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Cardiovascular aspects of primary hyperparathyroidism

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Abstract

Data concerning the cardiovascular manifestations of primary hyperparathyroidism (PHPT) are inconsistent, which is due, in part, to the decrease in disease severity over the last several decades. In areas where patients tend to be more symptomatic, data support the presence of cardiovascular findings including myocardial and vascular calcification as well as increased cardiovascular mortality. Data from the cohorts in whom the disease is characterized by mild hypercalcemia, suggest that clinically overt cardiovascular manifestations are unusual in PHPT. Recent data, however, support the presence of subtle cardiovascular manifestations in mild disease, such as changes in endothelial function as well as increased vascular stiffness and perhaps diastolic dysfunction. Left ventricular hypertrophy is a more consistent finding across a spectrum of disease severity, though this finding may be related to hypertension, which has long been associated with PHPT.

Keywords

Cardiovascular; mortality; primary hyperparathyroidism

INTRODUCTION

There is considerable debate regarding the cardiovascular (CV) manifestations of primary hyperparathyroidism (PHPT) with conflicting data concerning their extent and clinical significance. Many of these apparent disparities may be related to the evolution of the clinical presentation of PHPT over the last 70 years. Once a symptomatic disorder characterized by significant hypercalcemia (1), modern PHPT is frequently asymptomatic, with mild hypercalcemia discovered incidentally on routine biochemical screening (2). As a result, studies of the CV system in PHPT have enrolled populations with varying disease severity, often leading to discrepant findings. Additionally, investigations have explored different parameters of CV health using disparate modalities in patient populations of varying size. When these factors are considered, many of the ostensible inconsistencies within the literature can be resolved.

One might anticipate CV effects from PHPT. The biochemical features of PHPT include elevations in serum calcium and PTH, which are both known to affect the CV system.

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Hypercalcemia has been associated with hypertension, left ventricular hypertrophy (LVH), arrhythmias, vasoconstriction, as well as calcification of the myocardium, heart valves, and coronary arteries (3–8). PTH has been shown to have a vasodilatory effect and to exert direct positive chronotropic and indirect inotropic effects on the heart (9). Data suggest that PTH may also act as a “hypertrophic factor” on myocardial muscle cells, thereby inducing LVH (10). Numerous studies have explored many of these potential mechanisms of CV disease in PHPT by assessing mortality, hypertension, cardiac conduction abnormalities and arrhythmias, as well as CV structural and functional changes.

MORTALITY

There is ample documentation that CV mortality is increased in patients with severe and moderately severe PHPT (11–14). The higher mortality rate has been shown to decline with time from parathyroidectomy (PTX), but still persists long after surgical cure, suggesting that PHPT might cause enduring damage to the CV system (15). The few North American studies that assessed mortality in patients with PHPT have not found mortality to be adversely impacted (16, 17). In contrast to the European patients described in the studies cited above, PHPT patients diagnosed in Rochester, Minnesota between 1965 and 1992 had lower than expected overall mortality (17). Specifically, CV death rates were strikingly reduced (relative risk 0.6). However, consistent with the European studies, this study did demonstrate that higher maximal serum calcium levels were an independent predictor of mortality. These results are also in accordance with a Swedish investigation indicating that higher serum calcium level, even within the normal range, is an independent predictor of CV mortality (18).

One explanation for these incongruent mortality data is that more patients in the US studies had mild disease, with lower serum calcium levels [mean calcium 2.73 mmol/l (10.9 mg/dl)] and fewer symptoms than patients in the European studies, where average calcium levels were significantly higher. This hypothesis is supported by data from Nilsson et al. (19), who analyzed mortality over a 30 year time period in 10,995 Swedish patients who underwent PTX. While an increased risk of CV mortality was observed in the overall cohort, this risk dissipated in those enrolled later in the study, when the multichannel autoanalyzer allowed diagnosis of the disease in those with no symptoms and lower levels of serum calcium. Hedback et al. (15, 20) also found that survival in Swedish men and women with PHPT who had undergone PTX improved in those with a more recent calendar year of surgery. The decline in death risk paralleled the decrease in mean preoperative serum calcium level over time (15). While these data do lend credence to the idea that the decline in mortality in more recent years is due to lower calcium levels, there are also other potential interpretations. Among these are the possibilities that increased CV mortality in PHPT is reversed by earlier diagnosis and intervention, or that there was a change in the referral pattern for PTX. Alternatively, newly available treatments for CV abnormalities could explain the findings. Several studies that reported mean serum calcium and risk of death are summarized in Figure 1. These data suggest that relative risk of CV death in PHPT varies almost linearly with calcium level and that this is a plausible explanation for disparate findings.

HYPERTENSION

Hypertension is frequently seen in association with PHPT (21–23), even among those with mild disease. While a few studies have shown a reduction in blood pressure immediately after PTX (22, 24), which could be due to the non-specific effects of bed rest or anesthesia, the majority of studies indicate that hypertension is not reversible with surgical cure (21, 25–28). The cause of hypertension in PHPT, still unclear, has been hypothesized to be due to hypomagnesemia (29), increases in catecholamines (30), elevations in renin and aldosterone (31) or vasocontriction (22, 32). Because of uncertainties regarding the mechanism and reversibility of hypertension, the causal relationship between PHPT and hypertension has been questioned. One exception to this rule has been in those patients with multiple endocrine neoplasia, in whom hypertension may be due to catecholamine excess and pheochromcytoma resection curative. As there is no expectation that hypertension will improve in those with sporadic disease, the presence of hypertension in patients with PHPT is not currently an indication for PTX.

CARDIAC CONDUCTION ABNORMALITIES AND ARRYTHMIAS

The shortened QT interval, a well-described consequence of hypercalcemia, creates the potential for cardiac arrhythmia in PHPT (33). There is inconsistent data regarding the presence of cardiac rhythm disturbances in PHPT, but again, this appears to be related to the degree of hypercalcemia in the population studied. A study of pre-operative electrocardiograms in 139 Swedish patients with PHPT [mean calcium 3.03 mmol/l (12.1 mg/dl)] found that serum calcium levels correlated positively with T-wave duration and negatively with QT interval (34, 35). In patients with a similar mean calcium level [2.95 mmol/l (11.8 mg/dl)], Nilsson et al. (36) found a small increase in the number of ventricular extrasystolic beats in those with PHPT, which improved with PTX (36).

A small study in patients with more moderate hypercalcemia [mean calcium 2.85 mmol/l (11.4 mg/dl)] confirmed an increase in QT interval after PTX, but found no increased prevalence of supraventricular or ventricular arrhythmias or high-grade AV block (37). QT shortening was not observed in the small study of Barletta et al. [mean calcium 2.88 mmol/l (11.5 mg/dl)], but only 14 patients with PHPT were studied; they did, however, find evidence of increased sympathetic drive to the heart (38). A recent Italian study, that did not report calcium levels, also found QT shortening and higher sympathetic tone in those with PHPT (39).

CARDIAC STRUCTURAL ABNORMALITIES

Left ventricular hypertrophy

LVH, a strong predictor of CV mortality, has been associated with PHPT in most (40–45), but not all (38, 46, 47), studies across a wide range of calcium levels (2.63–3 mmol/l) (10.5–12 mg/dl). The coexistence of hypertension in many patients with PHPT raises the possibility that any LVH observed in PHPT could be attributable to elevations in blood pressure. However, data suggest that LVH is independent of hypertension (43). Instead, several studies support an association of LVH with PTH level (40, 41,43) in PHPT. Only one

report noted a correlation between left ventricular mass and calcium (42). The higher incidence of LVH in PHPT may be related to increased CV stiffness (48) (See “Vascular function” below) or a direct effect of PTH (10).

The issue of the reversibility of CV abnormalities is of significant interest in determining the management implications of these findings. LVH has been found to regress following PTX in a number of studies that have followed patients for at least 6 months post surgery (41,43, 44). Studies of shorter duration have not found LVH to improve after PTX (42). Stefenelli et al. reported that regression of LVH was most marked in those without a history of hypertension (44).

Valvular and myocardial calcification

Myocardial and valvular calcifications have clearly been demonstrated in PHPT patients with marked hypercalcemia (44, 49, 50). Stefenelli et al. reported an increased frequency of aortic (63% *vs* 12.5%), mitral (49% *vs* 15%) and myocardial calcification (69% *vs* 17.5%) in those with PHPT [mean calcium 2.98 mmol/l (11.9 mg/dl)], compared to controls (50). There was no change in valvular or myocardial calcification with PTX. Studies in patients with more modest increases in serum calcium [2.78 mmol/l (11.1 mg/dl)] are limited but indicate no increase in valvular or myocardial calcifications (41), suggesting that this phenomenon is related to the level of hypercalcemia and less likely to be seen in those with the milder biochemical phenotype of PHPT so common today.

ANATOMIC VASCULAR ABNORMALITIES

It is logical to expect that excess serum calcium might lead to deposition of calcium in the vascular wall, with resulting stiffening of the vessel. The resulting abnormalities, as in other endocrinopathies, may vary in different parts of the vascular tree.

Coronary artery disease

There are very limited data regarding coronary artery disease in PHPT. The autopsy study of Roberts and Waller (4) concluded that hypercalcemia and PHPT (which affected only half of the patients studied) caused coronary atherosclerosis. The range of calcium in that report was 4.2–6.85 mmol/l (16.8–27.4 mg/dl), making it impossible to generalize these data to patients with mild hyperparathyroidism. More recently, Lind et al. (51) have found serum calcium, even within the normal range, to be an independent, prospective risk factor for Ml in middle-aged Swedish men.

There are some data supporting an increased incidence of coronary artery disease in a cohort of PHPT patient with more moderate hypercalcemia [mean serum calcium 2.96 mmol/l (11.8 mg/dl)] (52). In this study, risk of myocardial infarction was increased before PTX compared to non-hypercalcemic controls and declined to the control level after surgery. Risk of CV death, however, was related to traditional risk factors but not to serum calcium or adenoma size and was decreased in those with kidney stones. This raises uncertainty about the exact nature of the relationship between the hyperparathyroid state and coronary disease.

The recently published Norwegian Tromsø study (53) found serum PTH to be an independent predictor of coronary heart disease in subjects who had normal levels of serum calcium. This report was not intended to specifically study those with primary rather than secondary hyperparathyroidism, and it is likely that the higher PTH levels may have been a surrogate for worse renal function or lower 25-hydroxy vitamin D.

Nilsson et al. investigated reversible signs of myocardial ischemia in those with PHPT [mean calcium 2.97 mmol/l (11.9 mg/dl)]. While there was no difference in ST-segment depression during exercise at baseline between those with PHPT and control subjects, there was improvement in the PHPT group with PTX compared to baseline but no change in controls (36, 47). More data regarding the risk of coronary artery disease are needed in patients with mild PHPT before definitive conclusions can be made.

Carotid vasculature

Carotid intima-medial thickness (IMT) is a strong predictor of systemic atherosclerosis and cerebral vascular events. Recent data from our group extend the previously demonstrated association between serum calcium and mortality. In a large epidemiological study, we have shown that serum calcium levels within the normal range are positively associated with carotid plaque thickness even after adjustment for traditional CV risk factors (54). The carotid vasculature has been incompletely investigated in PHPT. In one study of 20 patients with severe PHPT, carotid IMT was found to be markedly increased compared to controls (46). Other studies showing no effect on carotid IMT of PHPT or its cure are limited by the small sample sizes, and by technical inadequacies (IMT was measured at the common carotid or brachial arteries, rare sites for plaque, rather than at the bifurcation of the carotid and in the internal carotid artery, where the majority of subclinical atherosclerotic disease is found) (38, 55–58).

A recent study by Fallo was evocative but small, including 26 patients with PHPT (59). They reported that in PHPT, only those with traditional CV risk factors had increased IMT compared to controls, while those without risk factors did not. Those individuals with CV risk factors, however, also had higher serum calcium levels, suggesting that increased IMT might be attributable to the high serum calcium, though there was no significant correlation between calcium and IMT. More than anything, these data highlight the need for further study in this area. There are no data on regression of carotid IMT or plaque thickness following PTX.

CARDIAC FUNCTIONAL ABNORMALITIES

As the severity of PHPT has declined, investigators have begun to examine more subtle alterations in the CV system, including abnormalities of CV function. Theoretically, diastolic function may be negatively affected by intracellular calcium overload with decreased compliance from calcium deposition in the myocardium (60), and indeed diastolic dysfunction has been documented in patients with both more severe PHPT [mean calcium 2.9 mmol/l–2.97 (11.6–11.9 mg/dl)] (47, 61) as well as milder forms of disease [mean calcium 2.78–2.79 mmol/l (11.1–11.2 mg/dl)] (41,42), although interpretation of some data (41) are limited due to higher blood pressure in the PHPT group. Contradictory data come

from a study that included participants with mild hypercalcemia [(2.81 mmol/l (11.2 mg/dl)]. This study, which stratified patients according to hypertensive status, did not confirm diastolic dysfunction (43). Nor is it clear whether diastolic dysfunction, if present, is secondary to the effects of hypercalcemia or PTH excess. Data on improvement with surgical cure are also conflicting (40–42, 47, 62).

In contrast, systolic cardiac function appears unaffected by PHPT. One study reported a trend toward increased systolic function (ejection fraction), hypothesized to be due to the isotropic effect of elevated serum calcium, which decreased after PTX (47), but most studies have not confirmed this (42, 43, 50, 61).

VASCULAR FUNCTION

To date, different aspects of vascular function have been investigated, making it difficult to make a comprehensive statement concerning the overall effect of the disease on vascular function. Several studies have measured endothelial function. Endothelial cells, which form the inner lining of blood vessels, have a number of functions including mediating vasomotor tone, inflammation and coagulation among others. Endothelial cells synthesize nitric oxide, which causes vasodilation, inhibition of platelet aggregation and monocyte adhesion, as well as a reduction in prothrombotic factors. Endothelial dysfunction is thought to be an early and important step in atherogenesis. In a study of very limited size (12 volunteers), calcium infusion resulted in dose-related impairment in endothelial vasodilatory function and increased systolic blood pressure (32). Nilsson et al. reported an abnormal endothelial vasodilatory response in patients with severe PHPT [3 mmol/l (calcium 12.0 mg/dl)], as demonstrated by the response to infusion of metacholine and nitro-prusside (55) while Neunterfl et al. [(mean calcium 3.0 mmol/l (12.0 mg/dl)] (63) found normal endothelial-dependent dilation (assessed by flow-mediated dilatation). In contrast, Kosch et al. (56) also assessed flow-mediated vasodilation in severely hypercalcemic patients [(calcium 3 mmol/l (12.0 mg/dl)] and found that endothelium-dependent flow mediated vasodilation was impaired in PHPT, but improved with PTX (64). These differences may be due to the fact that the Neunteufl study included controls with a high incidence of other CV risk factors. Baykan et al. also found impaired flow mediated (endothelial) dilation in those with more mild PHPT [mean calcium 2.9 mmol/l (11.6 mg/dl)], which negatively correlated with calcium levels (65). The preponderance of data does seem to suggest that endothelial dysfunction is a feature of PHPT.

Since PTH raises intracellular calcium concentration (66), high calcium in myocytes could cause increased contractility or cell damage that impairs vascular smooth muscle relaxation. Neunterfl did find abnormal vascular smooth muscle reactivity (nitroglycrerin induced changes in arterial media), that was not reversible with PTX (63), though other studies have not confirmed this (55, 56).

Two studies have reported increased vascular stiffness, an independent marker of CV risk (67) in patients with mild PHPT [calcium 2.66–2.74 mmol/l (10.7–10.9 mg/dl)] (48, 68). While in one (48) this finding might have been explained by the inclusion of a younger, less overweight and less hypercholesterolemic control group, the study from our group found

that having PHPT was an independent risk factor for increased vascular stiffness (68). Indeed, PHPT was a stronger predictor of increased aortic stiffness than many traditional CV risk factors. Furthermore, vascular stiffness was associated with evidence of more active parathyroid disease. Stiffness was significantly positively correlated with the extent of elevation in PTH levels, and inversely associated with bone density at the distal one-third radius (54).

Hypothetically, arterial stiffness may result from either structural (arterial wall calcification) or functional (i.e. endothelial) abnormalities in large and medium-sized vessels, though there is no evidence for the former. Increased vascular stiffness may be responsible for LVH in PHPT patients without hypertension (48).

SUMMARY AND IMPLICATIONS

In summary, there is a large body of research dealing with various aspects of CV involvement in PHPT. Data on individual abnormalities have been touted to support the presence or absence of such involvement (Table 1). Unfortunately, some of the comparisons that have been made obscure rather than clarify the situation, as they compare studies of patients with varying degrees of disease severity, and look at studies in differing portions of the CV system.

This much is clear. CV mortality is increased in patients with moderate to severe hypercalcemia, but the limited available data have not confirmed this finding in those with mild disease. While PHPT is associated with hypertension, the nature of this association is poorly understood. Hypertension is not reversible with cure of the underlying disease and therefore should not be used as an indication for PTX in patients who do not have multiple endocrine neoplasia. CV structural abnormalities exist, with LVH being the most consistent finding across a spectrum of disease severity, while myocardial and valvular calcifications seem to be present only with severe disease. Even in patients with mild disease, it is essential to dissect out the effects of co-existing hypertension on the left ventricle in this regard. And while coronary and carotid calcifications are an issue in those with severe disease, there is insufficient data from which to draw conclusions in those with mild PHPT. Finally, recent data support the presence of subtle CV manifestations in mild disease, such as changes in endothelial function as well as increased vascular stiffness and perhaps diastolic dysfunction.

Further investigation in this area is clearly necessary. It is not likely that some of the data in this field are “right” and others “wrong”. Instead, many contradictions may well be due to comparisons among very different patient populations and/or different assessment techniques.

In particular, it is important to obtain a clearer picture of the extent and nature of CV involvement in those with very mild PHPT. In patients with very mild levels of hypercalcemia it may be more appropriate to seek subtle functional abnormalities that have been demonstrated to predict deleterious CV outcomes. Finally, longitudinal assessment is

needed. Demonstration of significant reversible CV abnormalities in asymptomatic PHPT would likely change recommendation for PTX.

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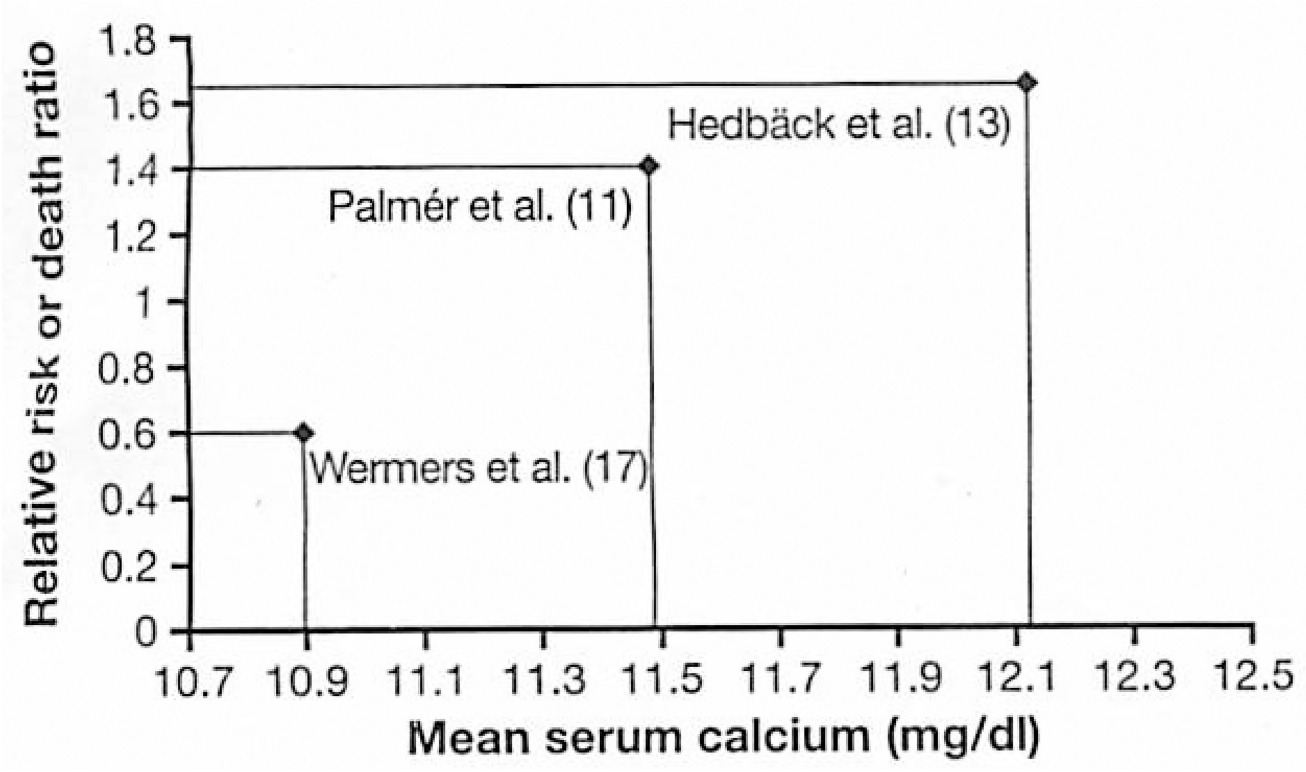

Fig. 1.
Serum calcium and relative risk of cardiovascular death.

Table 1

Select studies of cardiac abnormalities in primary hyperparathyroidism.

Author	Serum calcium	Year	Parameter studied	Results
Roberts and Waller (4)	4.85 mmol/l (19.4 mg/dl)	1981	Coronary calcification	Increased
Nuzzo (46)	3.05 mmol/l (12.2 mg/dl)	2002	Blood pressure	Not *increased*
			Left ventricular mass index	Not icreased
			Carotid intimal medial thickness	Increased
			Carotid atherosclerotic plaques	Not increased
Fallo (59)	3.05 mmol/l (12.2 mg/dl)	2003	Carotid mean and maximum intima-media thickness and carotid plaque number	Increased in those with traditional atherosclerotic risk factors
Stefenelli (44, 50)	3.03 mmol/l (12.1 mg/dl)	1993 1997	Left ventricular hypertrophy	Increased
Lind (35)	3.03 mmol/l (12.1 mg/dl)	1994	Electrocardiogram	QT interval decreased
Niederle (69)	3.02 mmol/l (12.1 mg/dl)	1990	Valvular and myocardial calcification	Increased
Kosch (64)	3.0 mmol/l (12.0 mg/dl)	2000	Endothelium-independent (nitrogen-induced) vasodilation	Normal
			Endothelium-dependent (flow-mediated) dilation	Impaired
			Carotid and brachial intima-media thickness	Normal
Neunteufl (63)	3.0 mmol/l (12.0 mg/dl)	1998	Endothelium-independent (nitrogen-induced) vasodilation	Impaired
			Endothelium-dependent (flow-mediated) dilation	Normal
Nilsson (47, 55)	2.97 mmol/l (11.9 mg/dl)	2000	Blood pressure	Not increased
			Heart rate	Normal
			Maximal workload	Normal
			Ventricular premature beats at maximal workload	Increased
			Endothelium-dependent (metacholine and nitroprusside induced) vasodilation	Impaired
Baykan (61,65)	2.9 mmol/l (11.6 mg/dl)	2007	Endothelium-dependent (flow-mediated) vasodilation	Impaired
			Diastolic function (Amax and E/Amax)	Impaired
			Interventricular septum, posterior wall, relative wall thickness	Increased
			Left ventricular mass index	Normal
			Ejection fraction	Normal
Barletta (38)	2.88 mmol/l (11.5 mg/dl)	2000	QT Interval	Normal
			Valvular and myocardial calcification	Not increased
			Left ventricular mass index	Not increased
			Arterial morphology	Normal
			Elastic properties	Normal

Author	Serum calcium	Year	Parameter studied	Results
			Sympathetic drive	Increased
Rosenqvist (37)	2.85 mmol/l (11.4 mg/dl)	1992	Electrocardiogram	No arrhythmia
Piovesan (43)	2.81 mmol/l (11.2 mg/dl)	1999	Left ventricular hypertrophy	Increased
Nappi (42)	2.79 mmol/l (11.2 mg/dl)	2000	Left ventricular mass	Increased
			Interventricular septal thickness	Increased
			Aortic root and left atrial dimensions	Increased
			Ejection fraction	Decreased
			Diastolic function (Amax and E/Amax)	Impaired
Dalberg (41)	2.78 mmol/l (11.1 mg/dl)	1996	Blood pressure	Increased
			Left atrial diameter	Increased
			Valvular and myocardial calcification	Not increased
Rubin (68)	2.66 mmol/l (10.7 mg/dl)	2005	Arterial stiffness (augmentation index)	Increased