Effect of hyperglycaemia on arterial pressure, plasma renin activity and renal function in early diabetes

Judith A. MILLER, John S. FLORAS, Bernard ZINMAN, Karl L. SKORECKI and Alexander G. LOGAN
Department of Medicine, University of Toronto, Canada
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1. In insulin-dependent diabetes mellitus, hyperglycaemia has a profound effect on renal and systemic haemodynamic function. The mechanism for this is unknown.

2. We conducted a study in 11 males with insulin-dependent diabetes mellitus, within 6 years of diagnosis. We examined the neurohumoral, haemodynamic and renal variables during euglycaemia (4.0–6.0 mmol/l) and after a 12h period of hyperglycaemia (8.5–10.5 mmol/l). Subjects were examined in a sodium-replete state during supine rest and during simulated orthostatic stress induced by lower body negative pressure at −15 mmHg.

3. Variations in glycaemia markedly influenced plasma renin activity, which was increased at baseline during hyperglycaemia (3.82 ± 0.66 pmol of angiotensin I h⁻¹ ml⁻¹ compared with 2.13 ± 0.33 pmol of angiotensin I h⁻¹ ml⁻¹ during euglycaemia, P = 0.009), and rose further during simulated orthostatic stress. Mean arterial pressure was also elevated during hyperglycaemia (89 ± 2 mmHg compared with 81 ± 3 mmHg during euglycaemia, P = 0.03), both at rest and during orthostatic stress.

4. The renal haemodynamic effects of hyperglycaemia included maintenance of glomerular filtration rate in the face of significant declines in renal blood flow, and a probable increase in filtration fraction (0.21 ± 0.01 compared with 0.18 ± 0.01 during euglycaemia, P = 0.06). The responses of mean arterial pressure and renal blood flow to simulated orthostatic stress were not affected by hyperglycaemia, but the forearm vascular response was significantly augmented.

5. These data suggest that sustained hyperglycaemia activates the renin-angiotensin system, thereby increasing systemic and renal vasomotor tone. Over time such changes may have deleterious microvascular consequences.

INTRODUCTION

Recent epidemiological evidence suggests that maintenance of euglycaemia in subjects with insulin-dependent diabetes mellitus (IDDM) delays the onset and/or prevents the occurrence of such microvascular complications as retinopathy and nephropathy [1]. The mechanisms for this benefit remain obscure. It is well known that acute infusions of glucose induce elevations of glomerular filtration rate (GFR), effective renal plasma flow (ERPF) and filtration fraction (FF) in patients with IDDM [2–6], and that poor metabolic control is associated with an increased cardiac output and elevated blood flow in other organ systems [7]. Similarly, there is some intriguing evidence that poor glycemic control may increase blood pressure [7, 8]. The mechanisms responsible for these effects on systemic and renal haemodynamic function have not yet been clarified.

Because of these deficiencies in our present understanding of this important condition, we examined the neurohumoral, systemic and renal haemodynamic responses to hyperglycaemia in humans with early uncomplicated IDDM. As diabetic humans are often mildly to moderately hyperglycaemic for prolonged periods of time, we elected to study these variables after a 12h period of hyperglycaemia. Therefore, responses were measured during euglycaemia and compared with those obtained after a period of moderate hyperglycaemia. The target plasma glucose concentration during the hyperglycaemic phase of the experiment was chosen to avoid glycosuria, thus preventing an osmotic diuresis and changes in extracellular fluid volume which could impact on the outcome measures. Subjects were studied in the sodium-replete state during supine rest, as well as during simulated orthostatic stress, induced by non-hypotensive lower
body negative pressure (LBNP) at \(-15\) mmHg [9, 10], to better replicate normal daily activity.

METHODS

Subjects

The subjects consisted of 11 diabetic males, mean age \(23 \pm 2\) years. Six of the 11 subjects had participated in a previous study from our laboratory [9] and their characteristics were therefore similar. They were all insulin dependent and studied within 6 years of diagnosis (mean \(3.5 \pm 0.6\) years, range \(1.2-5.5\) years). They were otherwise healthy, normotensive and non-obese, on no medication except for insulin and without evidence of retinopathy, microalbuminuria or an orthostatic decrease in blood pressure. HbA\(_{1c}\) was less than 10\% in all cases (mean \(7.5 \pm 1.2\)%). The study was performed with the approval of the University of Toronto Human Subjects Review Committee, and with the informed written consent of each subject.

Each subject was maintained on a 200 mmol sodium diet, supplemented with sodium chloride tablets where necessary, for 7 days before each study, and compliance was ascertained by measurement of 24-h urine sodium \((U_{\text{Na}}V)\) excretion on both the sixth and seventh days. Subjects were considered properly prepared for study if the excretion of sodium was \(180-220\) mmol in 24h. No subjects were excluded on this basis. All subjects refrained from tobacco and caffeine for 48 h before each study.

Subjects were studied on two occasions: a euglycaemic state and a moderately hyperglycaemic state (randomly determined). The time interval between the first and the second investigation was a minimum of 10 days and a maximum of 3 weeks. The subjects were admitted to the Clinical Investigation Unit of Toronto Hospital the evening before each study day. An 18-gauge peripheral venous cannula was inserted into a left antecubital vein for infusions of insulin. Blood glucose was measured every hour (Accucheck), and the insulin infusion was varied to maintain euglycaemia (4.0-6.0 mmol/l) or moderate hyperglycaemia without glycosuria (8.5-10.5 mmol/l).

Procedures

An 18-gauge peripheral venous cannula was inserted into the left antecubital vein and connected to a Harvard infusion pump (Harvard Apparatus) for infusions of inulin and para-aminohippurate (PAH). A polyethylene catheter was inserted into a right antecubital vein after the superficial injection of a local anaesthetic (Xylocaine 2\% without adrenaline), and was advanced into an intrathoracic vein for assessment of central venous pressure (CVP) and for blood sampling. CVP was measured with a Statham P231D pressure transducer calibrated with a mercury manometer using a horizontal plane 10 cm above the back of the supine subject as the zero reference point. CVP was measured continuously throughout the study and recorded and transcribed by a Gould recorder. Arterial pressure and pulse rate were measured non-invasively every 15 min during the baseline period and every 5 min during the LBNP period by an automatic blood pressure recorder (Dinamapp). The values for systolic and diastolic blood pressure, and mean arterial pressure (MAP) immediately before the administration of LBNP, after 45 and 90 min of LBNP and after 90 min of recovery, were used for data analysis.

LBNP at \(-15\) mmHg was used to produce reflex neurogenic vasoconstriction by simulating orthostatic stress, as in previous studies from this laboratory [9, 10]. Forearm blood flow (FFB) was measured by venous occlusion plethysmography, also as previously described [9].

Study protocol

Each patient voided and then drank 800 ml of water in the first 45 min in order to induce a water diuresis. Two hundred millilitres of water were ingested in each hour of the protocol to maintain an adequate urine output for collection of spontaneously voided samples. Venous catheters were inserted as outlined above. Haemodynamic parameters were recorded throughout the study. The insulin infusion was continued throughout the study, and plasma glucose was measured every 30 min by the glucose oxidase method (Beckman Glucose Analyzer II; Beckman Instruments Corp., Fullerton, CA, U.S.A.). Euglycaemia or hyperglycaemia were maintained throughout the study by small adjustments in the insulin infusion rate. Renal haemodynamic responses were measured using classic inulin and PAH clearance techniques [9, 10]. After a 60 min equilibration period, four timed urine collections of 20 min duration each were then obtained by spontaneous voiding with the subject remaining in the supine position. The inulin and PAH clearance results as well as the urine sodium from the final three urine collections were averaged to obtain the mean recumbent basal values. At the end of this supine control period (0 min), blood samples were drawn for plasma renin activity (PRA), aldosterone, plasma noradrenaline, electrolytes and complete blood count. Each subject was then placed in the LBNP chamber. Supine FBF was determined using plethysmography. Subatmospheric pressure of \(-15\) mmHg was applied for 90 min. Plethysmography was performed during the first and last 5 min periods of LBNP. Blood samples were drawn at 45 min of LBNP for PRA, aldosterone, plasma noradrenaline, electrolytes and com-
complete blood count, and repeated at 90 min along with collection of specimens for inulin and PAH. Immediately post-LBNP, urine was collected for inulin and PAH and sodium. The inulin and PAH clearance data from this 90 min collection period represented GFR and ERPF respectively during simulated orthostatic stress (LBNP). During recovery, four more timed 20-min inulin and PAH clearances were obtained along with necessary blood samples. The results of the final three collection periods were averaged and represented ERPF, GFR and $U_{Na}V$ during the recovery period.

Blood samples collected for plasma noradrenaline, aldosterone, PRA, inulin and PAH determinations were immediately centrifuged at 2000 g for 10 min at 4°C. Plasma was separated, placed on ice and then stored at −70°C before the assay. Urine samples collected for inulin and PAH were promptly alkalized by adding 23 μl of 4 mol/l NaOH to 4 ml of urine to prevent formation of an adduct between PAH and glucose [12]. PRA was determined by the quantification of angiotensin I generation by radioimmunoassay using the New England Nuclear Kit. Aldosterone was measured by radioimmunoassay using the Coat-A-Count system. Plasma noradrenaline was measured by HPLC with electrochemical detection [13]. Serum sodium concentration was measured by an ion-selective electrode method, and urine sodium by a flame photometry method. Inulin concentrations in plasma and urine were measured by a modified method of Walser, Davidson and Orloff [14], and PAH concentration by a spectrophotometric method according to Brun [15]. The inulin and PAH clearances, corrected for body surface area, represent GFR and ERPF, expressed per 1.73 m². FF was determined by dividing the GFR by the ERPF. Renal blood flow (RBF) was calculated by dividing the ERPF by (1 - haematocrit). Renal vascular resistance (RVR) was derived by dividing MAP by the RBF.

Statistical analysis

Results are presented as mean ± SEM. Haemodynamic data [CVP, MAP, FBF, forearm vascular resistance (FFR)], humoral data (plasma noradrenaline, PRA, aldosterone) and renal haemodynamic measurements (ERPF, GFR, FF, RBF, RVR) were analysed using a repeated measures analysis of variance to test for differences between euglycaemia and hyperglycaemia, under basal conditions and during orthostatic stress. Bonferroni’s adjustment was used to correct for multiple comparisons. Statistical significance was accepted at $P \leq 0.05$.

RESULTS

There were no significant differences between the studies in body weight, CVP, 24 h sodium excretion, $U_{Na}V$, haematocrit or plasma insulin (see Table 1).

<table>
<thead>
<tr>
<th>Table 1. Baseline measurements</th>
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<tr>
<td><strong>Subject variables</strong></td>
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<tr>
<td>Body weight (kg)</td>
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<tr>
<td>CVP (mmHg)</td>
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<tr>
<td>24 h Na⁺ excretion (mmol/day)</td>
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<tr>
<td>$U_{Na}V$ (mmol/min)</td>
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<tr>
<td>Haematocrit</td>
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<td>Plasma insulin (pmol/l)</td>
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Fig. 1. Response of PRA to hyperglycaemia and euglycaemia while supine (0 min), during simulated orthostatic stress (LBNP −15 mmHg at 45 and 90 min) and during recovery. Statistical significance: *$P<0.05$ compared with euglycaemia; †$P<0.05$ compared with supine value.

Humoral measurements

There was a significant effect of hyperglycaemia on PRA (Fig. 1). While supine, during hyperglycaemia, the PRA was 3.82 ± 0.66 pmol of angiotensin I h⁻¹ ml⁻¹, compared with 2.13 ± 0.33 pmol of angiotensin I h⁻¹ ml⁻¹ while euglycaemic ($P=0.009$). PRA continued to rise throughout the period of orthostatic stress and during the recovery period (4.59 ± 0.78 pmol of angiotensin I h⁻¹ ml⁻¹ at 45 min LBNP, 5.02 ± 1.04 pmol of angiotensin I h⁻¹ ml⁻¹ at 90 min LBNP and 5.33 ± 1.28 pmol of angiotensin I h⁻¹ ml⁻¹ during recovery, $P=0.02$ compared with baseline). During euglycaemia the results were 2.47 ± 0.34 pmol of angiotensin I h⁻¹ ml⁻¹ at 45 min, 2.62 ± 0.42 pmol of angiotensin I h⁻¹ ml⁻¹ at 90 min and 2.15 ± 0.33 pmol of angiotensin I h⁻¹ ml⁻¹ during recovery ($P=NS$ compared with supine, $P=0.009$ compared with hyperglycaemia).

Supine aldosterone was not significantly different between studies. During hyperglycaemia the aldosterone level was 95.5 ± 15.2 pmol/l while supine, 114.7 ± 21.5 pmol/l at 45 min of orthostatic stress, 114.6 ± 23.8 pmol/l at 90 min and 109.6 ± 22.8 pmol/l.
at recovery ($P=NS$ compared with supine). During euglycaemia the values were $104.5 \pm 17.8$ pmol/l while supine, $104.6 \pm 16.6$ pmol/l at 45 min, $103.0 \pm 13.1$ pmol/l at 90 min and $99.7 \pm 15.7$ pmol/l during recovery ($P=NS$ compared with supine, $P=NS$ compared with hyperglycaemia).

Hyperglycaemia did not affect supine plasma noradrenaline ($0.9 \pm 0.1$ nmol/l), compared with euglycaemia ($0.8 \pm 0.1$ nmol/l), nor did it affect the plasma noradrenaline response to orthostatic stress. There was no rise in plasma noradrenaline during LBNP, with plasma levels maintained at $1.1 \pm 0.2$ nmol/l at 90 min ($P=NS$ compared with supine). During the euglycaemic study there was also no rise in plasma noradrenaline during LBNP, with the level maintained at $0.9 \pm 0.1$ nmol/l at 90 min ($P=NS$ compared with supine, $P=NS$ compared with hyperglycaemia).

### Systemic haemodynamic measurements

MAP responses to hyperglycaemia are shown in Table 2. Hyperglycaemia resulted in a significant increase in MAP while supine and during orthostatic stress.

CVP was not affected by hyperglycaemia, and the response to orthostatic stress did not differ significantly. During hyperglycaemia the CVP declined to $1.2 \pm 0.6$ mmHg at 45 min, and to $1.0 \pm 0.4$ mmHg at 90 min ($P=0.001$ compared with baseline). During euglycaemia the CVP declined to $1.0 \pm 0.2$ mmHg at 45 min, and to $0.9 \pm 0.6$ mmHg at 90 min ($P=0.001$ compared with baseline, $P=NS$ compared with hyperglycaemia).

Baseline FBF values were not significantly different between studies. During hyperglycaemia, FBF was $3.3 \pm 1.2$ ml min$^{-1}$ 100 ml$^{-1}$ forearm volume while supine, and during orthostatic stress it was $2.1 \pm 0.9$ ml min$^{-1}$ 100 ml$^{-1}$ forearm volume ($P=NS$ compared with baseline). During euglycaemia, FBF was $3.4 \pm 1.5$ ml min$^{-1}$ 100 ml$^{-1}$ forearm volume while supine ($P=NS$ compared with hyperglycaemia) and $2.9 \pm 0.8$ ml min$^{-1}$ 100 ml$^{-1}$ forearm volume during orthostatic stress ($P=NS$ compared with supine, $P=NS$ compared with response while hyperglycaemic).

Baseline FVR values were not significantly different between studies. There was a significant difference ($P=0.04$ compared with euglycaemia) in the FVR response to hyperglycaemia during orthostatic stress. These results are shown in Table 2.

### Renal measurements

GFR, RBF, FF, and $U_{Na}V$ are depicted in Fig. 2. Maintained hyperglycaemia had no significant effect on GFR, with a supine value during hyperglycaemia of $112 \pm 4$ ml/min compared with $116 \pm 5$ ml/min during euglycaemia ($P=NS$). Orthostatic stress resulted in comparable values for GFR in both studies, but the difference from supine values was not statistically significant. During the hyperglycaemic study the GFR was $104 \pm 6$ ml/min ($P=NS$ compared with supine), and during the euglycaemic study it was $107 \pm 4$ ml/min ($P=NS$ compared with supine, $P=NS$ compared with hyperglycaemia). Supine ERPF was significantly affected by hyperglycaemia ($533 \pm 40$ ml/min during hyperglycaemia compared with $646 \pm 33$ ml/min during euglycaemia, $P=0.04$). The difference in supine RBF was also statistically significant ($880 \pm 64$ ml/min during the hyperglycaemic study compared with $1078 \pm 64$ ml/min during the euglycaemic study, $P=0.05$). With the application of orthostatic stress, there was no significant change in RBF [862 $\pm 88$ ml/min during hyperglycaemia ($P=NS$ compared with supine) and 994 $\pm 67$ ml/min during euglycaemia ($P=NS$ compared with supine, $P=NS$ compared with hyperglycaemia)]. Supine RVR was significantly affected by hyperglycaemia, as shown in Table 2. Baseline FF was not significantly affected by hyperglycaemia ($0.21 \pm 0.01$ during hyperglycaemia compared with $0.18 \pm 0.01$ during euglycaemia, $P=0.06$), although the trend appeared to be towards an increase. The results did not change significantly during LBNP [0.22 $\pm 0.02$ during hyperglycaemia ($P=NS$ compared with supine) and 0.17 $\pm 0.02$ during euglycaemia ($P=NS$ compared with supine, $P=NS$ compared with hyperglycaemia)].

All urine samples were tested for glucose and were negative. Hyperglycaemia did not affect supine $U_{Na}V$ ($256 \pm 50$ μmol/min during hyperglycaemia compared with $318 \pm 49$ μmol/min during euglycaemia, $P=NS$). There was no significant effect of hyperglycaemia on the $U_{Na}V$ response to orthostatic stress [215 $\pm 50$ μmol/min at 90 min during hyperglycaemia ($P=NS$ compared with baseline); $254 \pm 51$ μmol/min at 90 min during euglycaemia ($P=NS$ compared with baseline, $P=NS$ compared with hyperglycaemia)].

### Table 2. Vascular responses to hyperglycaemia. Statistical significance:

<table>
<thead>
<tr>
<th>Subject variables</th>
<th>Euglycaemia</th>
<th>Hyperglycaemia</th>
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<tbody>
<tr>
<td>MAP (mmHg) Rest</td>
<td>$81 \pm 3$</td>
<td>$89 \pm 2^t$</td>
</tr>
<tr>
<td>LBNP</td>
<td>$80 \pm 2$</td>
<td>$88 \pm 2^t$</td>
</tr>
<tr>
<td>Recovery</td>
<td>$82 \pm 2$</td>
<td>$88 \pm 2^t$</td>
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| FVR (units) Rest | $24 \pm 6$  | $27 \pm 5$  |
| LBNP            | $28 \pm 4$  | $38 \pm 3^t$ |
| Recovery        | $22 \pm 6$  | $24 \pm 8$  |

| RVR (mmHg/l/min) Rest | $76 \pm 3$  | $99 \pm 7^t$ |
| LBNP            | $86 \pm 7$  | $109 \pm 17$ |
| Recovery        | $78 \pm 8$  | $95 \pm 13$  |
DISCUSSION

Hyperglycaemia in subjects with IDDM can markedly influence renal and systemic haemodynamic function, but the mechanisms for this are poorly defined. The aims of this study were to determine neurohumoral, systemic and renal responses to a 12h period of moderate hyperglycaemia in sodium-replete males with early diabetes during a supine rest and simulated orthostatic stress induced by LBNP. The major findings of this study can be summarized as follows: (i) hyperglycaemia caused significant increases in MAP; (ii) PRA concentrations increased markedly during hyperglycaemia, with no accompanying change in aldosterone; (iii) hyperglycaemia did not significantly increase GFR, but did result in a decline in RBF and a rise in FF that approached significance \( (P = 0.06) \); (iv) hyperglycaemia augmented the response to simulated orthostatic stress, in that both FVR and PRA increased compared with euglycaemia.

The pressor effect of hyperglycaemia did not appear to be secondary to greater intravascular volume as this was similar on both study days. Moreover, this finding did not appear to be related to activation of the sympathoadrenal system, as supine and stimulated plasma noradrenaline values were comparable in both studies. These results suggest that activation of the renin–angiotensin system during hyperglycaemia influenced arterial pressure. There were no obvious decreases in extracellular fluid volume (as reflected by CVP, \( U_{Na} \), and haematocrit) or arterial pressure during the hyperglycaemic study which could explain this phenomenon, and glycosuria was absent in all urine samples throughout the study. It had been anticipated that PRA levels would normalize during recovery from orthostatic stress. The observation that this did not occur, and that PRA levels were not affected during LBNP in the euglycaemic phase, indicates that the principal stimulus to renin release was hyperglycaemia rather than increased sympathetic nervous system activity mediated by orthostatic stress.

The status of the renin–angiotensin system in diabetes is controversial, with different groups reporting increased, decreased and normal plasma concentrations \([2, 8, 16]\). The inconsistencies in these results probably arise from differences in patient population, extracellular fluid volume and glycaemia. Our results tend to compare well with those of O’Hare et al. \([8]\). These investigators studied normotensive diabetic subjects before and after an interval of improved metabolic control, and noted a significant decline in blood pressure in parallel with blood glucose. Plasma angiotensin II was markedly elevated during the period of poor control, but also normalized with improved control. In a study by Nützi et al. \([17]\) in normal subjects, acute increases in plasma insulin and glucose after glucose loading were accompanied by decreases in plasma cortisol and aldosterone and elevations in PRA. The means by which hyperglycaemia increases PRA is not clear. In some situations it is possible that a resultant osmotic diuresis reduces extracellular fluid volume, thus increasing the renin secretion rate. However, in the study by O’Hare et al. \([8]\), and in our study, there was no evidence of intravascular volume depletion during the hyperglycaemic phase, making this a less likely mechanism. In a study by Woods et al. \([18]\) in anaesthetized rats, the intrarenal infusion of glucose resulted in an increase in the renin secretion rate to greater
than twice the control level, but only in filtering kidneys, thus implicating a tubuloglomerular feedback mechanism. However, this cannot be affirmed from the present protocol and requires further study.

The renal haemodynamic data also deserve comment. In most [2-5], but not all studies in diabetic humans [6], hyperglycaemia has increased GFR and RPF. In longer-term studies it is evident that maintenance of euglycaemia can normalize diabetic hyperfiltration [19]. Hyperglycaemia is often considered as an explanation for the hyperfiltration state. We were therefore surprised to note that our manoeuvre did not cause a rise in GFR in parallel with blood glucose, but instead resulted in a decline in RBF with maintenance of GFR. This could be explained by the duration of the stimulus, in that most controlled physiological demonstrations of this phenomenon have examined the renal response to acute glucose infusion. It is possible that the increase in renin secretion which we observed after 12 h of hyperglycaemia negated its vasodilator effects. However, hyperglycaemia did influence renal haemodynamic function in that RBF declined significantly, and FF tended to increase. These observations are remarkably consistent with studies wherein subpressor doses of angiotensin II have been administered to diabetic patients [20], resulting in a fall in RBF and a rise in FF [21, 22]. There is now considerable evidence that activation of the renin-angiotensin system contributes to the renal complications of diabetes, both at a haemodynamic and a cellular level [23-27]. We are well aware of the limitations imposed by studying the intact organism and the difficulties involved in extrapolating from the controlled milieu of the physiology laboratory to the ‘real life’ situation. Bearing these caveats in mind, we feel that this series of experiments indicates the renin-angiotensin system may be activated by hyperglycaemia, thereby inducing renal and systemic haemodynamic changes which ultimately may have deleterious consequences.

There appeared to be a dissociation between the baseline responses of the forearm and the renal vasculature to hyperglycaemia, with RBF decreasing significantly while FBF remained constant. It has been shown that the renal vascular response to angiotensin II infusion is selectively enhanced compared with the response of the peripheral circulation, and that infusions of angiotensin II which are subpressor have profound renal effects [21, 22]. The relative reduction in the vasoconstrictor effect of renin-angiotensin system activation on the forearm compared with the renal vasculature is probably due to the decreased sensitivity of the peripheral circulation, and the opposing effect of hyperglycaemia.

Other interpretations of this data were considered. Hyperglycaemia can result in an osmotic diuresis and volume depletion, thus increasing renin secretion through baroreceptor mechanisms. However, we were scrupulous in our efforts to ensure that this did not occur. The target glucose ranges were selected with this phenomenon in mind, and all urine samples were negative for glucose. Although extracellular fluid volume was not directly measured, indirect evidence that volumes were similar during the two phases of the experiment included comparable measures of body weight, CVP, UNaV and haematocrit.

In summary, we have described a controlled physiological experiment which provides evidence that a moderately elevated blood glucose may influence arterial pressure and renal and peripheral vasomotor tone through activation of the renin-angiotensin system. These data suggest a mechanism by which poor glycaemic control in insulin-dependent diabetes may be related to progression of microvascular complications.

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Hyperglycaemia and plasma renin activity in diabetes


