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SQUATTING AMPLIFIES PULSE PRESSURE INCREASE WITH DISEASE DURATION IN PATIENTS WITH TYPE 1 DIABETES

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Short running title : Pulse pressure and type 1 diabetes duration

Summary

OBJECTIVE

To evaluate pulse pressure (PP) changes according to duration of type 1 diabetes mellitus (T1DM) and to assess the influence of posture.

RESEARCH DESIGN AND METHODS

Continuous measurement of blood pressure with a Finapres® device during a 3x1min posture test (standing-squatting-standing) in 159 T1DM patients divided into four groups according to diabetes duration (≤10 years, 11-20 years, 21-30 years and > 30 years from group 1 to group 4, respectively) and compared to age-matched nondiabetic subjects.

RESULTS

PP progressively increased according to T1DM duration ($p<0.0001$), especially in women, but not in age-matched nondiabetic subjects (NS). PP increase from group 1 to group 4 was amplified in squatting position (from 50±17 to 69±14 mmHg) compared to standing (from 44±15 to 55±12 mmHg).

CONCLUSION

PP increases according to T1DM duration, more in women than in men, and the squatting position sensitizes such PP increase in both genders.

Key-words : Arterial blood pressure – Arterial stiffness - Finapres - Pulse pressure – Squatting - Type 1 diabetes

Early vascular aging was reported in type 1 diabetes (T1DM) (1-5). Arterial pulse pressure (PP), a surrogate marker of artery stiffness, is an independent cardiovascular disease (CVD) risk factor in T1DM patients (6), as in non-diabetic (7-9) or T2DM (10,11) individuals. This cross-sectional controlled study investigated the influence of T1DM duration, gender and posture on PP.

RESEARCH DESIGN AND METHODS

Patients

We evaluated 159 T1DM patients (20-60 years). Subjects were retrospectively separated according to diabetes duration into four groups and compared to age-matched healthy controls to take into account normal aging (12) (Table 1).

Monitoring of blood pressure

Systolic and diastolic BP were measured continuously with a Finapres^{R} (FINger Arterial PRESsure) instrument (Ohmeda, USA) (13-15) during an orthostatic test (successively 1 min standing, 1 min squatting, 1 min standing) (16-18). Means (± SD) of mean blood pressure (MBP) and PP (systolic minus diastolic) were calculated throughout the test (overall), during initial standing only and in the squatting position.

Statistical analysis

We performed univariate analysis using ANOVA followed by Student's t test, with two-tailed p values < 0.05 considered as significant.

RESULTS

MBP remained almost stable across the four diabetic groups while PP progressively increased according to T1DM duration (ANOVA $p<0.0001$; Table 1). There was a marked difference in overall PP between groups 1-2 and groups 3-4 (49±14 vs 59±14 mmHg; $p<0.00002$), contrasting with no difference in age-matched controls (mean of 35 years for groups 1-2 vs 46 years for groups 3-4: 51±12 vs 50±15 mmHg; NS).

PP levels were lower in diabetic and non-diabetic women compared to men, except in group 4 with T1DM > 30 years (data not shown). The progressive PP increase from TIDM

group 1 to group 4 was almost double in women (from 44±16 to 63±11 mmHg) than in men (from 51±15 to 61±13 mmHg).

The graduate rise in PP from group 1 to group 4 in T1DM, already present in initial standing (from 44 to 55 mmHg), was markedly amplified in squatting (from 50 to 69 mmHg) (Table 1).

CONCLUSIONS

The present study essentially demonstrates: 1) a progressive PP increase according to T1DM duration, especially when it exceeds 20 years; 2) an early PP rise in T1DM subjects already below the age of 50 years, especially in women; and 3) the amplification of this phenomenon by squatting.

In the FinnDiane study, PP was higher in diabetic patients of all age categories, including in patients below 45 years (5). However, previous observations showed no (19) or only marginally increased PP values (< 5 mmHg) in young (25-30 years) T1DM patients (2,3,20). A recent study reported an 11 mmHg higher brachial PP and a 8 mmHg higher carotid PP in patients with 15.3 years T1DM duration as compared to controls (21). We observed markedly PP increase (difference of almost 10 mmHg) in T1DM patients aged > 40 years with disease duration above 20 years compared to age-matched controls. Multiple regression analysis of the FinnDiane study indicates that T1DM duration per se has a considerable impact on PP, independent of age and renal involvement (5). PP rises with age, more so in women (22). In healthy subjects, PP was higher in men than in women, although the difference decreased from <20 years to 40-49 years (12), while in the FinnDiane study lower PP levels in nondiabetic females compared to men below the age of 40-45 years tended to become higher afterwards. In the diabetic population, an earlier and steeper PP rise according to age was shown in women compared to men (5). Increased aortic wall stiffness with T1DM was more markedly related to diabetes duration in women than in men (23).

Squatting increases preload by augmentation of venous return and increases cardiac output without changes in systemic vascular resistance (16,17,24), resulting in greater increase of systolic than diastolic BP and PP augmentation (15,25). Interestingly, the squatting-induced PP rise markedly increased with T1DM duration, being almost doubled in patients with >20 years T1DM compared to patients with <20 years T1DM. Both increased arterial stiffness and alteration of wave reflection may contribute to the predominant PP increase in squatting position with T1DM duration (26). Furthermore, advanced glycation end

products (AGEs) may profoundly alter the histomorphometric arterial pattern, reducing compliance and distensibility, and NO-dependent vascular dilation (27).

Our study has some limitations. First, the cross-sectional design did not allow following patients prospectively. Second, PP was measured at the finger site. However, PP changes in radial artery and finger were almost similar during a head-up tilt (28). Finally, T1DM patients were not well controlled, precluding any extrapolation to T1DM patients with excellent glucose control.

The Framingham Heart Study showed that PP is an excellent predictor of CHD risk, at least in nondiabetic individuals >50 years of age (29). PP was also a major determinant of CVD complications in young T1DM individuals of the Eurodiab Prospective Complications study (6), in agreement with accelerated vascular aging and earlier arterial stiffening in T1DM (1,4,19,21). The greater PP increase in diabetic women according to disease duration (5) may contribute to the higher relative (versus age-matched nondiabetic controls) CVD risk compared to diabetic men (30). AGEs were associated with increased PP in T1DM (27), an additional argument for intensifying glucose control to reduce CVD risk (31).

In conclusion, T1DM is associated with a progressive PP increase according to disease duration, a finding suggestive of accelerated arterial stiffening that may explain the higher CVD risk of T1DM patients, especially in women. The squatting position sensitizes the detection of increased PP in diabetic patients and may help detect patients at higher risk.

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Table

Table 1: Characteristics of the type 1 diabetic patients (D) and nondiabetic subjects (ND) used as controls in the four subgroups divided according to diabetes duration and age matching, respectively, and mean blood pressure (MBP) and pulse pressure (PP) levels recorded during the whole test (overall), in the initial standing position and in the squatting position. Results are expressed as mean ± SD. NA : Not applicable.

	GROUP 1 D ≤ 10 years		GROUP 2 D 11 – 20 years		GROUP 3 D 21 – 30 years		GROUP 4 D ≥ 30 years		P value Anova G1-G4	
	D	**ND**	**D**	**ND**	**D**	**ND**	**D**	**ND**	**D**	**ND**
n	39	30	45	30	57	30	18	28		
Age (yrs)	34 ± 10	33 ± 10	37 ± 10	37 ± 11	45 ± 9	44 ± 11	48 ± 8	48 ± 9	0.0000	0.0000
Sex ratio	22F/17M	17F/13M	21F/24M	14F/16M	24F/33M	14F/16M	8F/10M	18F/10M		
BMI (kg/m^2)	22.6 ± 3.3	23.1 ± 2.8	23.5 ± 2.4	23.6 ± 3.3	24.3 ± 4.4	24.7 ± 4.5	23.1 ± 2.2	24.4 ± 3.7	0.1005	0.3055
T1DM duration (yrs)	6 ± 3	-	16 ± 3	-	26 ± 3	-	38 ± 8	-	0.0000	NA
HbA1c (%)	8.92 ± 1.68	-	8.72 ± 1.19	-	8.43 ± 1.25	-	8.85 ± 1.18	-	0.4215	NA
MBP Overall	80 ± 10	82 ± 11	80 ± 11	80 ± 13	86 ± 12	85 ± 16	80 ± 13	84 ± 14	0.0149	0.1946
MBP Standing	79 ± 10	81 ± 10	79 ± 12	79 ± 12	84 ± 12	84 ± 16	77 ± 13	83 ± 16	0.0496	0.1816
MBP Squatting	84 ± 13	85 ± 12	87 ± 13	86 ± 15	94 ± 13	90 ± 16	87 ± 14	89 ± 15	0.0000	0.2422
PP Overall	48 ± 16	49 ± 11	52 ± 13	53 ± 13	59 ± 14[a]	49 ± 14	62 ± 12[b]	51 ± 15	0.0001	0.3783
PP Standing	44 ± 15	45 ± 10	47 ± 13	48 ± 12	54 ± 14	46 ± 15	55 ± 12	49 ± 15	0.0004	0.1885
PP Squatting	50 ± 17	51 ± 13	56 ± 15	55 ± 13	64 ± 16[c]	51 ± 15	69 ± 14[c]	52 ± 15	0.0000	0.4851

a : p<0.05 D *vs* ND b : p<0.01 D *vs* ND c : p<0.001 D *vs* ND