Coronary Heart Disease

Coronary Microvascular Dysfunction Induced by Primary Hyperparathyroidism is Restored After Parathyroidectomy

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Background—Symptomatic primary hyperparathyroidism (PHPT) is associated with increased cardiovascular mortality. However, data on the association between asymptomatic PHPT and cardiovascular risk are lacking. We assessed coronary flow reserve (CFR) as a marker of coronary microvascular function in asymptomatic PHPT of recent onset.

Methods and Results—We studied 100 PHPT patients (80 women; age, 58±12 years) without cardiovascular disease and 50 control subjects matched for age and sex. CFR in the left anterior descending coronary artery was detected by transthoracic Doppler echocardiography, at rest, and during adenosine infusion. CFR was the ratio of hyperemic to resting diastolic flow velocity. CFR was lower in PHPT patients than in control subjects (3.0±0.8 versus 3.8±0.7; P<0.0001) and was abnormal (≤2.5) in 27 patients (27%) compared with control subjects (4%; P=0.0008). CFR was inversely related to parathyroid hormone (PTH) levels (r=−0.3, P<0.004). In patients with CFR ≤2.5, PTH was higher (26.4 pmol/L [quartiles 1 and 3, 16 and 37 pmol/L] versus 18 [13–25] pmol/L; P<0.0007), whereas calcium levels were similar (2.9±0.1 versus 2.8±0.3 mmol/L; P=0.2). In multivariable linear regression analysis, PTH, age, and heart rate were the only factors associated with CFR (P=0.04, P=0.01, and P=0.006, respectively). In multiple logistic regression analysis, only PTH increased the probability of CFR ≤2.5 (P=0.03). In all PHPT patients with CFR ≤2.5, parathyroidectomy normalized CFR (3.3±0.7 versus 2.1±0.5; P<0.0001).

Conclusions—PHPT patients have coronary microvascular dysfunction that is completely restored after parathyroidectomy. PTH independently correlates with the coronary microvascular impairment, suggesting a crucial role of the hormone in explaining the increased cardiovascular risk in PHPT. (Circulation. 2012;126:1031-1039.)

Key Words: coronary flow reserve • hyperparathyroidism • microvascular dysfunction • parathyroid hormone • risk factors

Parathyroid hormone (PTH) regulates calcium, phosphate, and vitamin D homeostasis and plays a crucial role in mineral metabolism and bone turnover. Untreated primary hyperparathyroidism (PHPT) is characterized by chronically elevated PTH and hypercalcemia with bone and renal disorders and is associated with increased cardiovascular morbidity and mortality.1 In symptomatic PHPT, parathyroidectomy has been shown to reduce cardiovascular mortality and has therefore become mandatory.2 Nowadays, the features of PHPT have shifted from a clinically manifest condition associated with severe hypercalcemia, kidney stones, bone disorders, and neuromuscular involvement toward an asymptomatic state. Currently, in most patients, PHPT is diagnosed on routine biochemistry in the absence of any clinical signs of PTH alterations.3 Data on the cardiovascular involvement in asymptomatic PHPT are limited, and it is not known whether calcium or PTH alterations may impair cardiovascular function already in the initial phase of the disease.2,4 Recently, mild alterations of circulating PTH, at the upper levels of the normal range,5 have been shown to predict cardiovascular mortality in a large cohort of elderly men. However, there is no evidence that reducing PTH levels will reduce cardiovascular risk in the general population.6 Furthermore, in asymptomatic PHPT, the optimal timing for parathyroidectomy is still controversial, and it is unknown whether early surgical intervention results in improved cardiovascular outcome.6 Traditionally, the association between PHPT and cardiovascular disease has been related to the higher prevalence in these patients of classic cardiovascular risk factors like diabetes mellitus, dyslipidemia, and hypertension1 and to

Received November 1, 2011; accepted June 29, 2012.
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The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.111.081307/-/DC1.
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Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.111.081307
mineral homeostasis disruption.7 However, several experimental studies have shown that PTH can selectively target the vascular wall, acting on specific receptors present on endothelial and smooth muscle cells.8,9 Therefore, PTH-mediated structural and functional cardiovascular alterations might play a causal role in the pathophysiology of atherosclerosis and ultimately heart failure.7–10 Several investigations have documented PHPT-associated endothelial dysfunction in the peripheral circulation11,12 and increased arterial stiffness.13 Indeed, the reversal of vascular dysfunction after successful parathyroidectomy further supports the concept of a specific role of PTH in the pathogenesis of cardiovascular disease in PHPT.11,12,14 The aim of the present study was to evaluate the influence of PHPT on coronary microvascular function, assessed by coronary flow reserve (CFR) by transhoracic Doppler echocardiography, in healthy subjects and in patients with asymptomatic PHPT without evidence for epicardial coronary artery disease (CAD) as assessed by multislice computed tomography (MSCT) coronary angiography. Coronary functional abnormalities represent the first marker of the atherosclerotic process in the coronary circulation; therefore, CFR may become of clinical relevance in the management and treatment of PHPT in its asymptomatic initial phase.

Clinical Perspective on p 1039

Methods

Patients
In this cross-sectional study, we enrolled 100 asymptomatic PHPT patients (80 women; age, 58±12 years) referred to the University Hospital of Padua for parathyroidectomy because of solitary PTH-secreting adenoma. Baseline evaluation included physical examination and collection of clinical and laboratory data (Table 1). The median time from PHPT diagnosis was 6 months (range, 1–109 months). Patients with a history or clinical evidence of cardiopulmonary, renal (serum creatinine >133 μmol/L in men and >120 μmol/L in women), or hepatic disease and malignant or infectious disease were excluded. Mild PHPT (ie, total serum calcium <3.0 mmol/L) was equally represented in patients with and without concurrent cardiovascular risk factors. The nonrandomized control group consisted of 50 normal volunteers recruited from institutional personnel who were matched for age and sex. They did not undergo any cardiovascular conditioning program. None had CAD. All control subjects were asymptomatic with no history of heart disease. Exclusion criteria for all subjects included any of the following conditions: cerebral vascular disease, carotid artery bruit, peripheral bruit or abnormal pulse, history of angina or myocardial infarction, hypertension requiring treatment, use of vasodilating drugs, or alcohol intake >10 oz per week. All participants had normal ECG at rest and during adenosine-induced hyperemia. Patients and control subjects came from the same geographic area (northeast Italy). The absence of CAD was evaluated by clinical history, physical examination, and ECG. Cardiovascular risk factor definition is provided in the online-only Data Supplement. The study was approved by the institutional ethics committee, and all patients gave written informed consent. None of the PHPT patients eligible for the study declined CFR evaluation.

Echocardiography
Transhorary Doppler echocardiography was performed with a commercially available ultrasound system (Vivid 7, GE Medical System, Inc, Hortem, Norway). All images were analyzed offline by a single investigator blinded to all clinical data. Echocardiographic methods are detailed in the online-only Data Supplement.

Coronary Flow Velocity Reserve Assessment
Images were obtained in the distal part of the left anterior descending coronary artery with a 7-MHz transducer. Coronary blood flow was obtained by color Doppler flow-mapping guidance, and a sample volume was positioned within the color signal in the left anterior

| Table 1. Characteristics of the Study Population (n=150) |
|----------------|----------------|----------------|
| **Age, y** | **Control Subjects (n=50)** | **PHPT Patients (n=100)** | **P** |
| Male sex, n (%) | 10 (20) | 20 (20) | 0.8 |
| PTH, pmol/L | 2.0 (0.8–2.4) | 20 (15–29) | <0.0001 |
| Serum total calcium, mmol/L | 2.3±0.1 | 2.95±0.1 | <0.0001 |
| Cardiovascular risk factors, n (%) | Current smokers | 12 (20) | 20 (20) | 0.8 |
| | Hypertension | 22 (44) | 45 (49) | 0.7 |
| | Diabetes mellitus | 5 (10) | 10 (10) | 0.8 |
| | Obesity | 8 (16) | 12 (12) | 0.5 |
| | Hyperlipidemia | 11 (22) | 23 (23) | 0.7 |
| | Echocardiographic characteristics | | | |
| | IVSd, mm | 9.0±2.2 | 8.4±1.5 | 0.2 |
| | PWtd, mm | 8.4±1.4 | 8.1±1.4 | 0.5 |
| | LVIDd, mm | 53±4.9 | 51.6±5.9 | 0.4 |
| | LVIDs, mm | 32.6±6.4 | 32.4±7 | 0.9 |
| | LV mass, g | 170±53 | 158±49 | 0.2 |
| | LV mass index, g/m² | 102±26 | 100±26 | 0.4 |
| | LV mass/height², g/m³ | 46±13 | 44±13 | 0.3 |
| | Relative WT | 0.32±0.05 | 0.32±0.09 | 0.9 |
| | LV hypertrophy, LVMI, n (%) | 17 (34) | 32 (32) | 0.8 |
| | LV hypertrophy, LVMH, n (%) | 22 (44) | 40 (40) | 0.9 |
| | LV mass/height², g/m² | 49 0.2 | 70 0.5 | 26 0.4 |
| | LV mass/height², g/m³ | 14.1 0.8 | 10.2 59.1 | 12.2 0.7 |
| | A wave, cm/s | 80.1±14.1 | 78.1±12.2 | 0.7 |
| | A wave, cm/s | 60.2±10.2 | 59.1±14.1 | 0.8 |
| | E/A | 1.38±0.21 | 1.35±0.42 | 0.8 |
| | DT, ms | 192±15 | 197±17 | 0.5 |
| | IVRT, ms | 70±5 | 73±4 | 0.6 |
| | Pts/PtVd | 1.20±0.18 | 1.23±0.21 | 0.6 |
| | E/E' septal | 7.41±1.42 | 7.61±1.71 | 0.7 |
| | E/E' lateral | 6.51±1.34 | 6.38±1.72 | 0.5 |

A wave indicates flow velocity during atrial contraction; BMI, body mass index; DT, deceleration time; E wave, early transmural diastolic flow velocity; E/E', ratio of early transmural diastolic flow velocity (E) and early diastolic velocity recorded by Doppler tissue imaging (E') in the mitral annulus; IVRT, isovolumetric relaxation time; IVSd, diastolic interventricular septal thickness; LV, left ventricular; LVEF, LV ejection fraction; LVIDd, LV internal diameter in diastole; LVIDs, LV internal diameter in systole; LVMH, LV mass index; LVMH, LV mass/height; PHT, primary hyperparathyroidism; PTH, parathyroid hormone; PVd, diastolic pulmonary venous velocity; PVs, systolic pulmonary venous velocity; PWtd, diastolic posterior wall thickness; and WT, wall thickness. Unless specified otherwise, values are mean±SD or median (quartile 1–3).
descending coronary artery by pulsed-wave Doppler. After baseline recordings of flow velocity, adenosine was administered by intravenous infusion (140 μg · kg⁻¹ · min⁻¹) for 3 minutes, obtaining hyperemic Doppler flow profiles. CFR was estimated to be the ratio of hyperemic to baseline peak diastolic coronary flow velocities.¹⁹ A CFR ≤2.5 was considered abnormal,¹⁶ and the population was dichotomized according to this cutoff. All patients abstained from caffeine-containing drinks for at least 24 hours before testing.

All CFR measurements were stored digitally for future offline analysis by investigators blinded to all clinical variables. The intraobserver and interobserver variabilities of CFR measurements were 4.3% and 5.8%, respectively.

**MSCT Coronary Angiography Protocol and Interpretation**

Patients with abnormal CFR underwent MSCT coronary angiography to exclude epicardial CAD. Coronary MSCT was performed with a 64-slice dual-source scanner (Definition; Siemens Medical System, Forchheim, Germany). The MSCT protocol is detailed in the online-only Data Supplement.

**Laboratory Methods**

Blood samples for biochemical and metabolic laboratory measurements were obtained at 8 AM after an overnight fast. Serum PTH was measured with the DiaSorin LIAISON N-tact PTH kit (Saluggia, Italy) with the CLIA method (normal range, 1.8–7.7 pmol/L [17 and 73 ng/L]). Intra-assay and interassay coefficients of variation were 4.3% and 5.8%, respectively.

**Statistical Analyses**

Continuous variables with no/mild skew were presented as mean±SD; skewed measures as median were represented with first and third quartiles [Q1–Q3]. Discrete variables were summarized as frequencies and percentages. The distribution of the data was analyzed with a 1-sample Kolmogorov-Smirnov test. Logarithmic transformation was performed to achieve normal distribution for skewed variables. Categorical variables were compared by the χ² test or the Fisher exact test as appropriate. Continuous data were compared by use of the 2-tailed paired or unpaired t test (for normally distributed data sets) or the Mann-Whitney U or Wilcoxon signed-rank test (for skewed variables). Bivariate correlations were assessed by the Pearson coefficient (r). Unadjusted and multiple linear regression analyses were performed between CFR and risk factors or clinical conditions. Stepwise logistic regression analysis was used to model normal versus abnormal CFR as a function of PTH and other coronary risk factors or clinical conditions. Baseline characteristics were chosen for entry into multivariable models on the basis of their discrimination between low and high CFR and on unadjusted association with CFR ≤2.5 of P≤0.1. A combination of forward and backward selection procedures was used to aid in determining the best model of factors independently associated with CFR. This was followed by forcing potential confounders into the models and determining their effect on the relationship of interest. Nonsignificant risk factors were removed if they did not significantly add to the model. Summary statistics for the regression models included the C statistic (a measure of association of predicted probabilities and observed prevalence of a binary outcome) and R² (rescaled for use in logistic regression by the Cox and Snell method). Intraobserver and interobserver reproducibility of CFR was evaluated by linear regression analysis and expressed as the correlation of coefficients (r) and standard error of estimates and by the intraclass correlation coefficient. Reproducibility is considered satisfactory if the intraclass correlation coefficient is between 0.81 and 1.0. Intraobserver and interobserver reproducibility measurements were calculated in all 100 patients. All tests were 2 sided, and statistical significance was accepted if the null hypothesis could be rejected at P<0.05. Data were analyzed with SPSS software version 18.0 (SPSS, Inc, Chicago, IL).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**Baseline Clinical Features and CFR Evaluation**

Patient characteristics are presented in Table 1. CFR was lower in patients than in control subjects (3.0±0.8 versus 3.8±0.7, P=0.0001; Table 1 in the online-only Data Supplement). The prevalence of CFR ≤2.5 was higher in patients compared with control subjects (27% versus 4%; odds ratio, 8.9; P=0.0008). Severe CFR (CFR <2) impairment was found in 8 patients (8%) and in no control subjects. CFR studies were always well tolerated. Overall, during adenosine infusion, compared with baseline, heart rate increased (74±12 versus 94±16 bpm; increase, 20.27±12.38; P<0.0001), systolic blood pressure decreased (132±17 versus 114±18 mm Hg; decrease, 15 mm Hg [quartiles 1 and 3, 10 and 2 mm Hg]; P<0.0001), and diastolic blood pressure decreased (79±14 versus 67±11 mm Hg; decrease, 10 mm Hg [quartiles 1 and 3, 0 and 20 mm Hg]; P<0.0001), whereas peak diastolic velocity in the left anterior descending coronary artery increased (23±6 versus 69±20 cm/s; increase, 46.18±18.38 cm/s; P<0.0001). There were no significant ECG changes or left ventricular wall motion abnormalities during adenosine infusion in any of our patients. Fourteen patients were treated with statins, 10 with aspirin, 2 with nitrates, 14 with angiotensin-converting enzyme inhibitors, 8 with calcium antagonists, and 18 with β-blockers.

**Hemodynamic Parameters Based on CFR Value**

Heart rate at rest and during adenosine infusion was higher in patients with CFR ≤2.5 (80±13 versus 72±11 bpm, P=0.005; and 100±16 versus 92±15 bpm, P=0.04, respectively). Among patients, systolic blood pressure at rest was higher in those patients with CFR ≤2.5 (138±17 versus 130±16 mm Hg, respectively; P=0.03). Baseline peak diastolic flow velocity was higher in patients with CFR ≤2.5 (26±9 versus 22±4 cm/s; P<0.002). Hyperemic peak diastolic flow velocity and CFR were significantly lower in patients with CFR ≤2.5 compared with patients with normal CFR (57±15 versus 74±16 cm/s, P<0.002; and 2.0±0.4 versus 3.4±0.6, P<0.0001, respectively). Intraobserver and interobserver reproducibility of CFR measurements is shown in the online-only Data Supplement.

**Characteristics of Patients With Coronary Microvascular Dysfunction (CFR ≤2.5)**

The clinical characteristics of patients with CFR ≤2.5 and patients with CFR >2.5 are given in Table 2. PTH levels were higher in patients with CFR ≤2.5 (Figure 1). Patients with coronary microvascular dysfunction (CFR ≤2.5) were older and had a higher prevalence of hypertension. Diastolic dysfunction and plasma calcium levels were comparable in the 2 groups, as well as echocardiographic features and left ventricular mass. Therapy was not different between groups (data not shown). Twenty-six patients with CFR ≤2.5 had normal coronary arteries at MSCT. Only 1 patient had a mild right coronary stenosis (<50%). Calcium score was <10 in all patients with CFR ≤2.5.
Table 2. Comparison Between Patients With Microvascular Dysfunction (Coronary Flow Reserve ≤2.5) and Patients With Normal Coronary Flow Reserve (n=100)

<table>
<thead>
<tr>
<th></th>
<th>CFR ≤2.5 (n=72)</th>
<th>CFR &gt;2.5 (n=73)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63±12</td>
<td>57±12</td>
<td>0.03</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>5 (18)</td>
<td>15 (20)</td>
<td>0.8</td>
</tr>
<tr>
<td>Time from diagnosis, mo</td>
<td>8 (4–25)</td>
<td>8 (4–21)</td>
<td>0.7</td>
</tr>
<tr>
<td>PTH, pmol/L</td>
<td>26.4 (16–37)</td>
<td>18 (13–25)</td>
<td>&lt;0.007</td>
</tr>
<tr>
<td>Serum total calcium, mmol/L</td>
<td>2.9±0.1</td>
<td>2.8±0.3</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Cardiovascular risk factors, n (%)
- Current smokers: 3 (11)
- Hypertension: 17 (63)
- Diabetes mellitus: 3 (11)
- Obesity: 4 (15)
- Hyperlipidemia: 9 (33)

Echocardiographic characteristics
- Wsd, mm: 8.6±2 vs 8.3±1.2, P=0.5
- PWtd, mm: 8.3±1.3 vs 8.1±1.1, P=0.6
- LVtd, mm: 52±4.1 vs 51±5.7, P=0.7
- LVds, mm: 33.4±6 vs 31.3±5, P=0.4
- LV mass, g: 160±51 vs 156±47, P=0.3
- LV mass index, g/m²: 100±22 vs 99±19, P=0.4
- LV mass/height², g/m²: 46±11 vs 44±12, P=0.4
- Relative WT: 0.32±0.04 vs 0.31±0.07, P=0.8
- LV hypertrophy, LVMi, n (%): 9 (33) vs 23 (31), P=0.3
- LV hypertrophy, LVMI, n (%): 13 (48) vs 27 (37), P=0.5
- LVEF, %: 63±2 vs 65±5, P=0.8
- E wave, cm/s: 77.2±13.1 vs 79.1±12.2, P=0.6
- A wave, cm/s: 62.1±10.1 vs 58.1±11.1, P=0.3
- E/A: 1.32±0.21 vs 1.37±0.32, P=0.3
- DT, ms: 199±13 vs 195±16, P=0.4
- IVRT, ms: 72±5 vs 75±5, P=0.4
- P/ePd: 1.25±0.16 vs 1.22±0.18, P=0.5
- E/E’ septal: 7.81±1.32 vs 7.53±1.61, P=0.5
- E/E’ lateral: 6.41±1.21 vs 6.39±1.51, P=0.4

Grade of diastolic dysfunction, n (%)
- None: 12 (44)
- Mild: 12 (44)
- Moderate: 3 (12)
- Severe: 0 (12)

A wave indicates flow velocity during atrial contraction; BMI, body mass index; CFR, coronary flow reserve; DT, deceleration time; E wave, early transmural diastolic flow velocity; E/E’, ratio of early transmural diastolic flow velocity (E) and early diastolic velocity recorded by Doppler tissue imaging (E’) in the mitral annulus; IVRT, isovolumetric relaxation time; IVSd, diastolic interventricular septal thickness; LV, left ventricular; LVEF, LV ejection fraction; LVtd, LV internal diameter in diastole; LVds, LV internal diameter in systole; LVMI, LV mass index; LVMIH, LV mass/height; PTH, parathyroid hormone; Pd, diastolic pulmonary vein velocity; Ps, systolic pulmonary vein velocity; PWtd, diastolic posterior wall thickness; and WT, wall thickness. Unless specified otherwise, values are mean±SD or median (quartile 1–3).

Factors Associated With CFR

In unadjusted linear regression analysis, PTH (P=0.004), age (P=0.01), heart rate (P=0.007), and systolic blood pressure (P=0.02) were significantly associated with CFR. In multivariable analysis, only PTH (P=0.01), age (P=0.04), and heart rate (P=0.006) were independently associated with CFR (Table 3). PTH also independently correlated with diastolic peak velocity during adenosine (P<0.01). If hypertensive and diabetic patients were excluded from the analysis, PTH (P=0.01), age (P=0.02), and heart rate (P=0.01) remained the only factors associated with CFR.

Table 3. Unadjusted and Multivariable Linear Regression Analyses Between Coronary Flow Reserve (Dependent Variable) and Risk Factors or Clinical Conditions (Independent Variables) (n=100)

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted Analysis, P</th>
<th>β</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.01</td>
<td>−0.232</td>
<td>0.04</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.5</td>
<td>−0.127</td>
<td>0.2</td>
</tr>
<tr>
<td>Time from diagnosis</td>
<td>0.8</td>
<td>0.046</td>
<td>0.6</td>
</tr>
<tr>
<td>PTH</td>
<td>0.004</td>
<td>−0.242</td>
<td>0.01</td>
</tr>
<tr>
<td>Serum total calcium</td>
<td>0.2</td>
<td>0.034</td>
<td>0.7</td>
</tr>
<tr>
<td>Current smokers</td>
<td>0.1</td>
<td>−0.174</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.09</td>
<td>−0.049</td>
<td>0.6</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.6</td>
<td>0.167</td>
<td>0.1</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.4</td>
<td>0.02</td>
<td>0.8</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.1</td>
<td>−0.126</td>
<td>0.2</td>
</tr>
<tr>
<td>HR at time of the CFRmeasurement</td>
<td>0.007</td>
<td>−0.265</td>
<td>0.006</td>
</tr>
<tr>
<td>SBP at time of the CFRmeasurement</td>
<td>0.02</td>
<td>−0.052</td>
<td>0.6</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.3</td>
<td>−0.078</td>
<td>0.4</td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>0.7</td>
<td>0.077</td>
<td>0.4</td>
</tr>
</tbody>
</table>

CFR indicates coronary flow reserve; HR, heart rate; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; and PTH, parathyroid hormone. R² of the multivariable model=0.545.
Factors Associated With Coronary Microvascular Dysfunction (CFR ≤2.5)

In unadjusted logistic regression analysis, the significant or marginally significant (P<0.1) risk factors were PTH (P<0.01), age (P<0.03), body mass index (P=0.08), history of hypertension (P=0.03), systolic blood pressure (P=0.03), heart rate (P<0.004), history of dyslipidemia (P=0.08), and diastolic dysfunction (P=0.06). Factors independently associated with abnormal CFR are summarized in Table 4. When modeled using a stepwise regression and adjusting for baseline differences, factors independently associated with CFR ≤2.5 were PTH (odds ratio, 3.03; 95% confidence interval, 1.56–5.9; P=0.01) and heart rate (odds ratio, 1.08; 95% confidence interval, 1.02–1.13; P=0.02; Table 4). Substituting the basal heart rate did not greatly affect the model and no other clinical characteristic entered as a significant covariate.

To exclude the modulating effect of other variables, we also added variables marginally significant in unadjusted logistic regression analysis (model 3). They were not independently associated with CFR ≤2.5, and their addition to the model did not affect the robust relationship between PTH and CFR ≤2.5. When other conditions (sex, time from diagnosis, current smoking, history of diabetes mellitus, use of statins or nitrates) were forced into the model (potentially overfitting it), PTH and heart rate remained significantly associated with CFR ≤2.5 (P=0.01 and P=0.03, respectively). The C statistic for model 1 was 0.746 (95% confidence interval, 0.633–0.859) without PTH and 0.794 (95% confidence interval, 0.693–0.895) with PTH.

CFR After Parathyroidectomy

All 27 PHPT patients with preoperative CFR ≤2.5 showed complete CFR normalization (CFR, 2.1±0.5 versus 3.3±0.7; increase, 1.21±0.6; P<0.0001) 6 months after parathyroidectomy (Figure 2). After parathyroidectomy, PTH and serum calcium levels decreased (26.4 pmol/L [quartiles 1 and 3, 16–37 pmol/L] versus 5.7 pmol/L [4.4–7.4 pmol/L], P<0.0001 for PTH; and 2.9±0.1 versus 2.1±0.1 mmol/L, P<0.001 for calcium). Four previously hypertensive PHPT patients no longer required antihypertensive drugs after parathyroidectomy. No other significant variations (new medications; evidence of cardiac, renal, or cerebrovascular damage; change in diet, lifestyle, smoking, physical exercise, or body weight) occurred in PHPT patients after parathyroidectomy.

Discussion

Our study demonstrates that asymptomatic PHPT of recent onset is associated with coronary microvascular dysfunction in patients without CAD. Indeed, early after short-term successful parathyroidectomy, we observed a complete normalization of this impairment, suggesting a novel role of PTH in the pathophysiology of cardiovascular disease.

Chronically increased PTH levels have long been associated with higher morbidity and all-cause and cardiovascular

<table>
<thead>
<tr>
<th>Model</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
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<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH</td>
<td>3.03</td>
<td>1.56–5.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Basal heart rate</td>
<td>1.08</td>
<td>1.02–1.13</td>
<td>0.02</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH</td>
<td>2.71</td>
<td>1.50–5.10</td>
<td>0.03</td>
</tr>
<tr>
<td>Basal heart rate</td>
<td>1.08</td>
<td>1.02–1.14</td>
<td>0.02</td>
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<tr>
<td>3</td>
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<tr>
<td>PTH</td>
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<td>1.51–6.04</td>
<td>0.01</td>
</tr>
<tr>
<td>Basal heart rate</td>
<td>1.08</td>
<td>1.02–1.15</td>
<td>0.03</td>
</tr>
<tr>
<td>4</td>
<td></td>
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<tr>
<td>PTH</td>
<td>3.00</td>
<td>1.51–5.90</td>
<td>0.01</td>
</tr>
<tr>
<td>Basal heart rate</td>
<td>1.08</td>
<td>1.02–1.15</td>
<td>0.03</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; OR, odds ratio; and PTH, parathyroid hormone. The following variables were considered by the stepwise procedure but were not included in the final models because they did not meet the criteria to enter or to stay in the model: age, history of hypertension or hyperlipidemia, systolic blood pressure, obesity, and diastolic dysfunction. The following variables were forced into the model one at a time, but their inclusion did not affect the relationship between coronary flow reserve ≤2.5 and PTH: sex, time from diagnosis, current smoking, history of diabetes mellitus, and use of statins or nitrates.

Figure 2. Plot of individual changes in coronary flow reserve (CFR) before and after parathyroidectomy. All 27 primary hyperparathyroidism patients with preoperative CFR ≤2.5 evaluated 6 months after parathyroidectomy showed complete CFR normalization. Error bars reflect SD.
mortality in PHPT but also in secondary hyperparathyroidism (SHPT), in which PTH is secreted by parathyroid glands, seeking to restore the dyshomeostasis of essential cations (i.e., hypocalcemia and hypomagnesemia), in conditions like chronic renal failure, low renin hypertension, primary aldosteronism, heart failure, and vitamin D deficiency. The latter is particularly common among women and the elderly, in whom lactose intolerance and reduced dietary Ca may be also contributory. Patients with symptomatic PHPT or SHPT are at increased cardiovascular risk for a long time after successful parathyroidectomy. This evidence implicates the presence of an irreversible cardiovascular damage, which was initially attributed to an uremic-like toxicity exerted by chronic PTH elevations intertwining with multiple cardiovascular risk factors, reported at higher prevalence in PHPT and SHPT patients. Nowadays in Western countries, PTH alterations are diagnosed in an early phase when overt bone, renal, and cardiovascular complications have not yet developed. Nevertheless, as recently shown, mild alterations of circulating PTH, at the upper levels of the normal range, are already associated with a higher incidence of cardiovascular events in individuals without any other sign of disturbed mineral metabolism. Moreover, in patients referred to coronary angiography, PTH levels have been associated with all-cause and cardiovascular mortality after adjustments for common cardiovascular risk factors and parameters of mineral metabolism. In patients with stable CAD followed up over 8 years, baseline PTH levels were an independent prognostic factor for secondary cardiovascular event incidence and all-cause mortality.

As a consequence, the hypothesis of specific cardiovascular actions of PTH, extending beyond the control of bone and mineral metabolism, has evolved over time and is supported by multiple lines of evidence. Interestingly, in different tissues, PTH may exert an ionophoric effect, causing intracellular Ca overload and reactive oxygen species generation. Indeed, impaired antioxidant defenses resulting from low intracellular zinc are often coupled to intracellular Ca overload and further worsen the redox imbalance, leading to severe cell injury and death.

In particular, PTH-mediated intracellular Ca accumulation, coupled to induction of excessive oxidative stress in cardiomyocytes and their mitochondria, has been linked to cell death and subsequent myocardial tissue repair. In the long term, progressive parenchymal loss and reparative fibrosis compromise cardiac function and cause heart failure. Moreover, Ca overload has been related to the electric remodeling and arrhythmogenic potential characterizing cardiomyocytes in heart failure.

The complexity of PTH functions is further highlighted by data indicating the existence of a bidirectional link between PTH and the renin-angiotensin-aldosterone-system, which may be relevant for the regulation of calcium metabolism and in the pathogenesis of cardiovascular disease. In particular, PTH can stimulate aldosterone secretion directly from the adrenals and indirectly by modulating angiotensin II signaling. Increased aldosterone levels are a well-known mediator in the pathogenesis of cardiovascular disease (i.e., higher risk of left ventricular hypertrophy and sudden cardiac death) and atherosclerosis because of proinflammatory, prothrombotic, and profibrotic effects.

On the other hand, in primary or secondary aldosteronism, the appearance of ionized hypocalcemia and hypomagnesemia, secondary to cation excretory loss, causes SHPT and bone resorption. Adrenalectomy and blockade of the mineralocorticoid receptor normalize the PTH profile in primary aldosteronism patients. Interestingly, in a model of secondary aldosteronism developing SHPT, PTH-mediated intracellular Ca overload and oxidative stress have been reported to promote an inflammatory phenotype in immune cells infiltrating coronary vessels, suggesting that PTH-mediated Ca overload and oxidative stress have a permissive role in the cardiovascular remodeling mediated by aldosterone. In addition, in patients with PHPT, aldosterone levels are elevated and correlate positively with PTH values, likely explaining the development of arterial hypertension and cardiovascular damage in patients with PHPT.

In line with other reports suggesting that PTH may influence the vascular system, namely endothelial and vascular smooth muscle cells, and may cause arterial stiffening and endothelial dysfunction, our findings point to the coronary vasculature as a novel putative PTH target. Data on the effects of PTH on the vessel wall are controversial. Whereas short-term PTH administration seems to have a vasorelaxing effect, its chronic elevation accompanied by excessive reactive oxygen species generation might contribute to vascular smooth muscle cell contraction and to the impairment of the endothelial vasoprotective properties, thus promoting atherosclerosis. Along this line, in PHPT patients, reduced nitric oxide (NO) bioavailability has been associated with peripheral endothelial dysfunction reversible after parathyroidectomy. Although molecular mechanisms regulating coronary function in PHPT are unknown, it is conceivable that the Ca-overloading paradigm could play an important role in explaining our findings in the coronary microvasculature. Accordingly, PTH-mediated intracellular Ca overloading occurring in the coronary endothelial cells would result in the induction of oxidative stress, which is known to impair NO bioavailability. NO is not only a major vasodilatory molecule but also the principal physiological antiatherosclerotic mediator because of its antiinflammatory, antiproliferative, immune-modulatory properties.

Thus, compromised NO bioavailability might be a major determinant of the impaired coronary microvascular dysfunction we observed and, on a broader perspective, a crucial factor explaining the higher risk for cardiovascular morbidity associated with PTH disturbances. In particular, PTH controls the expression and activity of endothelial NO synthase through protein kinase C (PKC) and A pathways. SHPT resulting from chronic renal insufficiency has been associated with reduced endothelial NO synthase expression and NO generation. Impaired NO availability was reversed by parathyroidectomy and by calcium channel blockade, suggesting that calcium dyshomeostasis might play a role in the phenomenon.

In endothelial cells, PTH induces the appearance of calcium channels and modulates the Ca signaling pathways,
resulting in activation of PKC. Some PKC isoforms like the PKC-β family are known to be activated by oxidative stress and to promote further reactive oxygen species production with detrimental effects on the vascular wall. Recently, in vitro, the mitochondrial Ca\(^{2+}\) homeostasis, a determinant of cell survival, has been shown to become dysfunctional in conditions of intracellular oxidative stress involving PKC-β and prolyl isomerase 1 (Pin1). Moreover, in the presence of SHPT resulting from renal failure, increased PTH expression has been linked to decreased Pin1 activity. Moreover, Pin1 pharmacological inhibition and genetic deletion have been shown to cause endothelial dysfunction and hypertension as a result of decreased endothelial NO synthase activity and NO production. Thus, it is conceivable that in a condition of elevated PTH, PKC isoform activation and/or decreased Pin1 activity might contribute to endothelial dysfunction owing to decreased NO production and increased oxidative stress. To date, however, the involvement of PKC isoforms and Pin1 signaling has not been investigated in the coronary microvasculature in the presence of PTH disturbances, and further studies are awaited.

From a pathophysiological point of view, reduced CFR can result from the combination of different alterations such as impaired vasodilation, enhanced vasoconstritor responsiveness, and/or structural remodeling of the coronary microvasculature. In PHPT, an involvement of both endothelium-dependent and -independent pathways has been reported. Baseline coronary flow was higher in patients with CFR ≤2.5 compared with patients with CFR >2.5, which is consistent with a resting microvascular vasorelaxation and could alone account for the lower CFR. This result could be in correlation with PTH-mediated endothelium-independent vasorelaxing effects on vascular smooth muscle cells. Interestingly, we observed in some patients a reduced CFR caused by abnormal flow velocity increase during adenosine. Although CFR assessment by adenosine does not allow us to distinguish between endothelium-dependent and -independent abnormalities, this functional alteration can be recognized as the earliest detectable impairment in the process leading to the coronary microvasculopathy. We could not exclude the presence of structural abnormalities affecting the microcirculation (e.g., arteriolar remodeling and calcification) by means of currently available imaging techniques. However, the CFR normalization after parathyroidectomy seems to rule out this possibility, at least in our patient cohort in which vascular calcifications are unlikely because the disease was mild (serum total calcium was >3 mmol/L in only 12% of patients) and in the early stage (median time from diagnosis, 6 months).

A recent evaluation of myocardial perfusion conducted by gated single-photon emission computed tomography has demonstrated that CFR is significantly reduced in PHPT non-CAD patients compared with control subjects, depending on disease duration. On the contrary, in our population, PTH, age, and heart rate were independently associated with CFR and not with disease duration. This difference might be explained by the very short median time of PHPT duration of our patients, reflecting an early phase in the development of PHPT cardiovascular abnormalities. However, because the relation between CFR and disease duration has been described, we also adjusted for this variable in the multivariable models. Furthermore, no follow-up data were available in the Marini et al study. On the contrary, CFR evaluation by means of a noninvasive technique such as transthoracic Doppler echocardiography provided us with a simple, objective, rapid diagnostic tool to detect coronary microvascular dysfunction and to follow it over time. Interestingly, CFR evaluation performed 6 months after parathyroidectomy allowed us to observe complete recovery of coronary microvascular function.

Study Limitations
First, our study is cross-sectional, and conclusions about causal and temporal order between PTH and CFR cannot be drawn. Second, sample variability in PTH and serum calcium assays may increase random error. However, all assays used in this study have acceptable levels of precision. Nevertheless, it is possible that the lack of significant results for serum calcium is due in part to random error. Third, it also cannot be excluded that disturbances in the renin-angiotensin-aldosterone-system, which are known to be associated with PHPT, may contribute to structural and functional alterations of the microvascular wall. Fourth, despite the relatively large cohort of patients, the small number of patients with abnormal CFR limits statistical power and creates the risk of overfitting the models when adding covariates. However, in this study, the addition of covariates, in any case, has influenced the relationship between PTH and CFR. Finally, none of the control subjects underwent MSCT or coronary angiography. It would be unethical to submit asymptomatic subjects with normal CFR to invasive diagnostic examinations. Similarly, patients with normal CFR did not undergo MSCT for ethical reasons.

Conclusions
Our findings unmask a specific role of PTH excess in early coronary microvascular dysfunction and show that parathyroidectomy performed shortly after PHPT diagnosis is able to completely restore this impairment. In our study, PTH per se correlates with CFR independently of established cardiovascular risk factors and other determinants of mineral metabolism. Our data can help to explain why PHPT is associated with increased cardiovascular mortality and risk, although the molecular mechanisms involved need to be investigated further.

Disclosures
None.

References


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**CLINICAL PERSPECTIVE**

Chronic elevations of parathyroid hormone (PTH) caused by primary (PHPT) or secondary hyperparathyroidism have long been associated with higher morbidity and all-cause and cardiovascular mortality. Multiple lines of evidence from experimental and clinical studies suggest that PTH could be causally involved in the pathophysiology of cardiovascular disease. Along with the shift in the clinical presentation of patients with PTH disorders toward an early and asymptomatic phase, as a result of improved diagnosis, current studies need to elucidate the frequency and clinical significance of subtle cardiovascular abnormalities associated with PTH alterations, trying to define their exact pathophysiological role and their reversibility. The present study aimed to evaluate the influence of PTH on coronary microvascular function, assessed by coronary flow reserve by transthoracic Doppler echocardiography, in healthy subjects and in patients with asymptomatic PHPT without evidence for epicardial coronary artery disease. Interestingly, asymptomatic PHPT of recent onset is already associated with coronary microvascular dysfunction, which is completely restored after short-term successful parathyroidectomy. Indeed, PTH per se is a determinant of coronary flow reserve independently of established cardiovascular risk factors and of other parameters of mineral metabolism. Our findings suggest a novel role of PTH in the pathophysiology of cardiovascular disease and a noninvasive, simple, and objective diagnostic tool for the assessment and follow-up of coronary microvascular function. Our data may improve the management and treatment of PHPT in its asymptomatic initial phase and may explain why PHPT is associated with increased cardiovascular mortality and risk, although molecular mechanisms involved need to be further investigated.
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_Circulation_. 2012;126:1031-1039; originally published online July 19, 2012;
doi: 10.1161/CIRCULATIONAHA.111.081307

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/126/9/1031

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SUPPLEMENTAL METHODS

Risk factor definition

Diabetes mellitus was diagnosed when patients were taking hypoglycemic medications or with fasting glycemia >126 mg/dl (7 mmol/L) in two consecutive determinations. Hyperlipidemia was defined as fasting total serum cholesterol >220 mg/dl (5.7 mmol/L) and/or serum triglycerides >1.56 mg/dl (1.8 mmol/L), or when patients were taking an oral lipid-lowering agent. We defined as hypertensive those patients taking antihypertensive drugs or showing a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg (average of two or more readings taken in the sitting position in different days). Secondary hypertension was excluded on the basis of standard biochemical, hormonal, and instrumental tests. A BMI ≥ 30 Kg/m² was considered as an index of obesity. Patients smoking at least one cigarette daily for 1 year within the last 5 years were considered smokers.

Echocardiography

From two-dimensional guided M-mode echocardiograms, left ventricular (LV) dimensions were measured by American Society of Echocardiography (ASE) convention; LV mass was calculated by the adjusted ASE method¹ and indexed for body surface area or height. LV mass/body surface area ≤ 116 g/m² in men and ≤ 104 g/m² in women was considered normal. LV mass/ height².⁷ was considered normal if ≤ 49.2 g/m²² in men and ≤ 46.7 g/m²² in women. Valvular disease was classified significant if moderate-severe stenosis and/or insufficiency was detected by TDE. None of the patients suffered from significant valvular disease. In each subject, ejection fraction was measured and diastolic dysfunction was defined according to the ASE criteria². These criteria integrate Doppler measurements of the mitral inflow and Doppler tissue imaging of the mitral annulus. This approach is the standard practice in our laboratory and enabled us to classify diastolic function in 4 categories: normal diastolic function, mild diastolic dysfunction (impaired relaxation without evidence of increased filling pressures), moderate diastolic dysfunction (impaired...
relaxation or pseudo-normal with moderate elevation of filling pressures), and severe diastolic
dysfunction (advanced reduction in compliance).³

**MSCT protocol**

To optimize imaging, participants without contraindications received β-blockade with oral and/or
intravenous metoprolol to slow the heart rate to 60-70 beats/min. An optimized dose modulation
approach using helical acquisition and reduced voltage was used to decrease radiation exposure.
Coronary MSCT was read by consensus of 2 cardiologists and radiologists. Coronary MSCT data
sets were evaluated for the presence of significant coronary artery stenosis within the left main
coronary artery; proximal, mid, and distal segments of the LAD coronary artery; first and second
diagonal branches; proximal, mid, and distal segments of the left circumflex coronary artery; first
and second marginal branches; proximal, mid, and distal segments of the right coronary artery; and
the posterior descending artery according to the 15-segment American Heart Association
classification⁴. The coronary artery calcium score was assessed with dedicated software (Syngo Ca
Score-Siemens Medical Solution). The total calcium burden in the coronary arteries was quantified
as previously described⁴.
SUPPLEMENTAL RESULTS

Correlation between CFR, Clinical and Biochemical Characteristics

Bivariate correlation analysis revealed significant and inverse correlations between CFR and log PTH ($r=-0.3$, $p<0.004$), age ($r=-0.24$, $p=0.01$), heart rate ($r=-0.26$, $p<0.007$) and systolic blood pressure ($r=-0.21$, $p=0.02$), whereas no correlation with serum calcium levels has been observed ($p=0.3$).

Intra- and Inter-Observer Reproducibility of CFR by Transthoracic Echocardiography

Intra-observer and inter-observer reproducibility of CFR measurements were assessed by repeating CFR evaluation twice, 1 h apart, by the same operator (F.T.) in all patients and by another operator (E.O.) in all patients as well. The intra-observer reproducibility was high ($r=0.92$, $SEE=0.10$); ICC was 0.969. The inter-observer reproducibility was also high ($r=0.90$, $SEE=0.11$); ICC was 0.961.
Supplemental Table: Hemodynamic Parameters during CFR Evaluation in the Study

**Population**

<table>
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<th>Controls (n=50)</th>
<th>PHPT (n=100)</th>
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<tbody>
<tr>
<td><strong>Basal heart rate, beats/min</strong></td>
<td>75 (67-82)</td>
<td>74 (65-82)</td>
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<tr>
<td><strong>Adenosine heart rate, beats/min</strong></td>
<td>96 (86-110)</td>
<td>95 (83-106)</td>
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<td><strong>Basal systolic blood pressure, mmHg</strong></td>
<td>120 (110-127)</td>
<td>130 (120-140)</td>
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<tr>
<td><strong>Adenosine systolic blood pressure, mmHg</strong></td>
<td>100 (95-115)</td>
<td>110 (100-123)</td>
<td>0.2</td>
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<tr>
<td><strong>Basal diastolic blood pressure, mmHg</strong></td>
<td>80 (67-83)</td>
<td>80 (70-83)</td>
<td>0.8</td>
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<tr>
<td><strong>Adenosine diastolic blood pressure, mmHg</strong></td>
<td>60 (60-70)</td>
<td>70 (60-80)</td>
<td>0.4</td>
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<tr>
<td><strong>Basal peak diastolic velocity, cm/s</strong></td>
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<td>23 (19-26)</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Adenosine peak diastolic velocity, cm/s</strong></td>
<td>84 (64-97)</td>
<td>71 (55-81)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Coronary flow velocity reserve</strong></td>
<td>3.8 ± 0.7</td>
<td>3.0 ± 0.8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are reported as mean ± standard deviation or median (Q1, Q3)
SUPPLEMENTAL REFERENCES


