Conflicting data concerning the cardiovascular manifestations of primary hyperparathyroidism (PHPT) may be explained by the decrease in disease severity observed over the past 30 yr. Whereas cardiovascular mortality is clearly increased in PHPT associated with moderate to severe hypercalcemia (1–7), data from the single epidemiologic study assessing patients with mild hypercalcemia found reduced cardiovascular mortality in af-
Subjects and Methods

This was a case-control study comparing cardiac structure and function in patients with PHPT to normal controls. All patients gave written, informed consent. This study was approved by the Institutional Review Board of Columbia University Medical Center.

Subjects

Participants with PHPT were referred from the Metabolic Bone Diseases Unit at Columbia University Medical Center and represent consecutive cases who agreed to participate in the study between October 2005 and September 2008. Cases were eligible if they were between the ages of 45–75 yr to study those at risk for cardiac disease and because this age range includes the vast majority of patients with PHPT. Patients had PHPT, diagnosed by the presence of hypercalcemia (calcium >10.2 but <12.0 mg/dl to study the presence of cardiovascular findings in those with mild hypercalcemia) and an elevated or inappropriately normal PTH level. Calcium to creatinine clearance ratio was measured to exclude familial hypocalciuric hypercalcemia, and none had thiazide-induced hyperparathyroidism. Exclusion criteria included reported use of bisphosphonates within 2 months and initiation or changes in cholesterol-lowering medications within 2 yr of entry to the study (by patient report). Some patients were on multivitamins, but none were taking more than 600 IU/d of vitamin D supplements.

Controls were from the Northern Manhattan Study (NOMAS), a population-based study designed to investigate cardiovascular risk factors in 3298 individuals. Recruitment and enrollment for NOMAS has been described (29, 30). From September 2005 through December 2008, NOMAS subjects older than age 50 yr who agreed to undergo brain MRI and echocardiographic evaluation that included diastolic function assessment were included in the Cardiac Abnormalities and Brain Lesion study. This subset of individuals constitutes the sample from which the control subjects of the present report were drawn. We matched each PHPT case by age, sex, and race- to one (or two when a second match was available) normocalcemic Cardiac Abnormalities and Brain Lesion control(s).

Cardiovascular risk factors

Demographic data, cardiac risk factors, and medical history were obtained from participants. These include race/ethnicity by self-identification; coronary artery disease (history of myocardial infarction, angina, angioplasty or coronary artery bypass surgery); hypercholesterolemia (a physician’s report of elevated lipid levels or being on a lipid lowering medication); hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or a patient’s self-report of hypertension or antihypertensive medication use); diabetes mellitus (fasting blood glucose level >126 mg/dl, patient’s self-report of diabetes, or use of insulin or other hypoglycemic medications); cigarette smoking (categorized as nonsmoker or ever smoked).

Biochemical evaluation

Fasting samples for serum calcium, creatinine, and total cholesterol were measured by an automated chemistry analyzer. PTH was measured by immunochemilumimetric assay for intact PTH (Scantibodies Laboratories, Inc., Santee, CA), which detects PTH (1-84) and PTH (7-84). Serum 25-hydroxyvitamin D was measured by RIA (Diasorin, Stillwater, MN).

Transthoracic echocardiography

Transthoracic echocardiography was performed and measurements were taken by standard two-dimensional protocols according to guidelines of the American Society of Echocardiography (31). LV diastolic dimension, interventricular septal thickness, and posterior wall thickness were measured. LV mass (LVM) was calculated by the corrected American Society of Echocardiography method: 0.8[1.04 ([LV diastolic dimension + interventricular septal thickness + posterior wall thickness]^3)] + 0.6 (32). LVM index (LVMI) was calculated as LVM divided by

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body surface area. Abnormal LVMI is defined as greater than 108 g/m² in women and greater than 131 g/m² in men (31).

Transmitral diastolic flow was obtained by pulsed-wave Doppler from an apical four-chamber view, with the pulsed Doppler sample volume placed perpendicular to the inflow jet previously identified with the use of color Doppler. LV myocardial velocities were evaluated by tissue Doppler imaging and sampled on the longitudinal axis from the apical four-chamber view. Two-dimensionally guided pulsed-tissue Doppler imaging sample volume was placed at the level of the lateral mitral valve annulus. Doppler gain and wall filter were adjusted to reduce artifacts and velocity scale was set to ±20 cm/sec. Four consecutive beats were recorded at a sweep rate of 100 mm/sec during patient apnea and stored for off-line analysis. Peak velocities of the early and late phase of the mitral inflow pattern from Doppler recordings were measured and their ratio (E/A) was calculated; peak early (e') diastolic velocity of the lateral mitral valve annulus by pulsed-tissue Doppler imaging was measured. Normal values for E/A and tissue Doppler e' were 0.75–1.5 and 7 mm or greater, respectively. Mitral annular calcification (MAC) was defined as an intense echocardiographic-producing structure with highly reflective characteristics that was located at the junction of the atrioventricular groove and the posterior or anterior mitral leaflet.

### Statistical analysis

Between-group differences in demographic and cardiovascular risk factors were evaluated by independent two-sided t test, χ², or Fisher’s exact test as appropriate and adjusted for multiple comparisons as noted. Critical test values were adjusted for unequal variances when variances tested unequal (SAS Stat; SAS Institute, Cary NC). Differences in echocardiographic outcomes (LVMI, MAC, E/A, and tissue Doppler e') between cases and controls were assessed with repeated-measures ANOVA using the pair as the observation unit and subject within pair as the repeated factor. Because of the differences in mean values for cholesterol, blood glucose between the cases and controls, hypercholesterolemia, hypertension, and diabetes were entered as categorical variables.

Relationships between calcium, PTH, 25-hydroxyvitamin D, and echocardiographic variables were assessed with Pearson correlation (continuous variables) or logistic regression (categorical variables). Stepwise multiple regression was used to evaluate the influence of cardiovascular risk factors and other biochemistries (PTH, serum calcium, male gender, hypertension, hypercholesterolemia, creatinine, diabetes, coronary artery disease, and smoking) on the relationship between 25-hydroxyvitamin D and LVMI. The stepwise selection process criterion for entry to the model was a univariate \( P \leq 0.3 \) and the criterion for retention in the model was a multivariate \( P \leq 0.10 \).

Serum levels of PTH, calcium, and 25-hydroxyvitamin D in those with normal vs. abnormal LVMI, E/A, and tissue Doppler e' as well as those with and without MAC were compared using independent two-sided t test. The study had 80% power with a 5% alpha to detect a 0.4-SD between-group difference under the simplifying assumption of a matched-pair t test with 50 pairs. For all analyses, a two-tailed \( P < 0.05 \) was considered to indicate statistical significance. Statistical analysis was performed using SAS (version 9.2.3; SAS Institute).

### Results

#### Clinical and biochemical data

Consistent with their diagnosis, the majority of participants were female and had biochemically mild PHPT [serum calcium (mean ± sd): 10.5 ± 0.5 mg/dl, normal 8.7–10.2 mg/dl; PTH: 96 ± 45, normal 10–66 pg/ml; 25-hydroxyvitamin D level: 37.4 ± 14 ng/ml; Table 1]. Whereas the racial distribution was similar among cases and controls, there were more Caucasians of Hispanic ethnicity in the control group. Body mass index (BMI) was higher and hypertension more common in control subjects, and diabetes as well as hypercholesterolemia tended to be seen more frequently in the control group as well (Table 1). However, when adjustment was made for multiple comparisons between groups, only the difference between ethnic groups remained significant. Finally, although the study was not powered to assess this point, patients who met one or more 2002 National Institutes of Health Consensus Workshop guidelines for parathyroidectomy (n = 35) were compared with those who did not meet any surgical criteria (n = 19). There were no differences between these groups in any biochemical, demographic or cardiovascular risk factor listed in Table 1. Of the cardiac structural and functional indices measured, only tissue Doppler e’ differed between the two groups (met guidelines: 11.9 ± 2.9 vs. no guidelines: 10.2 ± 2.4; \( P < 0.05 \)), and values for both groups were within normal limits.

#### Cardiac structure and function

Mean LVMI was normal in PHPT. LVMI was elevated in only 15% of patients, 50% of whom were hypertensive.
LVMI did not differ between PHPT and controls (98 ± 23 vs. 96 ± 24 g/m², P = 0.69; Table 2) with or without adjustment for group differences in cardiovascular risk factors (BMI, hypertension, diabetes, and hypercholesterolemia). Frequency of mitral annular calcification was similar in PHPT vs. controls before (13 vs. 21%; within pair difference 5.9%, P = 0.26) and after adjustment for disparities in cardiovascular risk factors (P = 0.38). Mean diastolic function values (E/A and tissue Doppler e’) were normal in both PHPT and controls, although they were higher (better) in cases within the normal reference range. In PHPT, E/A ratio and tissue Doppler e’ were below the normal cutoff values in only 22 and 6%, respectively.

**Relationship between PTH, calcium, vitamin D, and echocardiographic measures in PHPT**

There was no linear association between serum calcium or PTH level and LVMI, valvular calcification, or any diastolic function variable among participants with PHPT. Serum 25-hydroxyvitamin D (25OHD) level, however, negatively correlated with LVMI (r = −0.29, P = 0.04) but not other echocardiographic variables. Removal of the two participants with the highest LVMI values (Fig. 1) did not alter this finding (r = −0.28, P = 0.04). When stepwise multiple regression was used to evaluate the influence of cardiovascular risk factors and other biochemical measurements, only serum 25OHD and creatinine were significant predictors of LVMI. For every 1 ng/ml decrease in 25OHD, LVMI increased by 0.56 g/m² (P = 0.0086; Table 3). Furthermore, 75% (six of eight) of patients with vitamin D deficiency or insufficiency (25OHD <30 ng/ml) had LVMI above the cohort average of 97, as compared with 37% (16 of 43) of those with 25OHD levels in the vitamin D replete range (above 30 ng/ml). Finally, BMI does not seem to mediate the increase in LVMI. Of the 22 subjects with LVMI above the cohort average (97 g/m²), 18 had BMI between 20–30, whereas two were less than 20 and two had BMI greater than 30 kg/m².

There was no difference in PTH, calcium level, or 25OHD level between PHPT cases with normal vs. abnormal LVMI (PTH: 98 ± 47 vs. 88 ± 36 pg/ml, P = 0.56; calcium: 10.5 ± 0.5 vs. 10.3 ± 0.5 mg/dl, P = 0.23; 25OHD: 38 ± 14 vs. 34 ± 9 ng/ml, P = 0.48) or between those with or without MAC (PTH: 85 ± 50 vs. 98 ± 45 pg/ml, P = 0.47; calcium: 10.6 ± 0.6 vs. 10.5 ± 0.5 mg/dl, P = 0.64; 25OHD: 38 ± 16 vs. 37 ± 13 ng/ml, P = 0.79). Those with low E/A ratio had higher mean serum PTH and calcium levels but not lower vitamin D than those with E/A 0.75 or greater (PTH: 121 ± 36 vs. 89 ± 46 pg/ml, P = 0.03; calcium 10.8 ± 0.4 vs. 10.5 ± 0.5 mg/dl, P = 0.05; 25OHD: 36 ± 9 vs. 38 ± 15 ng/ml, P = 0.75; Fig. 2). There was no difference in PTH, calcium, or 25OHD level in those with low vs. normal tissue Doppler e’ (PTH: 129 ± 38 vs. 94 ± 46 pg/ml, P = 0.20; calcium: 10.8 ± 0.2 vs. 10.5 ± 0.5, P = 0.31; 25OHD: 32 ± 3 vs. 38 ± 13, P = 0.51). Among controls (calcium levels normal; PTH, 25OHD unavailable), there was no difference in calcium level between those with normal vs. abnormal E/A or tissue Doppler e’.

![Figure 1](https://academic.oup.com/jcem/article-abstract/jcem.endojournals.org/95/5/2172/2596788/2152)  
**FIG. 1.** Relationship between 25OHD level and LVMI in patients with PHPT.

### TABLE 2. Echocardiographic studies

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal range</th>
<th>PHPT Mean ± SD</th>
<th>Controls Mean ± SD</th>
<th>Within-pair difference ± SD</th>
<th>P value Within-pair difference</th>
<th>P value Within-pair differencea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early to late mitral annular velocity (E/A)</td>
<td>0.75–1.5</td>
<td>1.1 ± 0.3</td>
<td>0.9 ± 0.3</td>
<td>0.13 ± 0.40</td>
<td>0.0007</td>
<td>0.03</td>
</tr>
<tr>
<td>Tissue Doppler e’ (mm)</td>
<td>≥7</td>
<td>11.3 ± 2.6</td>
<td>9.6 ± 2.7</td>
<td>1.41 ± 3.63</td>
<td>0.0005</td>
<td>0.006</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>≤108 for women</td>
<td>96 ± 24</td>
<td>96 ± 24</td>
<td>2.8 ± 31.7</td>
<td>0.69</td>
<td>0.44</td>
</tr>
</tbody>
</table>

a Comparison adjusted for body mass index, hypertensive, diabetic and hypercholesterolemic status.

### TABLE 3. Multiple regression model of LVMI in PHPT patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>SE</th>
<th>P value</th>
<th>Model R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>25OHDa</td>
<td>−0.56</td>
<td>0.21</td>
<td>0.0086</td>
<td>0.18</td>
</tr>
<tr>
<td>Creatininea</td>
<td>23.65</td>
<td>10.62</td>
<td>0.03</td>
<td>0.01</td>
</tr>
</tbody>
</table>

a Selected from a model including PTH, serum calcium, 25OHD, male gender, hypertension, hypercholesterolemia, creatinine, diabetes, coronary artery disease, and smoking as potential variables.
Discussion

Many patients with asymptomatic PHPT are observed without surgical intervention, which heightens the importance of understanding whether cardiovascular abnormalities are associated with biochemically mild PHPT. This echocardiographic study of PHPT patients with mild hypercalcemia (mean \(0.5\) mg/dl above the upper limit of normal) studied both indices of cardiac structure and function and found no evidence of increased LVMI, mitral annular calcification, or diastolic dysfunction, although we did find that the presence of diastolic dysfunction was associated with higher serum calcium and PTH levels. Additionally, we demonstrated an inverse association between serum 25OHD and LVMI in PHPT.

Previous data on LVM in patients with PHPT have been inconsistent, although all have included subjects with more severe disease and higher mean serum calcium and PTH levels than those in our investigation. Many of the available studies are limited by absence of a control group or lack of consideration of coexisting cardiovascular risk factors (13, 14). Indeed, several studies that reported increased LVMI in a PHPT cohort found the result to be driven by those patients with coexisting hypertension (18, 19). Others report LVH in PHPT patients, regardless of hypertensive status (16, 28), and two studies found a positive association of PTH with LVMI (12, 15). Neither study provided data on vitamin D levels, nor did they investigate whether the relationship between PTH and LVMI could be due to lower vitamin D in those with the highest PTH values.

It has long been postulated that LVH, if present in PHPT, may be secondary to PTH excess. There are data suggesting that PTH has trophic effects on cardiomyocytes (24). However, the vitamin D receptor is also present on cardiomyocytes as well as in vascular endothelial and smooth muscle cells. Recent data suggest that vitamin D deficiency activates the renin-angiotensin-aldosterone system, and vitamin D receptor knockout mice have hypertension, cardiac hypertrophy, and fibrosis (33–36). A recent study in humans found that vitamin D deficiency was associated with incident cardiovascular disease (37). There are no data on whether the cardiovascular effects were secondary to elevated PTH levels, low vitamin D, or both. However, a study in patients with secondary hyperparathyroidism (renal failure) found that higher LVMI was related to a vitamin D receptor polymorphism, rather than PTH levels (38). Vitamin D deficiency and insufficiency are common in PHPT and lower serum 25OHD levels are associated with higher serum PTH levels in PHPT (39–42), making either or both plausible mediators of deleterious cardiovascular effects in PHPT. That we did not find an increase in LVMI among our patients with PHPT, despite the association between LVMI and vitamin D, may be due to the fact that the majority of patients were vitamin D replete (84%; mean 25OHD 37.4 ng/ml) and/or that the PTH levels were not as high (mean values \(\pm SD\): 96 \(\pm 45\) vs. 215 \(\pm 178\) and 161 \(\pm 73\) ) as those reported in prior studies (15, 16).

Few studies have studied cardiac calcifications in PHPT. As in our study, no increase in cardiac calcifications was seen at lower mean serum calcium levels (11.2 mg/dl) (13), whereas calcifications are reported in patients with higher calcium levels (12–12.3 mg/dl) (27, 28). Myocardial and valvular calcifications have not, however, been shown to correlate with calcium or PTH levels in PHPT (27).

Many studies investigating diastolic function in PHPT are limited by the same issues affecting those examining LVMI, and inevitably results have been contradictory (13–15, 18, 20). Whereas we did not find evidence of diastolic dysfunction in our group of patients with PHPT, our data do indicate that those with low E/A have higher
calcium and PTH levels than those with normal diastolic function. A similar association in those with low tissue Doppler ’e’ , another measure of diastolic dysfunction, could have been missed because only three patients had abnormal values. Our results therefore are consistent with the hypothesis that diastolic dysfunction is related to the severity of hypercalcemia and/or PTH elevation in PHPT. This finding could be explained by the fact that myocardial relaxation depends on cytosol clearance of calcium (43), which may be impaired by the hypercalcemic environment in PHPT.

In aggregate, our results along with those of previous studies suggest that increased LVMI, mitral calcification, and diastolic dysfunction are present only in those with biochemically more severe PHPT and/or when hypertension or other cardiovascular risk factors are present and not taken into account. Whereas we did not find evidence for an effect on cardiac structure or function, it is becoming clear that mild hyperparathyroidism has different effects on various aspects of the cardiovascular system. We recently reported that this cohort has abnormal carotid vasculature (44), increased carotid intima-media thickness (IMT), and decreased carotid compliance. Carotid stiffness, strain, and distensibility were associated with PTH levels. This suggests that mild PHPT may have different effects in differing portions of the vascular system, increasing the risk of carotid abnormalities, but not predisposing to abnormalities in cardiac structure or function. The mechanisms that underlie this differential effect on the cardiovascular system in PHPT are unknown. The pathophysiological pathways that influence the development of atherosclerosis in PHPT may be different from those that cause changes in cardiac structure or function. Alternatively, the same pathological factor(s) may be operative, but the vasculature may be more sensitive or respond differently to the effects. Whereas we have yet to examine the relationship between IMT and 25OHD level within our cohort of patients with PHPT, a recent study reported a negative association between internal carotid IMT and 25OHD level, but not PTH, among community-dwelling adults without PHPT (45). Lastly, it is possible that increased carotid wall thickness and arterial wall dysfunction are early manifestations of mild PHPT, whereas changes in cardiac structure and function may develop later in the disease.

Our study has a number of limitations. Although the control group was a random sample of free-living individuals, they had higher BMI and frequency of hypertension, and tended to have more hypercholesterolemia and diabetes than the PHPT patients. We did not find the association of mild PHPT with hypertension, increased BMI, diabetes, or hypercholesterolemia, suggested by others (46–51). It is unlikely that the healthier profile of the PHPT cohort is attributable to PHPT disease status (see adjusted P values, Table 1). However, although we adjusted for differences in these important cardiovascular risk factors in our analysis, the fact that they were greater in the control population may have biased against our finding echocardiographic abnormalities in PHPT. We therefore assessed our patients against published normal ranges and did not find any abnormalities using that method either. The study is also limited because it represents a convenience sample of patients with PHPT, including those who met as well as those who did not meet surgical criteria for parathyroidectomy (subgroup analysis precluded by sample size). Finally, we unfortunately did not have vitamin D or PTH data available on our control population, making it impossible to determine whether the association between LVMI and vitamin D status or PTH and E/A is different in PHPT and nonhyperparathyroid populations. The study is also limited by its cross-sectional design: the time course of possible cardiac manifestations could not be examined.

Despite these limitations, the study has several important strengths. We characterized the effect of PHPT on cardiac structure and function in a homogenous group of patients with mild disease, using validated techniques that detect subclinical markers associated with cardiovascular outcomes. The study provides the first data on the association between echocardiographic measures and 25OHD level in PHPT. We were able to adjust for differences in demographic and cardiovascular risk factors between cases and controls and had adequate power to detect small differences (<0.4 SD) between groups. Whereas it is possible that our study failed to reveal differences below this magnitude, we suspect that such differences would not be clinically meaningful.

In conclusion, in contrast to data from cohorts with more severe PHPT (higher serum calcium and PTH and perhaps lower vitamin D levels), we did not find increased LVMI, more frequent valvular calcification, or evidence of diastolic dysfunction in patients with biochemically mild PHPT. The data do, however, suggest a possible relationship between vitamin D deficiency and increased LVMI in PHPT and that diastolic dysfunction may occur only in those with higher calcium and PTH levels. Additionally, recent data suggest that mild PHPT does affect other aspects of the cardiovascular system. Therefore, further studies looking comprehensively at multiple facets of the cardiovascular system and examining the independent roles of PTH, calcium, and vitamin D in the pathogenesis of cardiovascular disease will be invaluable in fully characterizing the effect of mild PHPT on cardiovascular health.
Acknowledgments

Address all correspondence and requests for reprints to: Shonni J. Silverberg, M.D., 630 West 168th Street, PH8 West-864, New York, New York 10032. E-mail: sjs5@columbia.edu.

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