Short communication

Redistribution of blood volume in Type I diabetes

F.L. Ubels¹, J.H.J. Muntinga², T.P. Links³, K. Hoogenberg³, R.P.F. Dullaart³, W.D. Reitsma¹, A.J. Smit¹

¹ Department of Internal Medicine, University Hospital Groningen, The Netherlands

² Medical Physiology, University Hospital Groningen, The Netherlands

³ Endocrinology, University Hospital Groningen, The Netherlands

Abstract

Aims/hypothesis. Impaired activity of endothelium-derived nitric oxide in Type I (insulin-dependent) diabetes mellitus will cause an increased vascular tone. Considering the lower production of nitric oxide in veins than in arteries, an impaired activity would have less vasoconstrictive effect in veins. The reported minimally changed total plasma volume in diabetes might, therefore, indicate a redistribution of blood volumes from the arterial to the venous side of the circulation. This could be more pronounced in patients with microalbuminuria.

Methods. In 16 normoalbuminuric and 16 microalbuminuric Type I diabetic patients and 16 individually matched healthy control subjects, venous and arterial blood volumes, venous myogenic response and arterial distensibilities were assessed in the upper arm using an electrical bio-impedance method.

Results. In diabetic patients, the venous blood volume and venous myogenic response were increased

($p < 0.02$ and $p < 0.05$, respectively), whereas the arterial blood volume did not change. Moreover, in diabetic patients the distensibility of the large arteries was decreased ($p < 0.05$) but increased in the total arterial bed ($p < 0.05$). Therefore, the distensibility of the small arteries must have been increased. No differences were found between normoalbuminuric and microalbuminuric diabetic patients.

Conclusion/interpretation. The increase in venous blood volume and myogenic response and the decrease in distensibility of the large arteries in the upper arm are in agreement with the expected shift towards venous blood volume distribution in Type I diabetes with and without microalbuminuria. Furthermore, they support the haemodynamic hypothesis of the pathogenesis of diabetic microangiopathy. [Diabetologia (2001) 44: 429–432]

Keywords Diabetes mellitus, bio-impedance method, venous volume, blood volume, myogenic response, arterial distensibility.

A recent review [1] in this journal describes endothelium-derived nitric oxide as a possible important factor in the development of vascular changes in Type I (insulin-dependent) diabetes mellitus. Although many of the suggested effects of a reduced availability of, or an altered response to nitric oxide on the functioning of human arteries are yet to be elucidat-

ed, even less is known about possible changes at the venous side of the circulation. An impaired activity of nitric oxide in diabetes may cause an increased vascular tone at the arterial side of the circulation. Because veins produce a relatively lower amount of endothelium-derived nitric oxide than arteries [2], venous vessels may be less sensitive to a decreased activity of nitric oxide. Since the total plasma volume, measured using albumin labelled ¹²⁵I-iodine, has been reported to be unchanged in diabetes mellitus with and without microalbuminuria [3], a redistribution of the plasma volume from the arterial to the venous side can be postulated [4]. Microalbuminuria is associated with endothelial dysfunction [5], raising the

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Corresponding author: F.L. Ubels, MD, Department of Internal Medicine, University Hospital Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands

possibility that the vascular changes are more pronounced in diabetic patients with microalbuminuria. We, therefore, assessed venous and arterial blood volumes and distensibility of the vascular bed in Type I diabetic patients with normoalbuminuria and microalbuminuria and matched healthy subjects, using an electrical bio-impedance method [6].

Subjects and methods

Subjects. Measurements were made in male and female Type I diabetic patients with normoalbuminuria and microalbuminuria. Patients were individually matched with non-diabetic normotensive normoalbuminuric healthy subjects without clinically manifest cardiovascular disease with respect to sex, age (within 5 years), height (within 0.1 m) and body mass index (BMI, within 2.5 kg/m²). One and a half hours after breakfast during which the patients used their usual insulin dose, investigations were carried out in a quiet, temperature-controlled room after at least 15 min rest. During the measurements the subjects were sitting in an armchair with the upper arms at heart level and both arms on armrests. Blood glucose was allowed to range from 4.0 to 11.0 mmol/l during the measurements.

Laboratory analyses. Venous blood glucose was measured with a glucose analyser (Apec, Danvers, Mass. USA) and HbA_{1c} was assayed by HPLC (Bio-Rad, Veenendaal, The Netherlands, reference range in non-diabetic subjects 4.6–6.1 %). Urinary albumin was measured by RIA (Diagnostic Products Corporation, Apeldoorn, The Netherlands). Microalbuminuria was defined as a persistent (on two or more occasions) urinary albumin excretion rate (AER) between 20 and 200 µg/min.

Non-invasive vascular measurement. Various vascular properties of the left upper arm were investigated using an electrical bio-impedance method [6]. In brief, in sitting position, a specially designed blood pressure cuff around the left upper arm was rapidly inflated above the systolic blood pressure. After 2 min of suprasystolic pressure, the cuff was slowly deflated in 4 min. Blood pressure was simultaneously recorded at the contralateral hand using a Finapres device (Ohmeda 2300, Englewood, USA) and corrected for left-right and hydrostatic blood pressure differences. From the changes in electrical impedance, measured at the left upper arm underneath the cuff by a Minnesota impedance cardiograph (model 304A; Instrumentation for Medicine, Greenwich, USA), and the changes in transmural pressure, various physiological parameters were estimated. From the fluid shifts during changing cuff pressures, total, venous and arterial blood volumes were derived and expressed in ml/cm arm length. The difference between the reciprocal values of the impedances before and after a measurement was used as a measure of the myogenic response of the veins and expressed as a venous blood volume (ml/cm arm length). Since the arterial refill during cuff deflation starts with the refill of the largest arteries, functioning at high intra-arterial pressures, and proceeds in the direction of the arterioles, functioning at lower intra-arterial pressures, the parameters at zero transmural pressure are mainly assessed by the properties of the large arteries of the upper arm vascular bed. The arterial distensibility (in 10⁻³ · mmHg⁻¹) at zero transmural pressure therefore, was used as representative of the largest arteries, and at a higher transmural pressure, for example 80 mmHg, as representative of the distensibility of the arterial

bed as a whole. The reproducibility of the aforementioned vascular properties using this bio-impedance method, is comparable with established methods [7].

Statistical analysis. Statistical tests were carried out with SPSS version 8.0. Results are given in mean ± standard deviation (SD) and median with interquartile ranges for the urinary albumin excretion rate. Differences in clinical and vascular characteristics were evaluated by ANOVA. Unpaired-*t*-tests were used to compare the various characteristics between all diabetic patients and control subjects. Differences were considered statistically significant at *p*-values of less than 0.05.

Results

Patient characteristics are mentioned in Table 1. For the diabetic participants, both diabetes duration and HbA_{1c} were comparable. Diabetic retinopathy was present in 5 normoalbuminuric and 9 microalbuminuric diabetic patients. Furthermore, one patient with microalbuminuric had peripheral vascular disease. No other clinically manifest diabetic complication was present. As expected, urinary AER was higher in microalbuminuria compared with normoalbuminuric diabetic patients. All diabetic patients with microalbuminuria except one were treated with an ACE-inhibitor. The BMI was significantly higher in the diabetic patients than in the control subjects (*p* < 0.05) and in the microalbuminuric diabetic patients than in the normoalbuminuric diabetic patients (*p* < 0.02). The systolic blood pressure was significantly higher in the diabetic patient group than in the control group (*p* < 0.02).

The observed vascular parameters are given in Table 2. The total blood volume of the upper arm vascular bed tended to be higher in diabetic patients compared with the control subjects, but the difference did not reach statistical significance. The venous blood volume was significantly increased in diabetic patients than in the control subjects. The arterial blood volume was comparable for both groups. The myogenic response of the upper arm veins was significantly higher in diabetic patients than in the control subjects. All distensibilities of the upper arm arterial bed were compared at the same transmural pressure between the groups and are therefore indicated as isobaric distensibility (Table 2). The distensibility of the total arterial bed at 80 mmHg was increased in diabetic patients, with a decrease in distensibility of the large arteries compared with the control subjects. Therefore, the distensibility of the small arteries must have been increased. No differences were found between normoalbuminuric and microalbuminuric diabetic patients in vascular properties.

Table 1. Clinical characteristics of the diabetic patients and matched control subjects

	Normoalbuminuric diabetic patients	Microalbuminuric diabetic patients	Control subjects
Number (men/women)	11/5	11/5	11/5
Age (years)	46 ± 11	48 ± 10	46 ± 10
Diabetes duration (years)	24 ± 8	28 ± 9	
HbA _{1c} (%)	8.5 ± 1.3	8.1 ± 1.2	
Diabetic retinopathy (no/yes)	11/5	7/9	
AER (µg/min)	6.4 (4.2–11.4)	49.4 (16.0–62.1) ^b	
ACE-inhibitor (no/yes)	16/0	1/15	16/0
Body mass index (kg/m ²)	23.9 ± 2.2	25.8 ± 2.3 ^{a,b}	23.2 ± 2.8
Blood pressure (mmHg)	131/78 ± 12/9	139/77 ± 15/8 ^a	125/81 ± 12/6

Data in mean ± SD except for AER in median (interquartile range); ^a significant difference between all combined diabetic patients and control subjects; ^b significant difference between normoalbuminuric and microalbuminuric diabetic patients

Table 2. Properties of the upper arm vascular bed in diabetic patients and matched control subjects

	All diabetic patients ^a	Control subjects	<i>p</i> -value
<i>Blood volume</i>			
Total (ml/cm)	3.80 ± 1.43	3.02 ± 1.24	0.067
Venous (ml/cm)	1.74 ± 1.12	0.99 ± 0.83	< 0.02
Arterial (ml/cm)	2.06 ± 0.65	2.03 ± 0.80	N.S.
Venous myogenic response (ml/cm)	0.81 ± 0.59	0.38 ± 0.39	< 0.05
<i>Isobaric distensibility</i>			
Total arterial bed (10 ⁻³ · mmHg ⁻¹)	2.58 ± 0.92	1.98 ± 0.81	< 0.05
Large arteries (10 ⁻³ · mmHg ⁻¹)	26.76 ± 6.43	31.51 ± 6.97	< 0.05

^a both normoalbuminuric and microalbuminuric diabetic patients

Discussion

In Type I diabetic patients, we found an increased venous blood volume and an increased venous myogenic response in the upper arm bed. Because the arterial blood volume of the upper arm bed was comparable between the diabetic patients and the control subjects, the higher venous blood volume predominantly reflects a redistribution of blood in the diabetic patients. This is in agreement with the hypothesised redistribution of blood through the different effects of an impaired nitric oxide activity in Type I diabetes mellitus on arteries and veins. Using radioactive labelled albumin, others found that the total plasma volume did not change in diabetic patients but no measurements were made of the different intravascular volumes, i.e. total arterial and venous blood volumes separately [3]. Because of the unchanged plasma volume and, for the greater part, unchanged extracellular fluid volume, it is, however, not likely that the mathematically derived total blood volume would be significantly increased.

The increased venous myogenic response could result from the increase in venous blood volume [3] but also from a reduced venous availability of nitric oxide [1,2]. Because an increase in vascular volume usually implies a decrease in vascular compliance, one of the few studies concerning the venous side of the circulation in diabetes agrees well with our findings. It showed a decreased venous compliance in both nor-

moalbuminuric and microalbuminuric Type I diabetic patients, measured using strain gauge plethysmography and simultaneous intravenous pressure measurement [8]. These observed venous alterations fit in the haemodynamic hypothesis of the pathogenesis of microangiopathy in Type I diabetes [9], in which they affect postcapillary hydrostatics and thereby increase intracapillary pressure.

The lower distensibility of the large arteries in the diabetic patients agrees well with the findings of others [10] and could reflect the impaired nitric oxide activity and/or the response as suggested by others [1]. It may explain the higher systolic blood pressure in the diabetic patients as well. Because of the decreased distensibility, i.e. increased stiffness, of the larger arteries, more blood is driven into the smaller arteries during systole and less will be passed onward by recoil during diastole. The increase in small artery distensibility will help to absorb the increased blood volume during systole, while the rise in blood volume could help to maintain blood flow during diastole. The increased distensibility of the smaller arteries therefore, will compensate the effects of the decreased buffering function of the large arteries. Moreover, the increased distensibility of the smaller arteries supports the aforementioned haemodynamic hypothesis: the capillary pressure could be partly increased by a reduction in pre-capillary resistance [9].

Between the normoalbuminuric and microalbuminuric diabetic patients no differences were found

in vascular properties. This is in agreement with the comparable decrease in venous compliance for the normoalbuminuric and microalbuminuric diabetic patients [8] but also with the summarised conflicting results of the different in vivo endothelial function studies [1]. On the other hand, the use of ACE-inhibitors in most microalbuminuric patients could have masked possible differences in distensibility of large arteries, such as have been reported between normoalbuminuric and microalbuminuric diabetic patients without the use of ACE-inhibitors [10]. Cardiovascular medicines other than ACE-inhibitors were not used.

In conclusion, the increase in venous blood volume and myogenic response and the decrease in distensibility of the large arteries in the upper arm are in agreement with the expected shift in blood volume from the arterial to the venous side in Type I diabetes, possibly related to an impaired activity or response of nitric oxide. Furthermore, such vascular changes at the venous side support the haemodynamic hypothesis of the pathogenesis of diabetic (micro)angiopathy.

References

1. Chan NN, Vallance P, Colhoun HM (2000) Nitric oxide and vascular responses in Type I diabetes. *Diabetologia* 43: 137–147
2. Lüscher TF (1991) Endothelium-derived nitric oxide: the endogenous nitrovasodilator in the human cardiovascular system. *Eur Heart J* 12 [Suppl E]: 2–11
3. Hommel E, Mathiesen ER, Aukland K, Parving H-H (1990) Pathophysiological aspects of edema formation in diabetic nephropathy. *Kidney Int* 38: 1187–1192
4. Rothe CF (1983) Reflex control of veins and vascular capacitance. *Physiol Rev* 63: 1281–1342
5. Stehouwer CDA, Lambert J, Donker AJM, Hinsbergh VWM van (1997) Endothelial dysfunction and pathogenesis of diabetic angiopathy. *Cardiovasc Res* 34: 55–68
6. Muntinga JHJ, Visser KR (1992) Estimation of blood pressure-related parameters by electrical impedance measurement. *J Appl Physiol* 73: 1946–1957
7. Muntinga JHJ, Gels ME, Terpstra WF, Visser KR (1995) Investigation of the arterial and venous upper arm vascular bed. *Med Eng Phys* 17: 264–272
8. Schaper NC, Houben AJHM, Schoon Y, Kooman JP, Huvers FC, Nieuwenhuijzen Kruseman AC (1994) Venous compliance and the venodilatory effect of nitroglycerin in insulin-dependent diabetic patients with and without (incipient) nephropathy. *Eur J Clin Invest* 24: 382–387
9. Tooke JE (1995) Microvascular function in human diabetes. A physiological perspective. *Diabetes* 44: 721–726
10. Giannattasio C, Failla M, Piperno A et al. (1999) Early impairment of large artery structure and function in Type I diabetes mellitus. *Diabetologia* 42: 987–994