detection of other CAN markers during an orthostatic posture test, but with no significant differences in pulsatile stress or microalbuminuria. In this context, squatting-derived baroreflex gain appears to be more informative.

Keywords: Baroreflex gain; Cardiac autonomic neuropathy; Pulse pressure; Squatting; Type 1 diabetes

Résumé

Modifications hémodynamiques lors d'un test d'accroupissement, stress pulsatile et indices de neuropathie autonome cardiovasculaire chez des patients diabétiques de type 1 de longue durée d'évolution.

But. – La neuropathie autonome cardiaque (NAC) et le stress pulsatile sont considérés comme des facteurs de risque cardiovasculaire indépendants. Nous avons comparé les modifications hémodynamiques pendant un test actif d'orthostatisme chez des adultes diabétiques de type 1 (DT1) séparés selon la valeur de RR E/I ratio (basse versus élevée) comme marqueur de NAC.

Méthodes. – Vingt patients DT1 avec un ratio E/I abaissé ont été comparés à 20 patients DT1 avec un ratio E/I normal, appariés pour le sexe (1/1 ratio), l'âge (moyenne : 46 années) et la durée du diabète (22–26 années). Quarante sujets sains appariés ont servi de témoins. Tous les sujets ont été évalués par une mesure continue de pression artérielle (Finapres®) et de fréquence cardiaque lors d'un test postural standardisé (une minute debout, une minute accroupi, une minute debout) avec calcul d'un gain baroréflexe.

Résultats. – Comparés aux témoins, les patients DT1 ont un ratio E/I abaissé, un gain baroréflexe diminué, un stress pulsatile (pression pulsée × fréquence cardiaque) accru, une augmentation plus marquée de pression pulsée en position accroupie, une hypotension orthostatique et une tachycardie réflexe réduite. Comparés aux patients DT1 avec un ratio E/I préservé, les patients DT1 avec un ratio E/I abaissé ont une diminution de la tachycardie réflexe lors du redressement et une réduction du gain baroréflexe, un retard dans la correction de l'hypotension orthostatique,

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mais pas d'augmentation du stress pulsatile. Il est intéressant de noter que la diminution du gain baroréflexe est significativement associée au stress pulsatile et à la microalbuminurie.

Conclusion. – L'utilisation du rapport RR E/I pour séparer les patients DT1 permet de détecter d'autres marqueurs de NAC durant un test d'orthostatisme, mais sans différences significatives en ce qui concerne le stress pulsatile ou la microalbuminurie. De ce point de vue, le gain baroréflexe calculé lors du passage accroupi–debout apparaît plus discriminant.

Mots clés : Diabète de type 1 ; Gain baroréflexe ; Neuropathie autonome cardiaque ; Pression pulsée ; *Squatting*

1. Introduction

Cardiovascular autonomic neuropathy (CAN) is a common complication of diabetes, especially in patients with long-duration type 1 diabetes mellitus (T1DM) [1–4]. Of the initial battery of tests to assess CAN [5], the easiest, most informative and most popular marker in clinical practice is the R-R interval expiration/inspiration (RR E/I) ratio, measured during a deep-breathing test [6]. According to a recent experts' review [4], this index has the highest specificity (80%) in the detection of CAN. In a French population of T1DM patients, the total prevalence of CAN assessed by three standard tests averaged 51%, with 4.8% having severe CAN and 18.2% having moderate CAN [7]. Patients with T1DM are also characterized by accelerated arterial stiffness [8], which results in increased systolic blood pressure (SBP) and pulse pressure (PP) [9]. Both CAN [10] and increased PP [11,12] are considered to be independent risk factors of cardiovascular disease and total mortality in T1DM patients. Furthermore, CAN may be linked to aortic stiffness [13,14], endothelial dysfunction [15] and increased SBP [16] or PP [17] in T1DM patients. Moreover, CAN is known to be associated with a greater risk of orthostatic hypotension [18,19].

The squat test is a posture manoeuvre that can be used to assess orthostatic hypotension [20,21], CAN [17,22,23] and pulsatile stress [17,24] in patients with diabetes. Using this posture test, and continuous monitoring of BP and heart rate (HR), it was recently demonstrated that: the squatting position amplifies PP increases in T1DM patients [24]; PP and the product of PP × HR (so-called 'pulsatile stress') increase more rapidly with age in T1DM patients than in non-diabetic controls [17,25]; and pulsatile stress in middle-aged T1DM patients is similarly increased as that measured in age-matched patients with type 2 diabetes and the metabolic syndrome [26]. Careful analysis of the accompanying changes in SBP and HR during the squatting–standing transition allows calculation of a baroreflex gain, similar to the barosensitivity index derived from a pharmacological test using a combination of vasodilator/vasopressor agents [17,27].

The aims of the present study were: (1) to investigate haemodynamic changes, pulsatile stress and CAN indices (including baroreflex gain) during a squat test in T1DM patients compared with non-diabetic controls matched for gender, age and body mass index (BMI); (2) to compare the results in T1DM patients separated on the basis of the classical RR E/I ratio (decreased vs maintained) after matching for gender, age, BMI and duration of diabetes; and (3) to compare the relationships between baroreflex gain versus RR E/I ratio, pulsatile stress and microalbuminuria in T1DM patients.

2. Research design and methods

2.1. Patients

From our database, 20 T1DM patients (10 men and 10 women) with the lowest RR E/I ratios evaluated during a classical deep-breathing manoeuvre were selected, and compared with 20 T1DM patients (10 men and 10 women) with the highest RR E/I ratios. All of the patients were matched for age, BMI and duration of diabetes. Those with arterial hypertension, renal insufficiency or cardiovascular disease, or who were taking medications interfering with vascular reactivity (including any type of antihypertensive agents except for renin–angiotensin system blockers taken for microalbuminuria), were excluded from the study. All T1DM patients received intensified insulin therapy, comprising either four daily injections according to a basal–bolus scheme ($n = 35$) or continuous subcutaneous insulin infusion (CSII) using a portable pump ($n = 5$). Also, 40 non-diabetic subjects matched for gender (ratio: 1/1), age (25–60 years) and BMI (20–30 kg/m^2) served as controls.

The study protocol was accepted by our institution's ethics committee.

2.2. Dynamic tests

Slow deep-breathing (six breaths/min) over 3 min was performed by each subject to evaluate respiration-induced HR variability, which was assessed by measuring the classical RR E/I ratio [5], corresponding to the ratio between the longest R-R interval during the expiration (E) phase and the shortest R-R interval during the inspiration (I) phase. While CAN is classically defined as the presence of several abnormalities arising from a battery of tests [5], the RR E/I ratio is thought to have the greatest specificity [4]; it has been reported that knowledge of the degree of CAN, as defined by reduced HR variability, is not significantly increased when other functional tests are added to the RR E/I ratio [6].

The squat test (1 min of standing, 1 min of squatting and 1 min of standing again, in succession) is the original active orthostatic manoeuvre that leads to the most important and rapid variations in hydrostatic levels with posture [28]. Squatting produces a prompt increase in cardiac output and arterial BP, essentially attributed to the augmented venous return due to compression of the leg veins. These changes result in a significant increase in mean arterial BP (MBP) and PP [17,24], which is accompanied by an immediate decrease in HR and forearm vascular resistance, probably due to activation of cardiopulmonary and