Impaired flow-mediated vasodilation of the brachial artery in patients with primary hyperparathyroidism improves after parathyroidectomy

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Abstract

Objective: The endothelium is a newly recognised target tissue of parathyroid hormone (PTH). It is not clear whether hyperparathyroidism affects endothelial function and whether parathyroidectomy (Ptx) has an influence on arterial wall properties. We studied brachial flow-mediated vasodilation (FMD) and brachial and carotid intima-media thickness (IMT) in patients with primary hyperparathyroidism (pHPT) before and after Ptx and in healthy controls.

Methods: 19 patients with pHPT (mean±SEM, age 45±4.7 years, PTH 238±52 ng/l) were studied. Diabetes, hypertension and vascular disease were excluded. Twenty healthy volunteers matched for age, sex and blood pressure served as controls. Enddiastolic diameter, FMD and nitroglycerine-induced (NMD) dilation of the brachial artery were measured by a multigate pulsed doppler system (echo-tracking), IMT was determined using automatic analysis of the M-line signal. Healthy volunteers where studied on one occasion, patients were studied at baseline and 6 months after Ptx.

Results: Six months after Ptx PTH had decreased to normal, blood pressure levels remained unchanged. Endothelium dependent FMD at baseline was impaired in patients compared to controls (4.7±1.2 vs. 18.2±3.7%, P<0.01), however, FMD improved significantly after Ptx (16.7±3.0%, P<0.01). Nitroglycerine-induced dilation, IMT and artery diameter were not different between groups and did not change after Ptx.

Conclusions: Impaired endothelium dependent vasodilation in patients with primary hyperparathyroidism improves after successful parathyroidectomy. Endothelial dysfunction associated with primary hyperparathyroidism occurs without detectable structural wall alterations of the brachial artery and appears therefore to be an early and reversible arterial alteration.

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1. Introduction

There is an increasing body of evidence that parathyroid hormone (PTH) affects functional and structural properties of large arteries [1]. PTH can influence the vascular tone [1,2] and has been shown to stimulate structural alterations like proliferation of vascular smooth muscle cells and cardiomyocytes [3]. Elevated levels of parathyroid hormone have been demonstrated in patients with essential hypertension [4–6]. A positive relationship between PTH levels and blood pressure has been demonstrated in essential hypertension and acute infusion of PTH raises blood pressure in healthy humans [7,8]. Elevated parathyroid hormone levels are common in renal insufficiency and after kidney transplantation. We could demonstrate that hyperparathyroidism alters elastic properties of the arterial system in patients after kidney transplantation [9].

In the last couple of years there has been increasing evidence from animal studies that the endothelium is a target organ of PTH [10,11]. Endothelial dysfunction is a crucial factor in atherogenesis and an early event in the pathogenesis of arterial disease. Recently, our group found a significant relationship between endothelium-mediated vasodilation of the brachial artery and parathyroid hor-
mone levels in renal transplant recipients [12]. However, it is not clear whether endothelial function is impaired in hyperparathyroidism and whether endothelial impairment is reversible after parathyroidectomy. Moreover, it remains to be elucidated whether hyperparathyroidism directly influences the arterial wall or whether it is a permissive factor related to hypertension or uremia. In patients with renal impairment and hypertension confounding risk factors and concomitant disease do not allow the discrimination of vascular effects of hyperparathyroidism per se. Since it has been shown that PTH stimulates proliferation of smooth muscle cells and thus structural vessel wall alterations, assessment of structural vessel wall parameter and a possible relation to functional vessel wall properties in primary hyperparathyroidism are of interest.

An increase of intima-media-thickness (IMT) is an early structural alteration of the arterial wall in patients with renal failure and essential hypertension [13–15]. Moreover, flow-mediated vasodilation is a valid index of endothelial function in large arteries [16]. We therefore studied flow-mediated vasodilation and IMT of the brachial artery before and after parathyroidectomy in patients with primary hyperparathyroidism (pHPT) free of renal disease, arterial hypertension, cardiovascular risk factors or disease. The aim of the present study was to study influence of parathyroid hormone excess and of successful parathyroidectomy on endothelial function and early structural changes of the arterial wall.

2. Methods

2.1. Subjects

Our study conforms with the principles outlined in the declaration of Helsinki and was performed in accordance with protocols approved by the local ethics committee at the University of Münster. Each subject gave informed consent to participate. Patients who where admitted for surgery for pHPT between December 1997 and August 1999 were consecutively enrolled into the study. Patients and controls underwent physical examination, ECG, chest X-ray and routine laboratory analysis. The following exclusion criteria were used: coronary heart disease, heart failure, valvular heart disease, cerebral vascular disease, peripheral artery disease, diabetes mellitus, impaired renal function (serum creatinine >1.2 mg/dl), hypercholesterolemia (defined as serum cholesterol >230 mg/dl), intake of antihypertensive medication and smoking. Additionally, patients with diastolic blood pressure values of 90 mmHg or above or systolic blood pressure values of 140 mmHg or above measured in sitting position were excluded from the study. Thus 21 patients with primary hyperparathyroidism (pHPT) were eligible. One patient showed persistent hyperparathyroidism after surgery and one patient was lost to follow-up. Thus 19 patients (age 45±4.7 years, 11 women and 8 men) were followed up 6 months after parathyroidectomy. Twenty healthy volunteers (CON) matched for age, sex and blood pressure served as controls. Standard laboratory assays were used to determine fasting concentrations of serum creatinine, total cholesterol, triglycerides, glucose, total calcium and phosphate levels. Plasma intact (1–84) parathyroid hormone concentrations were determined using a radioimmunoassay (normal range: 12–65 ng/l).

2.2. Blood pressure measurements

Left brachial artery blood pressure was measured using an automatic sphygmomanometer (Critikon Dinamap model 1846 SX, Tampa, FL, USA). The measurements were done at rest and the mean value of five consecutive measurements over 15 min was calculated.

2.3. Vessel wall investigations

All studies were performed between 8 and 12 a.m. in supine position after at least 15 min at rest. Following blood sampling vessel wall properties of the left common carotid artery 1, 2 and 2.5 cm below the carotid bifurcation and of the right brachial artery approximately 5 cm proximal of the elbow were studied in a longitudinal projection with a multigate pulsed doppler system (Pie Medical Equipment, Maastricht, The Netherlands) [17,18]. The arteries were displayed in B- and M-Mode. Vessel wall movements could be monitored based on low-frequency doppler signals originating from the sample volumes coinciding with the anterior and posterior walls. The doppler signals in M-mode were temporarily stored and analyzed by a personal computer system. The system allows the assessment of the relative change of major peripheral artery diameter as a continuous function of time with an accuracy of about 0.5%. With this non-invasive method, the enddiastolic diameter [d (mm)] was measured using an ECG-trigger. Coefficient of variation was 4.5±0.7% (n=26) for the enddiastolic diameter of the brachial artery.

2.4. Intima-media-thickness

IMT of the common carotid artery and the brachial artery were measured using the radiofrequency ultrasound signal of the posterior wall acquired along an M-line by the perpendicular placed probe which was stored in a personal computer system. Using professional software (Pie Medical Equipment) the signal was processed according to the method described and validated elsewhere [19]. Hoeks et al. found a variation in the order of 45 µm using this technique in vivo [19]. Three measurements at three sites of the common carotid artery and of the brachial artery ~2–6 cm above the elbow were averaged to assess mean IMT.
2.5. Measurement of flow-mediated and nitroglycerine-induced vasodilation

The brachial artery of the right arm was visualized in a longitudinal scan 2–6 cm above the elbow using a 7.5 MHz linear array transducer software (Scanner 2000, Pie Medical Equipment). Using the multi-gate pulsed doppler system with ECG-trigger enddiastolic diameter of the brachial artery was determined over five consecutive cardiac cycles and the results were averaged to a single value. Coefficient of variation using this technique is 4.5±0.7% (n=26) for the enddiastolic diameter of the brachial artery. After three measurements at baseline were taken, a forearm cuff was inflated at 300 mmHg for 4 min distal the site of ultrasound measurement. During the last minute of cuff inflation and 1, 2, 3, 5, 7 and 10 min after cuff release further measurements of brachial artery enddiastolic diameter were taken. Additionally, brachial artery blood flow at baseline and during the initial 15 s of reactive hyperaemia was estimated using pulsed doppler and the degree of reactive hyperaemia in percent of the basal blood flow was calculated. 11 min after cuff release, when vessel diameter had returned to baseline values, 400 µg of glycerol trinitrate were administered sublingually and further scans of the brachial artery were taken after 1, 3 and 5 min. Flow-mediated vasodilation was calculated as the maximum absolute and relative increase in brachial artery enddiastolic diameter during reactive hyperaemia. Nitroglycerine-induced vasodilation was calculated accordingly as the maximum increase in artery diameter after sublingual application of glycerol trinitrate.

2.6. Statistics

Statistical analysis was performed using the computer software spss (statistical Package of Social Science, 4.0, 1990, SPSS, Chicago, IL, USA). Data are expressed as mean±standard error of the mean (SEM). Post hoc analysis of variance (Fishers PLSD) was performed for mean comparison of continuous variables between groups (controls, patients before and patients after Ptx). Nominal variables were compared by χ² test. Statistical significance was assumed at P<0.05.

3. Results

Clinical and biochemical data of patients and controls at baseline are given in Table 1. Age, sex, body mass index, serum lipids and serum creatinine levels were not significantly different between patients with primary hyperparathyroidism and healthy controls. Plasma intact parathyroid hormone and serum calcium levels at baseline were significantly higher, serum phosphate levels significantly lower in patients with primary hyperparathyroidism when compared to healthy controls (Table 2). Parathyroid hor-
Table 2
Blood pressure, biochemical data and structural and functional vessel wall parameter of patients with primary hyperparathyroidism (pHPT, \( n = 19 \)) before and after parathyroidectomy and of control subjects (\( n = 20 \))

<table>
<thead>
<tr>
<th>Parameter</th>
<th>pHPT Baseline</th>
<th>pHPT Post Ptx</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>127±5</td>
<td>125±6</td>
<td>125±2</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>77±3</td>
<td>75±4</td>
<td>76±2</td>
</tr>
<tr>
<td>Parathyroid hormone level (ng/l)</td>
<td>238±52</td>
<td>41±20*</td>
<td>28±3#</td>
</tr>
<tr>
<td>Calcium level (mmol/l)</td>
<td>3.0±0.08</td>
<td>2.4±0.06*</td>
<td>2.5±0.03#</td>
</tr>
<tr>
<td>Phosphate level (mg/dl)</td>
<td>2.0±0.16</td>
<td>3.4±0.40*</td>
<td>3.5±0.2#</td>
</tr>
<tr>
<td>Carotid artery diameter (mm)</td>
<td>6.0±0.6</td>
<td>6.3±0.4</td>
<td>5.9±0.3</td>
</tr>
<tr>
<td>Carotid IMT (mm)</td>
<td>0.64±0.05</td>
<td>0.63±0.05</td>
<td>0.62±0.04</td>
</tr>
<tr>
<td>Brachial artery diameter (mm)</td>
<td>3.4±0.2</td>
<td>3.5±0.3</td>
<td>3.3±0.3</td>
</tr>
<tr>
<td>Brachial artery IMT (mm)</td>
<td>0.49±0.05</td>
<td>0.47±0.07</td>
<td>0.47±0.06</td>
</tr>
<tr>
<td>Reactive hyperemia (%)</td>
<td>447±50</td>
<td>436±62</td>
<td>462±71</td>
</tr>
<tr>
<td>Absolute brachial FMD (mm)</td>
<td>0.16±0.06</td>
<td>0.58±0.14*</td>
<td>0.60±0.10#</td>
</tr>
<tr>
<td>Absolute brachial NMD (mm)</td>
<td>0.78±0.08</td>
<td>0.76±0.12</td>
<td>0.74±0.11</td>
</tr>
</tbody>
</table>

\* IMT, intima-media-thickness, FMD, flow-mediated vasodilation, NMD, nitroglycerine-mediated vasodilation.

\#, \( P < 0.05 \) for change of parameter before and after parathyroidectomy in patients.

and mortality [1,4,6,10]. Our finding of impaired endothelial vasodilatory function may be related to this clinical observations.

In the last few years there is increasing evidence that the endothelium is a physiologically relevant target organ of PTH. Schleiffer et al. observed a blood pressure fall due to increased endogenous nitric oxide release in hypoparathyroid rats [22]. Jiang et al. [23] demonstrated expression of the PTH/PTHrp-receptor in vascular endothelial cells, suggesting the endothelium as a target tissue of PTH. In patients with renal insufficiency and hypertension a negative influence of hyperparathyroidism on functional arterial vessel wall properties has been shown. In renal transplant patients endothelial dysfunction is correlated to PTH levels [12] and elevated parathyroid hormone concentrations have a deleterious effect on elastic properties of the arterial wall [9]. In patients with hypertension carotid artery distensibility has been found to be inversely correlated to PTH concentrations [21]. The mechanisms of these influences of hyperparathyroidism are not clear. Our study did not address the mechanisms by which hyperparathyroidism affects arterial vessel wall properties. However, the observed normalisation of endothelial dysfunction after parathyroidectomy in otherwise healthy patients with primary hyperparathyroidism suggests, that hyperparathyroidism per se affects the endothelium rather than potentiating the effects of renal insufficiency or hypertension.

Conditions known to affect endothelial function such as smoking, renal failure, hypercholesterolemia, presence of atherosclerotic plaques and possibly hypertension were excluded to highlight the effect of PTH excess [24–27]. However, the design of our study does not allow to discriminate direct, receptor-mediated effects of PTH from effects of chronic hypercalcemia, hypophosphatemia and other metabolic changes that are associated with hyperparathyroidism. It has been shown, that chronic hypercalcemia induces hypersecretion of ACTH and consequently cortisol and aldosterone [8]. The complex metabolic changes after parathyroidectomy may therefore contribute to the observed reversible alterations of endothelial function.

Additionally to functional effects, PTH has been shown to stimulate structural alterations like proliferation of smooth muscle cells and cardiomyocytes as well as to contribute to left ventricular hypertrophy and structural vessel wall alterations [3,28]. Ultrasound systems including echo-tracking devices are unable to differentiate between intima- and media-thickening. Early endothelial
alterations may be present before ultrasound parameters become pathologic. We could not detect structural changes such as an increase in IMT in our patients. This is in agreement with other studies of IMT in patients with primary hyperparathyroidism [29] and may in part be due to the fact, that we only included patients with most-likely early primary hyperparathyroidism, who were devoid of standard cardiovascular risk factors.

In contrast to our findings Neunteufl et al. [30] did not detect a significantly impaired endothelium-dependent vasodilation in patients with primary hyperparathyroidism. However, they reported a high incidence of cardiovascular risk factors like smoking, manifest hypertension and diabetes in both patients and controls, all known to affect endothelial function negatively. This may have obscured a possible difference between the groups in their study. Nilsson et al. [29] studied blood flow in patients with primary hyperparathyroidism by forearm plethysmography and described an increased response to infusion of metacholin after parathyroidectomy. In accordance with our data the authors suggest an improvement of endothelial function after correction of hyperparathyroidism. In contrast to our findings in their study endothelium-independent vasodilation decreased after parathyroidectomy. However, there are several differences in the design of their and our studies. Most importantly Nilsson et al. included a substantial proportion of patients with cardiovascular disease and/or vasoactive medication whereas in the present study only patients free of cardiovascular risk factors and medications were included which allows a clearer assessment of the effect of hyperparathyroidism per se.

It may surprise that endothelial function normalizes in a relatively short period of time after parathyroidectomy. However, there were no structural alterations of the vessel wall and it has been shown that endothelial dysfunction can recover as rapidly as 1 month after initiation of therapy with an HMG-coenzyme A reductase inhibitor [31]. Endothelium-dependent vasodilation improves also after cessation of smoking, during therapy with an ACE inhibitor and after initiation of vitamin C or folic acid supplementation [32–34].

We conclude that endothelial dysfunction in primary hyperparathyroidism is a reversible phenomenon that can be normalized by parathyroidectomy. Disturbed endothelial function may substantially contribute to the deleterious cardiovascular effects of PTH excess and therefore normalization of hyperparathyroidism by parathyroidectomy may be of prognostic relevance.

Acknowledgements

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References

[8] Hultcr et al. 1997;23:1017–1023. The study was supported by the Center of Clinical Research of the University of Münster Medical School


