Haemodynamic and catecholamine responses to induction of anaesthesia and tracheal intubation in diabetic and non-diabetic uraemic patients

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Summary

We have studied cardiovascular and catecholamine responses to induction of anaesthesia and tracheal intubation in 13 patients with diabetic nephropathy, in 12 patients with uraemia of other origin and in 12 ASA I control patients. All uraemic patients were undergoing renal transplantation. Cardiovascular autonomic function tests indicated that severe autonomic neuropathy was common in the diabetic patients; less severe impairment of autonomic function was found in the non-diabetic uraemic patients. The systolic pressor response to intubation was greater in diabetic uraemic patients than in the other groups (P < 0.05). Both uraemic groups had higher plasma catecholamine concentrations than the ASA I patients both before and after induction of anaesthesia. The increased plasma concentrations of catecholamines in the uraemic patients may be a result of impaired clearance of catecholamines and higher sympathoadrenal activity needed to maintain cardiac function. The normal systolic pressor response to tracheal intubation in the uraemic patients indicates that the capacity of the cardiovascular system to respond to a stressful stimulus was preserved in these patients also, in spite of autonomic neuropathy. The greater response in the diabetic group may be caused by increased sensitivity to catecholamines and loss of autonomic control. (Br. J. Anaesth. 1995; 74: 60-65)

Key words

Increased cardiovascular instability during anaesthesia and abnormal cardiovascular responses to intubation and induction of anaesthesia have been described in patients with diabetic autonomic neuropathy [1-4]. Both attenuated [1, 4] and enhanced [2, 3] pressor responses to intubation have been reported. These altered responses have been attributed directly to autonomic neuropathy.

Reduced plasma concentrations of noradrenaline have been reported both in supine and standing positions in subjects with diabetic autonomic neuropathy [5-8]. Both normal [6] and reduced [9, 10] noradrenaline responses to exercise have been described. The absence of a noradrenaline response to tracheal intubation has also been reported [4]. Both reduced [8, 9] and normal [6] plasma concentrations of adrenaline have been reported in patients with diabetic autonomic neuropathy. Increased sensitivity to catecholamines has been observed in patients with diabetic neuropathy and in autonomic neuropathies of other origin, probably because of denervation-induced supersensitivity of the receptors and also reduced neuronal uptake of noradrenaline [11-15].

Autonomic function is impaired also in terminal uraemia [16-19]. Plasma concentrations of noradrenaline are increased in uraemia [17, 20], and reduced end-organ responses to noradrenaline have been reported [17].

Previous studies on cardiovascular responses to induction of anaesthesia and intubation in patients with diabetic autonomic neuropathy have been contradictory. Similar studies have not been performed in patients undergoing renal transplantation. We have therefore examined the pressor, heart rate and catecholamine responses to induction of anaesthesia and tracheal intubation in diabetic and non-diabetic uraemic patients undergoing renal transplantation. An age-matched group of ASA I patients served as controls. Cardiovascular autonomic function tests were performed in all patients.

Patients and methods

We studied 13 patients with diabetic nephropathy (group A), 12 patients with uraemia because of other renal diseases (group B) and 12 ASA I patients (group C). Patients more than 50 yr of age and those who had taken cardiovascular medication within the previous 12 h before anaesthesia were excluded. All patients in group A had type I (insulin-dependent) diabetes mellitus. Patients in groups A and B were all dialysis-dependent and were undergoing renal transplantation. Nine patients in both uraemic groups were receiving continuous ambulatory peritoneal dialysis, the remainder haemodialysis. The uraemic
patients treated by haemodialysis underwent renal dialysis within the previous 24 h. Continuous ambulatory peritoneal dialysis was interrupted 1–2 h before transplantation. The control patients were undergoing elective general surgery. The study was approved by the Hospital Ethics Committee and all patients gave informed consent.

Before induction of anaesthesia, all uraemic patients had not received cardiovascular medication for at least 12 h. The patients were premedicated with oral diazepam 0.2 mg kg⁻¹, 1 h before anaesthesia.

In the operating room, a radial artery was cannulated for direct arterial pressure monitoring. A central venous catheter was inserted for blood sampling. The cannulations were performed under local anaesthesia. Potassium-free Ringer’s acetate and 4% human albumin solution were administered to the uraemic patients before induction, until central venous pressure was at least 4 mm Hg. The control patients were given approximately 500 ml of Ringer’s acetate solution as preanaesthetic volume loading.

Fentanyl 2 µg kg⁻¹ was given i.v. and immediately thereafter anaesthesia was induced with thiopentone 4–5 mg kg⁻¹ given over 60 s. Vecuronium 1 mg and 0.1 mg kg⁻¹ was used for neuromuscular block and anticholinergic agents were not used. The lungs were ventilated with 100% oxygen by face mask until intubation. An additional dose of thiopentone 50 mg was given 1 min before intubation. The trachea was intubated 180 s after the start of administration of thiopentone. Laryngoscopy was performed with a Macintosh laryngoscope and intubation (oral route) was successful at the first attempt in all patients. Intubation was performed by an experienced anaesthetist. End-tidal carbon dioxide was recorded immediately after intubation, and pulse oximetry was monitored continuously (Cardiocap, Datex Ltd, Finland). ECG was recorded continuously on paper. Systolic (SAP) and diastolic (DAP) arterial pressures and heart rate (HR) were recorded before and 60, 120 and 180 s after the start of injection of thiopentone, at the peak response and 180 s after intubation. Blood samples were obtained at the same times into pre-chilled tubes containing EDTA and placed immediately on ice. After centrifugation, plasma was stored at −70 °C until analysis. Plasma concentrations of catecholamines were measured by HPLC with electrochemical detection [21].

Tests for Autonomic Function

Autonomic function tests were performed 1–2 weeks after operation, when the patients were free from disturbing wound pain. No cardiovascular medication was given in the morning before the tests. Six standard non-invasive tests of cardiovascular autonomic function were performed [22, 23].

1. Beat-to-beat heart rate variation during deep breathing. The difference between minimum and maximum HR was determined in six consecutive cycles to calculate the mean difference.

2. Valsalva manoeuvre. Three to five consecutive manoeuvres were performed and the largest Valsalva ratio was used for the results.

3–4. Heart rate response to standing. The maximum/minimum R-R ratio was determined as the ratio of the longest R-R interval during relative bradycardia and the shortest R-R interval during the initial tachycardia in the first 30 s after standing up. Also, the maximum increase in HR was determined by subtracting mean HR during the last 30 s of the resting period before standing up from the maximum HR (determined by the shortest R-R interval) after standing up.

5. Arterial pressure response to standing. The reduction in SAP after 3 min of standing was determined using cuff sphygmomanometry.

6. Arterial pressure response to sustained hand grip. The increase in DAP from the resting value to the last measurement during hand grip was calculated.

The result of each test was classified as abnormal, borderline or normal according to age-related reference values determined previously in the Finnish population [22, 23]. The results were scored: abnormal = 0, borderline = 1, normal = 2. The tests were classified into those based on HR response (reflecting mainly parasympathetic function) and those based on arterial pressure response (reflecting mainly sympathetic function) and the scores of the respective tests were combined. The total score of the autonomic function tests was also calculated.

Statistical Analysis

Between groups, Fisher’s exact test (the Freeman–Halton exact test) was used to compare the scores of the autonomic tests; Kruskall–Wallis one-way analysis of variance (ANOVA) and unpaired t test were used to compare other variables. To compare haemodynamic and catecholamine responses between groups, analysis of variance (two-way ANOVA) for repeated measurements with Duncan’s test was used. Changes over time within each group were tested using ANOVA (one-way ANOVA) for repeated measurements. The time of 180 s after the beginning of induction of anaesthesia was taken as baseline for the response to intubation. The calculations were performed using the StatXact software (CyTEL Software Corporation, Cambridge, MA, USA) and the SOLO Statistical System 2.0 (BMDP Statistical Software Inc., LA, CA, USA). Data are expressed as mean (SD) (95% confidence limits of the mean), unless otherwise stated. A probability of < 0.05 was taken as significant.

Results

Patient characteristics, preoperative cardiovascular status and medications are shown in table 1. The duration of type I (insulin-dependent) diabetes in patients in group A was 25 (4) yr. None of the patients had hypoglycaemia at the time of induction of anaesthesia. Plasma potassium, serum ionized calcium, blood glucose and haemoglobin concentrations, and packed cell volume values at induction of anaesthesia are given in table 2. End tidal carbon dioxide after intubation was 4.2–5.6% in all patients and SpO₂ was within normal limits in all patients throughout induction.
**Table 1**  Patient characteristics, preoperative cardiovascular status and medication (mean (SD or range) or number) in group A (uremic patients with diabetic nephropathy), group B (non-diabetic uremic patients) and group C (control patients). ECG = Electrocardiogram, LVH = left ventricular hypertrophy, MI = myocardial infarction, CAD = coronary artery disease. † In the preoperative chest x-ray. **P < 0.01 between groups A and B

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 13)</th>
<th>Group B (n = 12)</th>
<th>Group C (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>5/8</td>
<td>7/5</td>
<td>5/7</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>36 (27-47)</td>
<td>34 (24-45)</td>
<td>37 (24-44)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63 (12)</td>
<td>72 (11)</td>
<td>67 (11)</td>
</tr>
<tr>
<td>Creatinine (µmol litre(^{-1}))</td>
<td>744 (253)**</td>
<td>1052 (250)</td>
<td>73 (15)</td>
</tr>
<tr>
<td>LVH in ECG</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>History of CAD</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Previous MI</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac enlargement†</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>β blockers</td>
<td>5</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Ca(^{2+}) channel blockers</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Diuretics</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Nitrates</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Digitalis</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 2**  Mean (SD) plasma potassium [K\(^+\)], serum ionized calcium [Ca\(^{2+}\)], blood glucose (Gluc.) and haemoglobin (Hb) concentrations and packed cell volume (PCV) at induction of anaesthesia. Groups as in table 1. ***/> < 0.001 compared with other groups

<table>
<thead>
<tr>
<th>Group</th>
<th>[K(^+)] (mmol litre(^{-1}))</th>
<th>[Ca(^{2+})] (mmol litre(^{-1}))</th>
<th>Gluc. (mmol litre(^{-1}))</th>
<th>Hb (g litre(^{-1}))</th>
<th>PCV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n = 13)</td>
<td>4.5 (0.7)</td>
<td>1.2 (0.1)</td>
<td>10.3 (4.4)†</td>
<td>83 (14)</td>
<td>24 (4)</td>
</tr>
<tr>
<td>B (n = 12)</td>
<td>4.4 (0.9)</td>
<td>1.3 (0.1)</td>
<td>5.6 (0.9)</td>
<td>85 (18)</td>
<td>25 (5)</td>
</tr>
<tr>
<td>C (n = 12)</td>
<td>3.9 (0.3)</td>
<td>1.3 (0.03)</td>
<td>4.5 (0.4)</td>
<td>139 (11)***</td>
<td>40 (4)***</td>
</tr>
</tbody>
</table>

**Figure 1**  Changes in heart rate (HR) during induction of anaesthesia and tracheal intubation in diabetic (○) and non-diabetic (●) uraemic patients and in ASA I (■) patients (mean, 95% confidence interval of the mean). P = Peak response, I = intubation. **P < 0.05 in the response between groups (two-way ANOVA).

**Figure 2**  Changes in systolic arterial pressure (SAP) during induction of anaesthesia and tracheal intubation in diabetic and non-diabetic uraemic patients and in ASA I patients. Symbols as in figure 1.

**HAEMODYNAMIC CHANGES**

In group B (non-diabetic uraemic patients), HR was significantly higher than in group C (control) until intubation (P < 0.05), with an increase in HR after the start of induction (P < 0.05) and a decrease thereafter. In group A (diabetic nephropathy), HR decreased after the start of induction (P < 0.001). In group C, no changes in HR were observed until intubation. The changes in HR before intubation were significantly different between groups (P < 0.05). HR increased similarly in all groups in response to intubation (P < 0.001) (fig. 1). No cardiac arrhythmias were noted.

SAP was significantly higher in group A than in groups B and C (P < 0.01) throughout the study. In all groups SAP decreased significantly after the start of induction (P < 0.001) and increased in response to intubation (P < 0.001). The response to intubation was significantly greater in group A than in groups B and C (P < 0.05) (fig. 2).

There were no significant differences in DAP between groups. In the uraemic groups, DAP decreased significantly in response to induction (group A, P < 0.001; group B, P < 0.01). DAP increased in response to intubation (P < 0.001) similarly in all groups (fig. 3).
Responses to intubation in diabetes and uraemia

Table 3  Results of cardiovascular autonomic function tests. Combined scores of the tests based on heart rate response, arterial pressure response and total scores (median (range)). Each test scored: 0 = abnormal, 1 = borderline, 2 = normal.

<table>
<thead>
<tr>
<th>Group</th>
<th>Heart rate response</th>
<th>Arterial pressure response</th>
<th>Total scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1 (0–6)</td>
<td>2 (1–4)</td>
<td>3 (1–10)</td>
</tr>
<tr>
<td>B</td>
<td>5 (1–7)</td>
<td>3 (2–4)</td>
<td>9 (3–10)</td>
</tr>
<tr>
<td>C</td>
<td>8 (3–8)</td>
<td>4 (4–4)</td>
<td>12 (7–12)</td>
</tr>
</tbody>
</table>

CATECHOLAMINE RESPONSES

In both uraemic groups, plasma concentrations of noradrenaline were significantly higher than in the control group both at the times before (P < 0.01) and after (P < 0.05) intubation. In both uraemic groups plasma noradrenaline concentrations decreased significantly after the start of induction (P < 0.001). The response was significantly different (P < 0.001) from that in the control patients. In group A, plasma concentrations of noradrenaline increased in response to intubation (P < 0.001), while in groups B and C, there was no significant response to intubation. The differences in the intubation response were not statistically significant (fig. 4).

Plasma concentrations of adrenaline were higher in the uraemic patients than in the control patients (P < 0.05) throughout the study. In groups B (P < 0.01) and C (P < 0.001), plasma concentrations of adrenaline decreased after the start of induction. An increase in plasma concentrations of adrenaline after intubation was observed in group A (P < 0.01), but not in groups B and C. There were no statistically significant differences in the responses between groups (fig. 5).

CARDIOVASCULAR AUTONOMIC FUNCTION

In the autonomic function tests, patients in group A had significantly lower scores both in the tests based on HR response and in those based on arterial pressure response than control patients, indicating severe autonomic neuropathy. In group B, the scores from the tests based on arterial pressure response were significantly lower than in group C. The total scores were significantly different between all groups (table 3).

Discussion

Induction of anaesthesia in our diabetic and non-diabetic patients with terminal uraemia was surprisingly stable, and no cardiac arrhythmias were observed. Despite severe autonomic nervous dysfunction, the pressure response was brisk in the diabetic uraemic patients.

The increase in HR after intubation in all groups was probably reduced by the small dose of fentanyl administered to the patients. Also, the lack of statistically significant catecholamine response to intubation in the non-diabetic uraemic and the control patients was probably a result of administration of fentanyl. Kautto [24] demonstrated that in healthy subjects, fentanyl 2 μg kg⁻¹ attenuated cardiovascular responses to laryngoscopy and intubation, but did not abolish them. The use of fentanyl in our study was warranted, as symptom-free coronary artery disease is common in diabetic
patients [25]. Furthermore, a long QT interval (a predisposing factor for arrhythmias) has been reported in patients with diabetes and uraemia [26]. Fentanyl, even in small doses, protects against cardiac arrhythmias during induction of anaesthesia [27].

In our study, the decrease in arterial pressures was moderate in all groups after induction. This contrasts with studies by Burgos and colleagues [1] and Linstedt, Jaeger and Petry [2] who reported overt decreases in arterial pressures in response to induction in patients with diabetic autonomic neuropathy. We believe that our results reflect the effect of adequate intravascular volume loading before induction of anaesthesia. The aggravated systolic arterialpressor response to intubation in the diabetic patients with autonomic neuropathy agrees with the observations by Vohra and colleagues [3] and Linstedt, Jaeger and Petry [2]. Thepressor response possibly reflects supersensitivity to catecholamines and loss of autonomic control in these patients.

Abnormalities of cardiac autonomic function were apparent in both uraemic groups in our study; in diabetic uraemic patients severe impairment of autonomic function was common, affecting both parasympathetic and sympathetic function. In the other uraemic patients, parasympathetic function was less affected. It could be argued that the autonomic function tests were performed 1–2 weeks after renal transplantation, and thus improvement of autonomic function could have taken place. In uraemic patients without diabetes this might be true [28], but in diabetics, it has been shown that autonomic function does not improve after renal transplantation [29]. The cardiovascular medication in the uraemic patients probably affected the test results to some extent.

In contrast with previous studies [5–8] in patients with diabetic autonomic neuropathy, plasma concentrations of noradrenaline were higher in our diabetic uraemic patients with severe autonomic neuropathy than in control patients. In contrast with our data for adrenaline, normal [6] or reduced [8, 9] concentrations have been reported in diabetic autonomic neuropathy. In our patients, elevated catecholamine concentrations may reflect underlying impaired cardiac function [30–33], decreased neuronal uptake [14] and reduced plasma clearance [33] of noradrenaline. The effects of uraemia on catecholamine concentrations in patients with diabetic autonomic neuropathy are unknown. Apparently, increased catecholamine concentrations are partly caused by uraemia [17, 20].

Our results support previous studies showing that in uraemia, plasma concentrations of catecholamines are increased [17, 20], although in our patients with terminal uraemia, impaired cardiac function caused by uraemia and hypertension may also have contributed to the higher catecholamine concentrations [30–33].

Acknowledgements

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References

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methoxy-4-hydroxyphenylglycol (MHPG) are insensitive indicators of alpha2-adrenoceptor mediated regulation of norepinephrine release in healthy human volunteers. Life Sciences 1991; 49: 75-84.


