

Decreased Circulatory Response to Hypovolemic Stress in Young Women With Type 1 Diabetes

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OBJECTIVE—Diabetes is associated with hemodynamic instability during different situations involving acute circulatory stress in daily life. Young men with type 1 diabetes have been shown to have impaired circulatory response to hypovolemic stress. The effect of type 1 diabetes on cardiovascular response to hypovolemia in young women is unknown, however.

RESEARCH DESIGN AND METHODS—Lower body negative pressure of 30 cm H₂O was used to create rapid hypovolemic stress in 15 young women with type 1 diabetes (DW) and 16 healthy women (control subjects [C]). Compensatory mobilization of venous capacitance blood (capacitance response) and net fluid absorption from tissue to blood were measured with a volumetric technique. Overall cardiovascular responses and plasma norepinephrine levels were measured.

RESULTS—Capacitance response was reduced (DW, 0.67 ± 0.05 ; C, 0.92 ± 0.06) and developed slower in DW ($P < 0.01$). Capacitance response was further reduced with increasing levels of HbA_{1c}. Fluid absorption was almost halved in DW ($P < 0.01$). The initial vasoconstrictor response was reduced and developed slower in DW ($P < 0.05$). Arterial vasoconstriction was further reduced in the presence of microvascular complications ($P < 0.05$).

CONCLUSIONS—DW present with decreased and slower mobilization of venous capacitance blood and decreased net fluid absorption from tissue to blood during hypovolemic circulatory stress. Collectively, this indicates that DW are prone to hemodynamic instability, especially in the presence of microvascular complications and poor glycemic control.

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Diabetes is associated with increased risk of hemodynamic instability and reduced tolerance to hypovolemia, including higher risk of cardiovascular instability during surgery (1–7) and hemodialysis (8,9). Diabetes patients with cardiovascular autonomic neuropathy (CAN) are at even greater risk of hypotension during surgery (2,3,5,6). Orthostatic hypotension is more common in diabetes patients (1,2,5,10,11), but diabetes patients with no detectable or only mild CAN also have an increased risk of hypotension during orthostatic stress and surgery, indicating the presence of other contributing mechanisms (1,6). Two important and rapid mechanisms to

maintain cardiovascular homeostasis during acute hypovolemic stress are mobilization of venous capacitance blood from peripheral tissues to the central circulation (capacitance response) and net capillary fluid absorption from extravascular to intravascular space (12–15).

Young men with type 1 diabetes without overt microvascular complications present with reduced net capillary fluid absorption in response to experimental hypovolemic stress (16,17). We recently presented evidence of further reduction in net capillary fluid absorption as well as reduced mobilization of venous capacitance blood (capacitance response) in men with type 1 diabetes

with microvascular complications (18). In comparison with age- and sex-matched humans, aortic stiffness increased relatively more in women with type 1 diabetes (DW) than in men with type 1 diabetes (19). Moreover, healthy young women are more susceptible to acute hypovolemic stress than age-matched men, making women a particularly interesting group to study (20). The ability to increase effective circulating blood volume by net fluid absorption and mobilization of capacitance blood during hypovolemic stress is, however, unknown in young DW.

The aim of the current study was to investigate the mechanisms to increase effective circulating blood volume during rapidly induced hypovolemic circulatory stress in DW, focusing on the capacitance response and net capillary fluid absorption from tissue to blood. We hypothesized that DW would display a reduced ability to defend effective circulatory blood volume in responses to hypovolemic stress.

RESEARCH DESIGN AND METHODS

DW who were patients in the Endocrinology Department of Linköping University Hospital were asked to participate in the study if they met the inclusion and exclusion criteria. Inclusion criteria were as follows: age between 18 and 30 years; duration of diabetes of at least 5 years; and willingness to participate in the study. Exclusion criteria were as follows: current smoking; sedentary lifestyle/obesity; and cardiovascular disease. Fifteen DW were included in the study. They were all receiving a multiple-dose insulin regimen or were being treated with an insulin pump without any other chronic cardiovascular medication, with HbA_{1c} at $7.4 \pm 0.2\%$ (66 ± 2 mmol/mol; range 5.5–8.9% [47–82 mmol/mol]; reference value $<5.3\%$ [45 mmol/mol]). Sixteen healthy age-matched women (control subjects [C]) were selected from the general population meeting the same inclusion/exclusion criteria with the exception of having type 1 diabetes. Subgroup analyses were conducted for differences in glycemic control as well as the presence of microvascular disease. In

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order to elucidate the effect of hyperglycemia over time, the mean HbA_{1c} level percentage from 5 years preceding the study (HbA_{1c5}) was calculated, as in the study by Yu et al. (21), as $7.4 \pm 0.3\%$ (67 ± 2 mmol/mol; range 5.9–9.7% [51 – 84 mmol/mol]) in DW, whereas the HbA_{1c} level in C was $4.0 \pm 0.1\%$ (31 ± 1 mmol/mol). Based on their HbA_{1c5} levels, all participating subjects were divided into the following three groups: normal ($n = 16$); mid ($n = 7$; HbA_{1c5}: range 5.9–7.3% [51 – 66 mmol/mol], mean $6.7 \pm 0.2\%$ [58 ± 2 mmol/mol]); high ($n = 8$; HbA_{1c5}: $>7.4\%$ [>67 mmol/mol], mean $8.2 \pm 0.3\%$ [74 ± 2 mmol/mol]) (HbA_{1c5} groups: low vs. mid and high $P < 0.0001$; mid vs. high $P < 0.0001$). Microvascular disease was present in seven DW (all with background retinopathy [RET], of whom four had slight or minimal background RET) and comprised a subgroup of DW with RET (RET+), while the remaining eight DW comprised a subgroup of DW without RET (RET–). Kidney function was normal. All women were scheduled in the middle part of the menstrual cycle, with 15 women (6 DW) studied while they were receiving oral contraceptives. Only a minor impact of menstrual cycle and oral contraceptives has been seen in similar studies (12). Each subject provided written informed consent to the experiments, which were approved by the local Ethics Committee and conformed to the Helsinki Declaration.

The experiments started 1 h after a light meal at random times in the morning or afternoon. No circadian variations have been seen in previous, similar experiments in our laboratory (12). Room temperature was held constant between 23 and 25°C. The subjects were instructed to abstain from drinking caffeinated beverages for 24 h prior to the investigation. DW received their ordinary insulin doses. The subjects were placed in the supine position, with the lower part of the body up to the level of the iliac crest, and were enclosed in an airtight box connected to a vacuum source, enabling stable negative pressure to be produced within 5 s (lower body negative pressure [LBNP]). LBNP is an established technique, and is an excellent model for hypovolemic circulatory stress and hypotension, causing well-defined circulatory stress by the pooling of blood and net fluid filtration in the lower part of the body, with a reduction in central blood volume and unloading of central low-pressure as well as high-pressure baroreceptors (14,22).

Changes in calf volume were measured using strain-gauge plethysmography applied at the maximal calf circumference (12,23). Calf volume increase during LBNP was separated into blood pooling and net fluid filtration according to the technique described by Lindenberger and Länne (23). The coefficient of variation for blood pooling and net fluid filtration is good (8 and 19%, respectively) (23). Capillary fluid coefficient (CFC; in $\text{mL} \cdot 100 \text{ mL}^{-1} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$) was calculated as the net fluid filtration divided by transmural pressure gradient (24). Calf volume increase was used as a surrogate measure for central hypovolemia, and a clear correlation between calf blood pooling and LBNP level was found (15,20,24). The venous compartments in the legs rather than the pelvic or abdominal region seem to be of hemodynamic importance during orthostatic stress (25).

The increase in effective circulating blood volume during hypovolemia (i.e., the compensatory venous capacitance response and capillary fluid absorption) was assessed with the aid of air plethysmography in the upper arm. The technique has been described in detail by Lindenberger et al. (12). Briefly, a cylindrical plethysmograph was fitted to the subject's upper arm and sealed tight with a latex compound that did not cause any pressure or irritation to the skin. A piston recorder connected to the plethysmograph measured tissue volume changes with the arm placed at heart level. Continuous recordings ensured that the volume of the enclosed arm was stable for at least 5 min before each LBNP trial. The application of LBNP leads to a rapid series of events, as depicted in Fig. 1: I, an initial mobilization of regional blood toward the central circulation (arm capacitance response); II, net capillary absorption of extravascular fluid to intravascular space; III, rapid recovery of regional blood after the termination of LBNP; IV, total net capillary fluid absorption during LBNP; and V, capillary filtration from the intravascular to the extravascular space. This interpretation of tissue volume changes has been validated with the use of technetium-marked erythrocytes (13,26). The capacitance response and net capillary fluid absorption were assessed from volume recordings in each subject according to the technique described in detail by Lindenberger et al. (12).

Forearm blood flow (FBF) was measured in the right forearm by standard

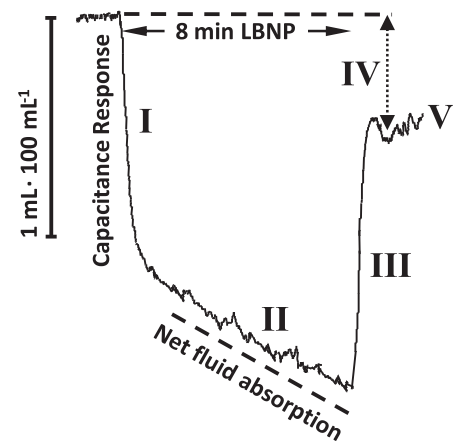


Figure 1—Original tracing illustrating tissue compensatory volume changes evoked by LBNP₃₀. The initial rapid decrease in volume reflects the mobilization of regional blood from peripheral to central circulation (capacitance response), whereas the much slower, but continuous, decline reflects capillary fluid absorption. After the cessation of LBNP, there is a rapid return of blood volume. The remaining deficit reflects extravascular fluid absorbed during LBNP. See text for explanation of roman numerals.

venous occlusion strain-gauge plethysmography (EC-6; D.E. Hokanson, Bellevue, WA). The FBF was measured repeatedly at baseline directly prior to and twice more at 30 s, and 1, 3, 6, and 8 min after the institution of LBNP. Simultaneously, blood pressure was measured noninvasively (Dinamap Pro200; Critikon, Tampa, FL), with forearm vascular resistance (FVR) and forearm vascular conductance (FVC) calculated, respectively, as follows: $FVR = \text{MAP}/\text{FBF}$; $FVC = \text{FBF}/\text{MAP}$, where MAP is mean arterial pressure.

After at least 45 min of experimental setup and supine rest, an LBNP of 30 cm H₂O (LBNP₃₀) was instituted and maintained for 8 min. Assessment of the increase in effective circulating blood volume (compensatory capacitance response and net fluid absorption) was measured during the first LBNP run, whereas FBF recordings (it was not possible to measure LBNP and FBF simultaneously) was measured during a second LBNP experiment following the first, with at least 20 min of supine rest in between to restore fluid shift over vessel walls. When needed, the above procedure was repeated in order to acquire accurate data.

Venous blood from an indwelling catheter, obtained with participants at rest and after they had undergone 4 min of LBNP₃₀, was analyzed for the plasma

concentration of norepinephrine (P-NE [in picomoles per liter]). The chilled samples were cold-centrifuged within 20 min, stored in a -70°C freezer, and later analyzed with the high-performance liquid chromatography technique. P-NE is known to correlate well with the overall sympathetic activation secondary to the induced hypovolemic stress. Blood glucose levels were measured before the initiation of LBNP. The experiments were postponed if blood glucose level was high or if the subject had experienced symptoms of hyperglycemia or hypoglycemia prior to the experiment.

Values are expressed as means \pm SE if not stated otherwise. Mean values were calculated for cardiovascular parameters (area under the curve [AUC]), and group differences in volumetric measurements in the arm and calf were assessed using Student *t* test. Repeated-measures ANOVA were used to assess responses to LBNP over time. Regression analyses were applied to assess correlations within the groups (e.g., to evaluate the presence of microvascular disease or level of HbA_{1c} on cardiovascular response in DW). $P < 0.05$ was considered to be statistically significant.

RESULTS—No differences were seen between DW and C in age (DW 24.6 ± 0.8 years; C 22.8 ± 0.4 years), body height (DW 166 ± 2 cm; C 170 ± 2 cm), or body weight (DW 66 ± 2 kg; C 61 ± 2 kg), but BMI was slightly higher in DW (DW 23.7 ± 0.5 kg/m²; C 21.2 ± 0.4 kg/m²; $P < 0.01$).

Blood pooling in the calf during LBNP₃₀ was similar between the groups

(DW 1.1 ± 0.07 mL \cdot 100 mL⁻¹; C 1.2 ± 0.08 mL \cdot 100 mL⁻¹). Total net fluid filtration in the calf was 0.46 ± 0.04 mL \cdot 100 mL⁻¹ for DW and 0.53 ± 0.02 mL \cdot 100 mL⁻¹ for C, with a trend toward lower fluid filtration in DW ($P = 0.08$). CFC was 0.0040 ± 0.0003 mL \cdot 100 mL⁻¹ \cdot min⁻¹ \cdot mmHg⁻¹ for DW and 0.0047 ± 0.0002 mL \cdot 100 mL⁻¹ \cdot min⁻¹ \cdot mmHg⁻¹ for C ($P = 0.08$). Furthermore, CFC was inversely correlated with resting heart rate ($r = -0.41$, $P = 0.02$).

Table 1 shows cardiovascular data at baseline and during LBNP. At rest, systolic blood pressure (SBP) as well as MAP were similar, whereas DW had lower diastolic blood pressure (DBP) ($P < 0.05$) and concomitantly greater pulse pressure (PP) ($P < 0.01$). Resting heart rate was higher in DW ($P < 0.001$), and DW had greater FBF, resulting in higher calculated FVC (both $P < 0.05$). All subjects tolerated LBNP₃₀ well without vasovagal reactions. LBNP₃₀ induced a significant decrease in SBP, PP, FVC, and FBF, whereas DBP, FVR, and P-NE increased (at least $P < 0.01$). No differences between DW and C were seen in changes in mean (AUC) blood pressure parameters or heart rate. P-NE increased in response to LBNP ($P < 0.0001$), without differences between the groups. FVC response decreased rapidly after the initiation of LBNP in both groups. FVC decreased the percentage of the resting value to $79 \pm 5\%$ and $76 \pm 5\%$ in DW 30 and 60 s after LBNP initiation, with corresponding numbers of $65 \pm 3\%$ and $79 \pm 5\%$ in C. The change in FVC during the initial 30 s was both reduced and

slower in DW than in C (both $P < 0.05$), and FVC decrease in C was maximal 30 s after LBNP initiation and recovered during the next 30 s ($P < 0.05$). From then on, FVC was stable throughout LBNP in both groups with no significant differences.

Figure 2A shows the arm capacitance response to LBNP₃₀ (DW 0.67 ± 0.05 mL \cdot 100 mL⁻¹; C 0.92 ± 0.06 mL \cdot 100 mL⁻¹), with reduced capacitance response in DW ($P < 0.01$). Figure 2B shows the net capillary fluid absorption in the arm (mL \cdot 100 mL⁻¹) during 8 min of LBNP₃₀ (DW 0.30 ± 0.03 mL \cdot 100 mL⁻¹; C 0.52 ± 0.07 mL \cdot 100 mL⁻¹), which was reduced in DW ($P < 0.05$). Figure 2C displays the initial volumetric response in the calf (eliciting central hypovolemia) and the concomitant compensatory fluid mobilization from the arm. Calf volume increase reflects mainly blood pooling but also, to a smaller extent, net fluid filtration, whereas arm volume decrease mainly reflects a decrease in venous blood volume but also, to a lesser extent, net fluid absorption. No overall difference was seen in volume increase in the calf. In contrast, the compensatory mobilization of fluid from peripheral to central circulation was both markedly slower ($P = 0.0006$) and reduced ($P = 0.004$) in DW. Moreover, the pattern with slower initial fluid mobilization in DW was still evident when accounting for group differences in fully evoked capacitance response ($P = 0.02$). For instance, the amounts of mobilized fluid 30 s after LBNP initiation were $75 \pm 2\%$ of fully evoked capacitance response for DW, and $83 \pm 2\%$ of fully evoked

Table 1—Cardiovascular parameters at rest and during LBNP₃₀

Parameters	DW			C		
	REST	LBNP		REST	LBNP	
		Abs	%		Abs	%
HR (bpm ⁻¹)	69 \pm 2***	4 \pm 2	6 \pm 2	58 \pm 2	4 \pm 0.9	7 \pm 2
SBP (mmHg)	110 \pm 2	-1 \pm 0.5	-1 \pm 0.4	106 \pm 1	-1 \pm 0.5	-1 \pm 0.5
DBP (mmHg)	61 \pm 1*	1 \pm 0.4	2 \pm 0.8	65 \pm 1	2 \pm 0.4	3 \pm 0.7
MAP (mmHg)	78 \pm 1	1 \pm 0.4	1 \pm 0.6	78 \pm 1	1 \pm 0.4	1 \pm 0.5
PP (mmHg)	49 \pm 2**	-2 \pm 1	-5 \pm 1	41 \pm 2	-3 \pm 0.6	-7 \pm 1
FBF (mL \cdot 100 mL ⁻¹ \cdot min ⁻¹)	2.6 \pm 0.2*	-0.5 \pm 0.1	-17 \pm 4	1.9 \pm 0.2	-0.3 \pm 0.1	-15 \pm 4
FVR (units)	31 \pm 2**	8 \pm 2	28 \pm 8	45 \pm 4	9 \pm 4	23 \pm 6
FVC (units), E ⁻³	34 \pm 2*	-6 \pm 1	-17 \pm 4	25 \pm 3	-4 \pm 1	-16 \pm 4
P-NE (pmol/L)	1.2 \pm 0.2	0.4 \pm 0.1	38 \pm 10	1.2 \pm 0.1	0.3 \pm 0.1	36 \pm 8

Values are mean \pm SE. REST, values before LBNP; LBNP, AUC absolute (Abs) and relative change (%) during LBNP₃₀; HR, heart rate. * $P < 0.05$, group differences in resting values. ** $P < 0.01$, group differences in resting values. *** $P < 0.001$, group differences in resting values. No group differences were seen in response to mean values during 8 min of LBNP.

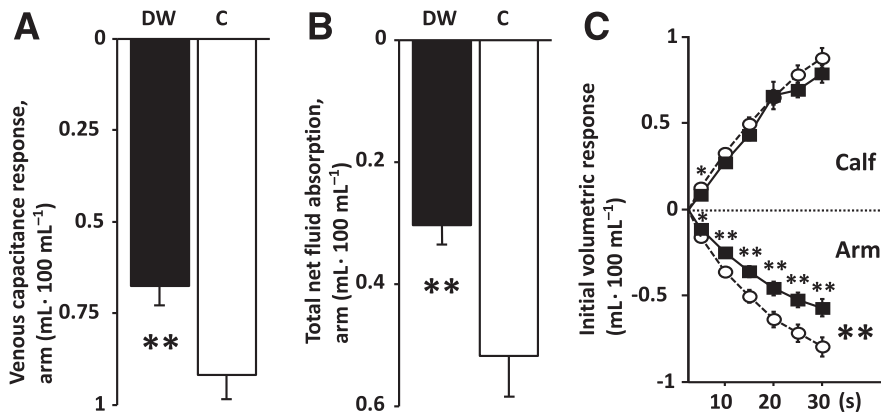


Figure 2—A: Capacitance response (fluid mobilization from peripheral to central circulation) in response to LBNP₃₀ (DW, black; C white). Capacitance response was reduced in DW (**P < 0.01). B: Net capillary fluid absorption from extravascular to intravascular compartments in response to LBNP₃₀. Net capillary fluid absorption was almost halved in DW (**P < 0.01). C: Initial calf volume increase (top) and fluid mobilization from peripheral to central circulation (bottom) during the first 30 s after the initiation of LBNP. The compensatory mobilization of fluid from peripheral to central circulation was both slower (ANOVA, P = 0.0006) and reduced in DW (**P = 0.004). *P < 0.05 and **P < 0.01, group difference for each point in time.

capacitance response for C (P = 0.03). A correlation was seen between initial vasoconstrictor response and capacitance response in C (e.g., the initial percentage FVC decrease vs. capacitance response during the first 30 s after LBNP initiation; $r = -0.57$, P = 0.02). However, the vasoconstrictor response and capacitance response were uncorrelated in DW ($r = 0.03$, P = 0.94).

Figure 3A presents resting heart rate in correlation with the level of HbA_{1c5}. Resting heart rate increased with increasing level of HbA_{1c5} (P = 0.0002). Figure 3B illustrates the correlation between resting heart rate and compensatory capacitance response. An increased heart rate at rest was inversely correlated with capacitance response ($r = -0.45$, P = 0.01). Figure 3C depicts compensatory capacitance response to LBNP₃₀ in correlation with the level of HbA_{1c5}. The capacitance response were 0.92 ± 0.07 mL · 100 mL⁻¹ (low), 0.73 ± 0.07 mL · 100 mL⁻¹ (mid), and 0.60 ± 0.09 mL · 100 mL⁻¹ (high), with decreasing capacitance response with increasing group level of HbA_{1c5} values (P = 0.02). Calculations using the present HbA_{1c} value obtained equal findings (data not shown). Diabetes duration was not significantly correlated to the level of HbA_{1c}. Figure 3D shows the mean as well as the maximal decrease in FVC in response to LBNP₃₀ in RET+ and RET-. RET+ demonstrated a smaller decrease in FVC, measured both as the mean and maximal FVC (P < 0.05). RET+ also

seemed to have higher levels of HbA_{1c5}, although they failed to reach significance (P = 0.06).

CONCLUSIONS—The main findings of the study were as follows: the rapid mobilization of venous capacitance blood from peripheral tissues to the central circulation is both slower and reduced in young DW compared with a healthy population. DW demonstrate impaired net capillary fluid absorption from tissue to blood in response to hypovolemic stress. The fast initial arterial vasoconstrictor response was absent in women with diabetes. Overall, these defense mechanisms seemed aggravated when microvascular disease and autonomic dysfunction was present in DW.

Hemodynamic considerations

Hemodynamic instability and reduced tolerance to hypovolemia seem more common in patients with diabetes, both in the shorter and longer time periods. In the long term (minutes to hours), diabetes is associated with increased hemodynamic instability during hemodialysis as well as general anesthesia (2–9). In the short term (seconds to minutes), diabetes is associated with hemodynamic instability and hypotension during the induction of anesthesia, as well as with change in body position (1–5,7,11). LBNP is an excellent model for hypovolemic circulatory stress by inducing central hypovolemia and unloading of baroreceptors with

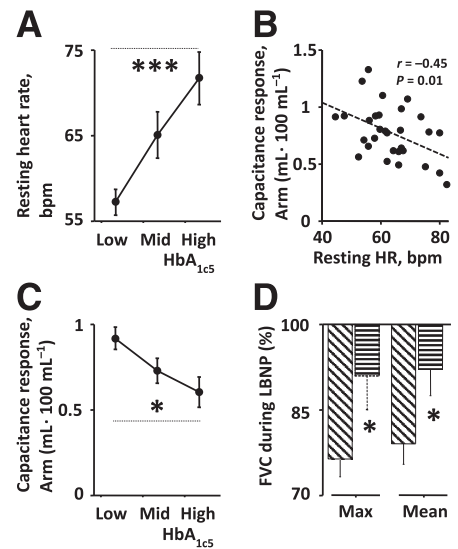


Figure 3—A: Resting heart rate (a surrogate marker for autonomic dysfunction) in correlation to level of HbA_{1c5} (low <5.3%; mid 5.3–7.3%; high >7.4%). Resting heart rate increased with increasing level of HbA_{1c} (**P = 0.0002). B: Correlation between resting heart rate and capacitance response, with heart rate being inversely correlated with capacitance response ($r = -0.45$, P = 0.01). C: Venous capacitance response in relation to level of HbA_{1c5} (low <5.3%; mid 5.3–7.3%; high >7.4%). Venous capacitance response decreased with increasing HbA_{1c} (*P < 0.05). D: Decrease in FVC in response to LBNP (initial and mean FVC response, respectively) in DW RET- (bars with diagonal lines) and RET+ (bars with horizontal lines). FVC response was decreased in DW RET+ (*P < 0.05). HR, heart rate; Max, maximum.

activation of the sympathetic autonomic system (22). Our group has previously studied the rapid hypovolemic circulatory response in young men with type 1 diabetes and found decreased defense of central hypovolemia evident in the form of a diminished ability to recruit extravascular fluid to increase the effective circulating blood volume (16–18). If microvascular disease was evident, the ability to mobilize venous capacitance blood was also impaired (18). Indications of orthostatic intolerance were also seen in diabetes patients with microvascular complications at fairly low levels of LBNP (43 cm H₂O) (18). These hemodynamic responses to hypovolemia have not been studied in DW. In the general population, young women have lower tolerance to hypovolemic circulatory stress than men (20). Compared with the nondiabetic population, the presence of diabetes increases the risk for enhanced vascular stiffness

as well as cardiovascular disease more in women than men (19). Taken together, this increases the importance of studying hemodynamic responses to circulatory stress in women.

Cardiovascular response

The initial rapid vasoconstrictor response was both reduced and slower in DW and seemed to be linked to disease severity (Fig. 3D). The DW were all free of signs of peripheral neuropathy and had normal kidney function. CAN is, however, common in patients with diabetes, often remains asymptomatic during the initial course, and increases with the duration of disease (5,27). CAN has been proposed as a major etiological factor contributing to hemodynamic instability in diabetes patients (5,7,10,25). DW presented with increased heart rate at rest, suggesting autonomic dysfunction (28). Furthermore, resting heart rate increased with the level of HbA_{1c5} (Fig. 3A and Table 1). The both slower and reduced initial vasoconstrictor response seen in DW could be attributable to CAN (Fig. 3D). However, decreased hemodynamic stability is also present in type 1 diabetes patients with no or only mild CAN, indicating that other mechanisms are involved (1,6). Both venous capacitance response as well as net capillary fluid absorption seem to constitute important compensatory responses for the restitution of plasma volume and hemodynamic stability during acute hypovolemia (12,14,15,26), and decreased net capillary fluid absorption has been described in men with type 1 diabetes mellitus without overt signs of CAN (16–18).

Advanced glycation end products

Hyperglycemia induces increased glycation of proteins, and they undergo further complex reactions to become irreversibly cross-linked, then termed advanced glycation end products (AGEs). The formation and accumulation of AGEs have been known to progress at an accelerated rate in diabetes. AGEs accumulate on collagen and elastin in the vessel wall, and have been implicated in both the microvascular and macrovascular complications of diabetes (29), for instance, in the increase in vascular stiffness in diabetes patients (30,31). They also lead to deteriorated structural integrity and physiological function of multiple organ systems, including the microcirculation. For instance, capillary basement membranes are thickened in diabetes patients (29).

The interaction between AGEs and receptors for AGEs elicits oxidative stress generation and is also involved in diabetic macrovascular and microvascular complications, in part via endothelial dysfunction (29,32). Both endothelium-dependent as well as endothelium-independent vasodilatation seem impaired in type 1 diabetes patients (32). Ultimately, it is microvascular function that dictates blood flow, and, all in all, many of our findings could be attributed to the increased number of AGEs and their role in the pathogenesis of diabetes, which is discussed below.

Capacitance response

The mobilization of venous capacitance blood from the peripheral to central circulation in response to acute hypovolemia was both slower and reduced in DW (Fig. 2A and C). The capacitance response is to a major extent a passive mechanism depending on the following two factors: 1) decrease in transmural pressure over the venous wall; and 2) compliant venous walls (i.e., high venous compliance). LBNP induces baroreceptor-mediated vasoconstriction and maintains blood pressure through increased peripheral resistance. Concomitantly, the venous pressure decreases (14), which is also shown by the correlation between vasoconstriction and capacitance response in C. Thus, the attenuated initial vasoconstriction in DW probably leads to a slower decrease in venous pressure and might explain their slower rate of development of initial capacitance response (Fig. 2C). However, no correlation between vasoconstriction and capacitance response was found in DW, indicating the presence of other plausible mechanisms for the reduced capacitance response. This is further corroborated by the fact that no reduction in arterial vasoconstriction was seen 1–3 min after LBNP initiation, at which time the capacitance response is fully developed (13,26). One contributing factor could be the impaired endothelium-dependent as well as endothelium-independent vasodilatation associated with type 1 diabetes (32). Reduced venous compliance has been associated with type 1 diabetes (33,34). AGEs are increased early in patients with type 1 diabetes, and increase with diabetes duration, elevated HbA_{1c} levels, and the presence of microvascular complications (30,35,36). Increased AGEs in vessel walls seem directly correlated to increased vessel stiffness, at least in elastic arteries (30). Increased numbers of AGEs in

extracellular matrix proteins such as elastin and collagen would bring forth lower viscous elasticity and greater inertia to a change in geometry, secondary to increased venous wall thickness. The resulting reduced venous compliance could explain both the reduced and the slower development of capacitance response seen in DW. Levels of different AGEs in type 1 diabetes are strongly correlated with both recent and cumulative HbA_{1c} values (last 5 years) (21). In analogy, capacitance response was reduced with increasing levels of HbA_{1c5} (Fig. 3C). The level of HbA_{1c5} was also highly correlated to resting heart rate, a surrogate measure for the presence of autonomic dysfunction (28) (Fig. 3A), and, in its turn, was inversely correlated with capacitance response (Fig. 3B).

Capillary fluid filtration

Net capillary fluid absorption was almost halved in DW in response to hypovolemic stress (Fig. 2B). An efficient capillary fluid absorption is dependent on both high hydrodynamic conductivity (measured as CFC) as well as a great decline in capillary pressure caused by autonomic reflex adjustments of both α - and β -adrenergic receptors, creating a net driving force over the capillary wall by affecting the precapillary to postcapillary resistance ratio. Patients with type 1 diabetes might present with reduced transcapillary driving force due to reduced precapillary resistance (37), and net fluid absorption could be further affected by the presence of microvascular dysfunction, and impaired endothelium-dependent and endothelium-independent vasodilatation associated with type 1 diabetes (32) as well as with AGEs (29). We found reduced initial arterial vasoconstriction in DW (mainly α -receptor-mediated), but no difference in mean arterial vasoconstriction during LBNP. Reduced transcapillary driving force attributable to CAN could, however, still contribute to the decreased net fluid absorption seen in DW. In addition, we found a significant inverse correlation between CFC and resting heart rate, a surrogate measure for autonomic dysfunction (see Results), in analogy with reduced CFC in men with diabetes (17,18).

Clinical implications

The redistribution of blood and fluid in order to increase the effective circulating blood volume is a crucial line of defense against hypovolemic circulatory stress

and comes into play within seconds in order to preserve homeostasis (Figs. 1 and 2C) (12,14,15,26). The large skeletal muscle mass constitutes an important blood reservoir, and up to 1000 mL of fluid could rapidly be mobilized in response to acute hypovolemic stress (12,26). We could not detect any group differences in blood pressure parameters despite the differences in capacitance response and net fluid absorption. During LBNP, the blood pressure is held constant through baroreceptor activation and tends to decrease first at higher LBNP stimuli (22). However, Philips et al. (11) found a greater initial decrease in blood pressure during orthostatic maneuvers in subjects with diabetes. Moreover, they found that the return to baseline values in blood pressure also tended to be delayed (11). The decreased initial vasoconstrictor response and reduced and slower mobilization of peripheral capacitance blood in DW could at least in part explain these findings. The both slower and reduced venous capacitance response found in patients with diabetes leads to decreased venous return and to a reduced cardiac output, which are likely to enhance the hemodynamic instability also seen during the induction of anesthesia (2–6). In corroboration with our data, the need for comprehensive preoperative assessment for optimal anesthetic management of patients with diabetes has been postulated (2,5–7,38). Besides the increased use of vasopressors during anesthetic induction in diabetes patients, mainly targeting CAN (2,3,6), vigorous infusion of plasma volume expanders might be useful in patients with diabetes to help promote venous return, which seemingly is even more important in the presence of autonomic dysfunction (Fig. 3B). Increased plasma volume due to net capillary fluid absorption from extravascular to intravascular space is a slower but ongoing process (26). It can be seen as a delicate internal control of the plasma volume in the body. The decreased net fluid absorption in patients with type 1 diabetes could therefore affect hemodynamic stability over time, as seen with the greater incidence of hemodynamic instability during dialysis in patients with diabetes (8,9) as well as during continued general anesthesia (2–7). The decreased ability to increase effective circulating blood volume in diabetes patients also implies a diminished possibility to endure major trauma and other causes of blood and fluid losses (e.g., labor or burn injuries).

Limitations of the study

We did not assess maximal LBNP tolerance because the evaluated responses to hypovolemic stress (e.g., assessment of net fluid absorption) requires the absence of vasovagal reactions to be interpreted. Hemodynamic responses were instead studied during LBNP₃₀, which is known to rapidly displace roughly 10% of total blood volume from the central circulation (22). If greater hypovolemic stress had been applied, the effect of type 1 diabetes on net fluid absorption and capacitance response would have been more apparent, because group differences increase with increasing hypovolemic stress (15,16).

We did not assess heart rate variability or the presence of CAN. Many patients with CAN remain asymptomatic during the initial course, making a diagnosis difficult (5). CAN is associated with poor glycemic control and the presence of RET (27,39), making it likely that the DW with signs of RET and worse glycemic control had CAN. Resting heart rate, a surrogate marker of autonomic dysfunction (28), increased with increasing level of HbA_{1c5} (Fig. 3A). Furthermore, significant correlations between resting heart rate and reduced capacitance response as well as lower CFC were found (Fig. 3B) (see RESULTS). Nevertheless, the fact that we did not directly assess CAN and venous compliance obliterates a more direct correlation with our positive findings. Finally, insulin is known to affect various cardiovascular responses. However, the difference in daily insulin dose or blood glucose level was not correlated with the studied cardiovascular parameters, in corroboration with a previous study with no effect of insulin infusion on fluid mobilization (40).

In conclusion, rapid mobilization of venous capacitance blood from peripheral tissues to the central circulation was both slower and reduced in young DW, and was further reduced if diabetic control was poor or when indications of autonomic dysfunction were present. Capillary fluid absorption from tissue to blood was also impaired in DW. Initial vasoconstriction was slower in DW. Collectively, these novel findings shed new light on the pathophysiology in the hemodynamic instability associated with diabetes.

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M.L. participated in study design; conducted the study and collected, analyzed, and interpreted data; and wrote the majority of the manuscript. T.Li. participated in study design, recruited women with type 1 diabetes, and critically revised the manuscript. T.Lä. participated in study design, interpreted data, and critically revised the manuscript. All authors have approved the final version of the manuscript. M.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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