SATU NÄPPI

Cardiac Function in Primary and Secondary Hyperparathyroidism

ACADEMIC DISSERTATION
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CONTENTS

LIST OF ORIGINAL PUBLICATIONS ....................................................... 7

ABBREVIATIONS .............................................................................. 8

INTRODUCTION ................................................................................. 9

REVIEW OF THE LITERATURE ......................................................... 11

1. Metabolism of calcium ................................................................. 11

2. Evaluation of cardiac structure and function .............................. 13
   2.1. Evaluation of left ventricular structure and systolic function .... 13
   2.2. Evaluation of left ventricular diastolic function ...................... 13
   2.3. Measurement of the QT interval and QT dispersion ............... 14

3. Calcium and cardiac function ....................................................... 16
   3.1. Role of calcium in cardiac function ....................................... 16
      3.1.1. Systolic function ......................................................... 16
      3.1.2. Diastolic function ...................................................... 16
      3.1.3. QT interval ............................................................... 16
   3.2. Cardiac systolic function in hypocalcemia ............................ 17
      3.2.1. Acute hypocalcemia .................................................. 17
      3.2.2. Chronic hypocalcemia ............................................... 17
   3.3. Cardiac systolic and diastolic function in hypercalcemia ......... 18
      3.3.1. Acute hypercalcemia ............................................... 18
      3.3.2. Chronic hypercalcemia ............................................. 20
   3.4. Effect of hemodialysis-induced changes in serum calcium
       on cardiac function ............................................................ 20
      3.4.1. Systolic function ......................................................... 20
      3.4.2. Relaxation ............................................................... 21
   3.5. Effect of calcium on cardiac electrical stability during hemodialysis .... 22

4. Parathyroid hormone and cardiac function ............................... 24
   4.1. Direct effects of PTH on the myocardium .............................. 24
      4.1.1. Cardiac metabolism .................................................. 24
      4.1.2. Effect of reduced energy production on cardiac function .... 25
      4.1.3. Myocardial compliance ............................................. 26
   4.2. Primary hyperparathyroidism ................................................. 26
      4.2.1. Calcium metabolism in primary hyperparathyroidism .......... 27
      4.2.2. Systolic function ......................................................... 27
      4.2.3. Cardiac structure and diastolic function ......................... 27
      4.2.4. Effect of parathyroidectomy ...................................... 28
   4.3. Secondary hyperparathyroidism in chronic renal failure ......... 29
      4.3.1. Calcium metabolism in secondary hyperparathyroidism ...... 29
      4.3.2. Myocardial metabolism ............................................. 30
      4.3.3. Systolic function ......................................................... 30
4.3.4. Left ventricular hypertrophy ................................................. 31
4.3.5. Diastolic function .............................................................. 33
4.3.6. Effect of parathyroidectomy and vitamin D treatment .......... 34

5. Vitamin D and cardiac function ................................................. 36
  5.1. Myocardial vitamin D receptors ............................................. 36
  5.2. Direct effects of vitamin D on cardiac structure and function .... 36
  5.3. Vitamin D deficiency ........................................................... 37
  5.4. Vitamin D and treatment of secondary hyperparathyroidism .... 38

AIMS OF THE PRESENT STUDY .................................................... 39

SUBJECTS .................................................................................. 40

METHODS .................................................................................. 41
  1. Study protocol ........................................................................ 41
  2. Echocardiographic examinations ............................................. 42
  3. Electrocardiographic examinations ......................................... 43
  4. Biochemical methods ............................................................ 44
  5. Statistical methods ............................................................... 44

SUMMARY OF RESULTS ............................................................ 46
  1. Cardiac structure and function in primary hyperparathyroidism... 46
  2. Cardiac structure and function in secondary hyperparathyroidism. 46
  3. Effect of parathyroidectomy on cardiac function in primary
     hyperparathyroidism .............................................................. 47
  4. Effect of vitamin D treatment on cardiac function in secondary
     hyperparathyroidism .............................................................. 47
  5. Effects of acute changes in serum ionized calcium on cardiac function
     during hemodialysis ............................................................... 47

DISCUSSION .............................................................................. 50
  1. Cardiac structure and function in primary and secondary
     hyperparathyroidism .............................................................. 50
  2. Reversibility of cardiac dysfunction in primary and secondary
     hyperparathyroidism .............................................................. 52
  3. Cardiac function during hemodialysis ....................................... 53
  4. Cardiac electrical stability during hemodialysis ......................... 55

SUMMARY AND CONCLUSIONS .................................................. 57

ACKNOWLEDGEMENTS ............................................................. 59

REFERENCES ............................................................................. 61

ORIGINAL PUBLICATIONS .......................................................... 83
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to in the text by their roman numerals I-IV.


<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Amax</td>
<td>peak late diastolic velocity</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine 5'-triphosphate</td>
</tr>
<tr>
<td>ATPase</td>
<td>adenosine 5'-triphosphatase</td>
</tr>
<tr>
<td>CAPD</td>
<td>continuous ambulatory peritoneal dialysis</td>
</tr>
<tr>
<td>CaR</td>
<td>Ca++-sensing receptors</td>
</tr>
<tr>
<td>CRF</td>
<td>chronic renal failure</td>
</tr>
<tr>
<td>dCa++</td>
<td>dialysate Ca++ concentration</td>
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<tr>
<td>DT</td>
<td>deceleration time</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>EF</td>
<td>left ventricular ejection fraction</td>
</tr>
<tr>
<td>Emax</td>
<td>peak early diastolic velocity</td>
</tr>
<tr>
<td>E/Amax</td>
<td>peak early diastolic velocity/peak late diastolic velocity</td>
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<tr>
<td>ESRF</td>
<td>end-stage renal failure</td>
</tr>
<tr>
<td>FS</td>
<td>left ventricular fractional shortening</td>
</tr>
<tr>
<td>HD</td>
<td>hemodialysis</td>
</tr>
<tr>
<td>IVRT</td>
<td>isovolumic relaxation time</td>
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<tr>
<td>IVST</td>
<td>thickness of intraventricular septum</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricle</td>
</tr>
<tr>
<td>LVEDD</td>
<td>left ventricular end diastolic dimension</td>
</tr>
<tr>
<td>LVESD</td>
<td>left ventricular end systolic dimension</td>
</tr>
<tr>
<td>LVH</td>
<td>left ventricular hypertrophy</td>
</tr>
<tr>
<td>LVM</td>
<td>left ventricular mass</td>
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<tr>
<td>PHPT</td>
<td>primary hyperparathyroidism</td>
</tr>
<tr>
<td>PTH</td>
<td>parathyroid hormone</td>
</tr>
<tr>
<td>PTX</td>
<td>parathyroidectomy</td>
</tr>
<tr>
<td>PWT</td>
<td>thickness of left ventricular posterior wall</td>
</tr>
<tr>
<td>QTc</td>
<td>QT interval corrected for heart rate by Bazett’s formula</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SR</td>
<td>cardiac sarcoplasmic reticulum</td>
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INTRODUCTION

Abnormalities of left ventricle (LV) structure and function are present in 70-80% of patients with chronic renal failure (CRF), and more than half of these die of cardiovascular disease (Huting et al. 1993, Covic et al. 1996, Parfrey and Foley 1999, Tsakiris et al. 1999, Foley et al. 2000). In these patients the hemodialysis (HD)-induced changes in cardiac preload, blood pressure, heart rate and blood chemistry predispose the heart to a further impairment of LV systolic and diastolic function during treatment. Additionally, the risk of ventricular arrhythmias is known to increase during HD (Ramirez et al. 1984, Kimura et al. 1989, Strata et al. 1994). The etiology of cardiac dysfunction in CRF would appear to be multifactorial, and anemia, age, hypertension, coronary artery disease, valvulopathies and electrolyte disturbances have been proposed to be involved (London et al. 1987, Huting et al. 1988 and 1993, Foley et al. 1995 and 1996a).

In CRF, changes in the metabolism of calcium, phosphate and vitamin D lead to the development of secondary hyperparathyroidism. Further, HD treatment induces acute changes in serum ionized calcium which are directly related to the dialysate Ca\(^{++}\) concentration (Saha et al. 1992 and 1996). The appropriate functioning of the myocardium is markedly dependent on the serum concentration of calcium and movements of calcium inside cardiac cells (Opie 1997). In addition to the major role of parathyroid hormone (PTH) and vitamin D in regulating serum calcium, convincing evidence has accumulated to indicate that PTH and vitamin D may also affect cardiac function directly (Walters et al. 1986, Weishaar et al. 1987a and 1987b, Zhang et al. 1994).

It would thus seem reasonable to assume that uremic cardiomyopathy is related at least partially to secondary hyperparathyroidism and that HD-induced acute changes in serum calcium regulate LV function and electrical stability during treatment. The fact that patients with primary hyperparathyroidism (PHPT) are also subject to increased mortality from cardiovascular diseases (Palmer et al. 1987, Hedbäck et al. 1990) would further
support the conception of an adverse effect of excess PTH and calcium on the myocardium.

Studies addressing these issues are, however, limited and have yielded controversial results. Additionally, little is known regarding LV diastolic function in these patients. The present work was designed to evaluate the roles of calcium, PTH and vitamin D in the development and therapy of cardiac dysfunction in patients with primary or secondary hyperparathyroidism.
**REVIEW OF THE LITERATURE**

1. Metabolism of calcium

   Ninety-nine percent of total body calcium is located in the skeleton, and only one percent of this is rapidly exchangeable with the nonosseous extracellular calcium. This calcium pool, in turn, is in equilibrium with the intracellular calcium of the body. In blood, 35-40 % of calcium is bound to proteins, mainly albumin and globulins, while 10-15 % is complexed with low molecular weight ligands. Biologically active free (ionized) calcium constitutes about 50 % of the total calcium (Fogh-Andersen 1988, Thode 1989).

   The ionized calcium in serum is tightly controlled by the activity of the parathyroid glands, gastrointestinal tract, bone and kidneys. Some 30 to 35 % of the calcium in food is absorbed in the duodenum and proximal jejunum, the net daily uptake being approximately 200 mg (Bringhurst et al. 1998). In the intestine, calcium is absorbed by three pathways: the active transcellular route, vesicular calcium transport, and paracellular diffusional transport. The first two of these are regulated by vitamin D (Bringhurst et al. 1998).

   Vitamin D is obtained alternatively from dietary sources or from conversion of the cutaneous precursor vitamin D, 7-dehydrocholesterol, after exposure to ultraviolet irradiation. In the liver, vitamin D undergoes 25-hydroxylation and is thereafter converted by 1α-hydroxylation to its active hormonal form 1,25(OH)2D3 in the kidneys. Vitamin D regulates the body calcium homeostasis by enhancing the intestinal absorption of calcium. In addition, it has a direct inhibitory effect on parathyroid cells and numerous regulatory effects on bone (Birkenhager-Frenkel et al. 1989, Dunlay et al. 1989, Marie et al. 1990).

   Calcium is lost in the urine, feces and, to a minor extent, sweat. The major route of calcium excretion, and the site of further regulation of the serum calcium concentration, lie in the kidneys. The daily urinary excretion of calcium from the kidneys varies between 50 to 300 mg (Finkelstein et al. 1993). Sixty-five percent of calcium reabsorption takes place in the proximal tubule, 20 % in the thick ascending limb of Henle’s loop and 10 % in the distal convoluted and connecting tubules (Bringhurst et al. 1998). Most of the calcium reabsorption occurs by a passive, paracellular route, while half of the reabsorption in the loop of Henle and nearly all of it in the distal tubular
segments is controlled by PTH. Convincing evidence has accumulated to indicate the presence of extracellular Ca\(^{++}\)-sensing receptors (CaR) in the kidneys (Hebert et al. 1996, Riccardi et al. 1998, Bapty et al. 1998). The effect of hypercalcemia in lowering the glomerular filtration rate, reducing the renal cortical synthesis of calcitriol (Weisinger et al. 1989) and increasing urinary excretion of calcium and volumes of diluted urine may be, at least partly, attributable to activation of the Ca\(^{++}\)-sensing receptors within various parts of the nephron (Coburn et al. 1999).

PTH is a peptide hormone secreted from the parathyroid glands as intact PTH (84-amino-acid peptide). PTH secretion is controlled by the Ca\(^{++}\)-sensing receptors located on the parathyroid cell membrane (Brown et al. 1993). The CaR regulates the secretion of PTH in response to small changes in extracellular Ca\(^{++}\) concentration: hypocalcemia stimulates and hypercalcemia suppresses the secretion (Brown et al. 1997, Coburn et al. 1999). Additionally, the synthesis and secretion of PTH is known to be directly inhibited by 1,25(OH)\(_2\)D\(_3\) and phosphate (Russell et al. 1986, Sugimoto et al. 1988, Slatopolsky et al. 1999).

The secreted intact PTH is rapidly metabolized by the liver (79 %) and the kidneys (20 %) (Armitage et al. 1986). The biologic activity of PTH resides in the first 34 amino acid residues, the midregion and the carboxy-terminal fragments being biologically inactive (Aurbach et al. 1985). PTH increases the serum calcium concentration via its effects on bone, kidneys and vitamin D metabolism. It reduces the urinary calcium excretion by enhancing the tubular reabsorption of calcium. Additionally, it strongly inhibits renal phosphate reabsorption and hence reduces the serum phosphate concentration. PTH also enhances the intestinal absorption of calcium by stimulating the synthesis of 1,25(OH)\(_2\)D\(_3\) in the proximal tubule (Bringhurst et al. 1998). Further, it increases bone resorption and thereby releases calcium and phosphate into the serum (Finkelstein et al. 1993).
2. Evaluation of cardiac structure and function

2.1. Evaluation of left ventricular structure and systolic function

The LV mass, wall thicknesses and systolic performance can be assessed by standard M-mode echocardiography. This technique uses a narrow beam of ultrasound to provide an image of the position of the cardiac structures plotted versus time. Measurements of the LV are obtained from the parasternal long-axis view, the cursor being placed immediately below the mitral valve tips.

The left ventricular end-diastolic dimension (LVEDD), thickness of interventricular septum (IVST) and posterior wall (PWT) are measured at the onset of the electrocardiographic (ECG) Q wave. The left ventricular mass (LVM) is calculated as $1.04 \times (LVEDD + PWT + IVST)^3 - LVEDD^3$ (Devereaux RB et al. 1986). The left ventricular end-systolic dimension (LVESD) is measured at the time of the smallest LV diameter. The generally reliable measures of LV systolic function, fractional shortening (FS) and ejection fraction (EF) are defined as $(LVEDD - LVESD) \times 100/LVEDD$ for FS and as $(LVEDD^3 - LVESD^3) \times 100/LVEDD^3$ for EF.

2.2. Evaluation of left ventricular diastolic function

The cardiac diastole can be divided into four phases: isovolumic relaxation, early rapid filling, diastasis and atrial contraction (Nishimura et al. 1989, Little et al. 1990). During isovolumic relaxation, there is little alteration in LV volume, while during the early rapid filling phase LV volume increases rapidly and the bulk of blood flowing into the LV during the diastole enters the chamber. This rapid filling phase is modulated by cardiac relaxation, i.e. the energy-dependent process of the cardiac diastole, the viscoelastic forces, loading conditions and the inotropic state of the LV (Nishimura et al. 1989, Little et al. 1990). During diastasis, relaxation ceases and a further increase in LV chamber size is limited by the passive stiffness (compliance) of the myocardium (Nishimura et al. 1989, Kass et al. 1993). Finally, the remainder of the LV diastolic filling volume is propelled into the LV during the phase of atrial contraction.

Pulsed Doppler echocardiography is a clinically practical and reliable technique for the evaluation of LV diastolic function. The ultrasound beam is directed from the apex of the LV through the mitral valve orifice, parallel to the direction of the diastolic
blood flow through the valve. The sample volume is placed at the level of the mitral annulus or at the tips of the mitral valve. The rate of LV filling is proportional to the Doppler-measured mitral-flow velocity. The peak early diastolic velocity (Emax) represents the early rapid filling of the LV, while peak late diastolic velocity (Amax) is a measure of atrial contraction. The E/Amax ratio is widely used as an index of LV diastolic function, but several physiological factors affecting the Doppler indices must be taken into account in order to make the results reliable. A reduction in cardiac preload decreases Emax and E/Amax (Stoddard et al. 1989, Sadler et al. 1992, Chakko et al. 1997), and an increase in cardiac afterload is known to reduce Emax (Nishimura et al. 1989). E/Amax decreases with ageing, and Doppler indices should therefore be assessed with reference to age-specific values (Spirito and Maron 1988, Iwase et al. 1993). Additionally, the heart rate correlates inversely with E/Amax (Galderisi et al. 1993). The deceleration time (DT) is defined as the time from the peak to the end of the E wave. The isovolumic relaxation time (IVRT) is defined as the period from aortic valve closure to mitral valve opening.

2.3. Measurement of the QT interval and QT dispersion

The QT interval, measured from the beginning of the QRS complex to the end of the T wave on a standard 12-lead ECG, is an indirect measure of myocardial depolarization and repolarization. The first part of the QT interval, QRS duration, reflects the activation time, and the ST-T complex is an integrated signal of repolarization wave fronts (Burgess 1979, Abildskov et al. 1980). The onset of the QRS complex or the end of the T wave may be difficult to define, but the point at which the line of the maximal downslope of the T wave crosses the baseline helps to identify the end of the T wave (Browne et al. 1983, Fisch C 1997). The duration of the QT interval varies with cycle length, and numerous formulas have been suggested to correct for heart rate. That most widely used is Bazett’s formula: QTc = QT/(RR)\(^{1/2}\).

Any regional differences in cardiac electrical recovery times – i.e. the QT interval – predispose the heart to ventricular re-entry arrhythmias (Merx et al. 1977). The nonuniform electrical conduction of the myocardium can be assessed by measuring the interlead variability of the QT interval in the standard 12-lead ECG (=QTmax – QTmin).
This disparity of cardiac recovery times is called QT dispersion. QTc is obtained by using heart rate-corrected values for the QT interval. High values for QT dispersion have been reported in patients with cardiac hypertrophy (Mayet et al. 1996, Perkiömäki et al. 1996, Ichkhan et al. 1997, Gonzales-Juanatey et al. 1998), diabetes and CRF (Kirvelä et al. 1994). Moreover, an increased QT dispersion has been linked to the occurrence of ventricular arrhythmias in patients with long QT interval (Day et al. 1990) or myocardial infarction (Van De Loo et al. 1994, Perkiömäki et al. 1995), and to sudden cardiac death in patients with chronic congestive heart failure (Barr et al. 1994).
3. Calcium and cardiac function

3.1. Role of calcium in cardiac function

3.1.1. Systolic function

At the beginning of the cardiac systole, the extracellular calcium ions enter the myocardial cells through voltage-dependent calcium channels. The resultant rise in intracellular calcium concentration acts as a trigger to a release of a much larger quantity of calcium ions from the sarcoplasmic reticulum (SR). The high intracellular calcium concentration activates the contractile system of the heart; calcium ions interact with the regulatory protein troponin-C, enabling the cardiac myofilaments actin and myosin to interact. Consequently, the cross-bridge cycle of the contractile proteins is started, adenosine 5’-triphosphate (ATP) is utilized as an energy source and the myocardium contracts (Opie 1997).

3.1.2. Diastolic function

The diastolic phase of the myocardium begins as the cytosolic calcium concentration decreases and calcium ions depart from their binding sites on troponin-C. Thereafter, cross-bridge cycling ceases, the myofilaments dissociate from each other and the myocardium relaxes (Opie 1997). The decrease in cytosolic calcium concentration is a result of several energy-requiring processes taking place during cardiac relaxation; calcium ions are restored by the calcium-pumping adenosine 5’-triphosphatase (ATPase) to the SR and removed outside the cell by the sarcolemmal Na++/Ca++ exchanger and ATP-dependent Ca++ pump (Bers et al. 1993, Arai et al. 1994).

In summary, both cardiac systolic function and relaxation are energy-requiring processes and highly dependent on the concentration and movements of calcium ions inside the cardiomyocyte.

3.1.3. QT interval

The QT interval on a standard ECG reflects the duration of cardiac depolarization and repolarization. The duration of the slow inward calcium current during the plateau phase of the action potential parallel with the length of the ST segment and, especially, the QT interval. During hypocalcemia, the plateau phase of the action potential is
prolonged, leading to a lengthening of the QT interval. Hypercalcemia, in turn, shortens the plateau phase and induces a shortening of the QT interval. (Fisch 1997).

Clinical studies by groups under Bashour (1984) and Erem (1995) have shown that a rapid inducement of hypocalcemia by citrated blood results in an increase in the QT interval. Correspondingly, several authors have reported the interval to lengthen along with a decrease in serum calcium after parathyroidectomy (PTX) in patients with PHPT (Douglas et al. 1984, Behrmann et al. 1992, Rosenqvist et al. 1992). An increase in serum calcium after calcium replacement therapy due to primary hypoparathyroidism (Giles et al. 1981, Levine et al. 1985, Csanady et al. 1990) or vitamin D insufficiency (Bashour et al. 1980) is, in turn, known to shorten the QT interval.

3.2. Cardiac systolic function in hypocalcemia

During hypocalcemia the cytoplasmic free calcium level, derived from extracellular fluid and intracellular stores, is reduced. Since a rise in intracellular calcium concentration is an essential trigger for myocardial contraction, cardiac systolic function is likely to be impaired during hypocalcemia (Opie 1997). Studies evaluating the effect of hypocalcemia on cardiac function have focused solely on systolic function, while studies on the effect of hypocalcemia on cardiac diastolic function are lacking.

3.2.1. Acute hypocalcemia

Groups under Stulz (1979) and Drop (1980) carried out studies on the effects of acute hypocalcemia on cardiac function in anesthetized closed-chest dogs. A rapid inducement of hypocalcemia by intravenous administration of citrate solutions was followed by a deterioration in cardiac systolic function. Thereafter, Bashour and associates (1984) demonstrated that acute hypocalcemia caused by rapid transfusion of citrated blood induces cardiogenic shock.

3.2.2. Chronic hypocalcemia

Several studies have shown chronic hypocalcemia due to primary hypoparathyroidism to cause cardiac systolic dysfunction (Giles et al. 1981, Levine et al. 1985, Csanady et al. 1990). In addition, hypocalcemia due to vitamin D insufficiency
(Bashour et al. 1980, Avery et al. 1992) or CRF (Wong et al. 1990b, Ghent et al. 1994) is also known to impair LV systolic performance. In all of these studies, echocardiographic examination revealed LV dilatation and impaired systolic function, while the restoration of serum calcium level was accompanied by an improvement in the M-mode echocardiographic indices. The improved cardiac systolic function was detectable within hours to weeks after commencement of replacement therapy with calcium or vitamin D derivatives, and lasted during the follow-up period of several months.

In contrast, the studies by Wong and colleagues (1990a and 1992) have suggested that although acute calcium replacement enhances cardiac contractility in hypocalcemic patients, the improvement in LV systolic function cannot be sustained with long-term replacement therapy. Nonetheless, the same authors showed that when patients were studied during exercise, an improvement in cardiac output and exercise tolerance could also be achieved after long-term calcium replacement. These results may explain why some hypocalcemic patients do not have clinical signs of cardiac failure; hypocalcemic heart failure may be asymptomatic and become exacerbated only during exercise (Vered et al. 1989).

3.3. Cardiac systolic and diastolic function in hypercalcemia

3.3.1. Acute hypercalcemia

Gwathmey and associates (1991) studied the effect of extracellular ionized calcium on human ventricular muscle preparations. They showed that the active tension development, i.e. systolic function, of the heart trabeculae was enhanced as the calcium concentration outside the cell increased. Than and colleagues (1994) obtained similar results when examining the effect of increasing extracellular calcium on the contractile function of ferret papillary muscle.

The mechanism of the inotropic action of an acute calcium overload on a myocardial cell is obvious; the force developed by the cardiac myofilaments actin and myosin is regulated by the amount of activating calcium in the cytoplasm. The mechanism is similar to that of most inotropic agents, including digitalis and beta-adrenergic agonists, which act by increasing the intracellular ionized calcium concentration in cardiac cells (Hallaq et al. 1989, Gambassi et al. 1992, Holubarsch et al. 1994).
While several studies have shown that hypocalcemia impairs and calcium replacement therapy restores myocardial systolic function (Bashour et al. 1980, Giles et al. 1981, Levine et al. 1985, Csanady et al. 1990, Wong et al. 1990b, Avery et al. 1992, Ghent et al. 1994), there are only a few reports on the effect of acute hypercalcemia on cardiac function in previously normocalcemic subjects. Drop and associates (1981) in studies on dogs demonstrated that calcium infusion in previously hypocalcemic subjects improves LV contractile function, while hypercalcemia induced in previously normocalcemic subjects does not affect cardiac systolic performance. In a study of patients with moderate to severe CRF, Virtanen and associates (1998) showed that an acute increase in serum ionized calcium close to the upper limit of the normal range by calcium infusion does not affect LV systolic function.

Myocardial relaxation is initiated as the cytosolic calcium concentration is restored to its normal low level and the myofilaments become able to dissociate. Consequently, cardiac relaxation is highly susceptible to an acute calcium overload inside the cells. Morgan and colleagues (1984) confirmed this by showing that an increase in end-diastolic intracellular calcium concentration prolongs the contraction in rat papillary muscle preparations. Gwathmey and colleagues (1987) demonstrated that in myocardial cells from patients with end-stage congestive heart failure there is a delay in the decline of the cytosolic ionized calcium concentration to its normal low level during the diastole. Subsequently the same authors showed that an acute increase in extracellular calcium concentration prolongs the relaxation of the human ventricular trabeculae (Gwathmey et al. 1991). The clinical study by Virtanen and associates (1998) is well in accord with the findings in these experimental reports. They showed that acute induction of hypercalcemia by calcium infusion impairs Doppler indices of LV relaxation in patients with CRF.

In short, although acute hypercalcemia would not appear to enhance the cardiac contractile force during the systole in previously normocalcemic subjects, it has been shown to slow down the rate of myocardial relaxation.
3.3.2. Chronic hypercalcemia

A chronic excess of calcium within a myocardial cell is known to have several adverse effects on cardiac morphology, biochemical activity and contractile function. Groups under Baczynski (1985), El-Belbessi (1986) and Zhang (1994) in studies on rats demonstrated that a PTH-mediated calcium entry into the cardiac myocytes causes mitochondrial calcification, with subsequent impairment of mitochondrial oxidation and ATP production. Additionally, Takeo and colleagues (1991) showed that the energy production of rat cardiac myocytes deteriorates after myocardial calcification induced by three-day treatment with excess vitamin D.

Since LV systolic function and relaxation are highly dependent on ATP produced by the cardiac mitochondria, mitochondrial calcification may easily lead to an impairment of cardiac function. Furthermore, continuous calcium entry into cardiac myocytes reduces the passive compliance of the myocardium and thus the late phase of LV diastolic filling (Smogorzewski et al. 1995, Brutsaert et al. 1997). Several authors have indeed reported impaired LV systolic and diastolic function in patients with primary (Ohara et al. 1995) or secondary (Rostand et al. 1988, Hara et al. 1995) hyperparathyroidism.

While a number of studies have demonstrated that PTH- or vitamin D-induced accumulation of calcium inside the myocardial cells has adverse effects on the heart, no investigators have addressed the question whether chronic hypercalcemia per se has the same effect on myocardial calcium load, energy production and function. Extensive mitochondrial calcification may also occur in other clinical situations of hypercalcemia, for example with iatrogenic hypercalcemia or malignant neoplastic diseases, or following rhabdomyolysis or extensive immobilization.

3.4. Effect of hemodialysis-induced changes in serum calcium on cardiac function

3.4.1. Systolic function

During HD serum ionized calcium varies directly with the dialysate calcium concentration, resulting in rapid and substantial changes in serum calcium during the treatment (Saha et al. 1996). In view of the known effects of acute hypo- and hypercalcemia on LV systolic function and relaxation, the HD-induced changes in serum calcium may thus substantially affect myocardial function during the dialysis session.
In 1983 Nixon and associates suggested that an HD procedure increases the contractile state of the myocardium. Thereafter it was proposed that HD treatment, with (Lang et al. 1988) or without (Henrich et al. 1984) fluid removal, improves LV systolic function when a high-calcium dialysate is used. Additionally, Wizemann and colleagues (1986) demonstrated that HD improves myocardial contractility if serum ionized calcium increases and plasma potassium decreases during the treatment. The findings of these studies are quite inconsistent with subsequent reports. In 1989 a group under Stoddard documented that an acute change in cardiac preload (comparable to the effect of fluid removal during HD) has no effect on LV systolic function. Moreover, the aforementioned study by Virtanen and colleagues (1998) proved that an acute increase in serum calcium does not affect LV contractility. In agreement with these later reports, it has been shown that an HD procedure, even with a rise in serum calcium, does not induce changes in the echocardiographic indices of LV systolic performance (Rozich et al. 1991, Sztajzel et al. 1993).

3.4.2. Relaxation

A reduction in LV end-diastolic pressure (preload) induces changes in the indices of pulsed Doppler echocardiography; Emax and E/Amax decrease, while Amax remains unchanged (Stoddard et al.1989). During HD treatment, fluid removal reduces cardiac preload and results in a decreased LV inflow. During the interval between HD sessions, fluid retention, in turn, expands the circulating blood volume and thus increases the cardiac preload. This results in a “pseudonormalization” of Doppler indices of LV diastolic filling between sessions. Such a conception was supported by Sadler and colleagues (1992) and Chakko and colleagues (1997), who documented that the HD procedure impairs Doppler indices of LV inflow only if there is a concomitant decrease in cardiac preload.

In addition to decreased preload, other factors may affect LV diastolic filling during the HD procedure. An HD-induced decrease in plasma volume tends to raise the heart rate during treatment. As the heart rate increases, the LV diastolic filling time is shortened and the atrial filling fraction increases. In consequence, the Doppler indices show impairment of LV filling (Galderisi et al. 1993).
HD-induced changes in total plasma volume and insufficient cardiovascular compensatory mechanisms result in changes in cardiac afterload. This is observed as an increase or decrease in arterial blood pressure during treatment. Changes in cardiac loading conditions, in turn, are known to influence the Doppler parameters of LV relaxation (Nishimura 1989, Yellin et al. 1990, Zile et al. 1990). Intradialyptic changes in blood pressure are particularly common in patients on HD and account for the most important complications occurring during a session (Daugirdas et al. 1991). There is convincing evidence showing that changes in serum ionized calcium may modulate systemic arterial blood pressure and thus cardiovascular stability during dialysis (Fellner et al. 1989). Studies by groups under Van Kuijk (1997) and Van der Sande (1998) showed that arterial blood pressure decreases significantly during HD with low-calcium dialysate, while dialysis with high-calcium dialysate maintains the intradialytic blood pressure stable. These findings were reinforced by reports that HD with a positive calcium balance does not affect blood pressure (Rozich et al. 1991, Ształzel et al. 1993, Chakko et al. 1997).

Studies concerning the effect of serum calcium on LV diastolic filling during HD treatment are limited. Groups under Rozich (1991), Ształzel (1993) and Chakko (1997) have all reported that HD treatment impairs the Doppler indices of LV diastolic filling. However, in all of these series there was a significant increase in the serum concentration of calcium during treatment due to the use of high-calcium dialysate. In fact, no studies exist evaluating the effect of the HD procedure on LV diastolic filling during treatment with a moderate increase in serum calcium or with a negative calcium balance. It is obvious that HD-induced changes in cardiac preload, afterload and heart rate dispose the heart to a deterioration in LV diastolic function during treatment. However, knowing the adverse effect of acute hypercalcemia on LV relaxation (Virtanen et al. 1998), it seems reasonable to assume that a rise in serum calcium during HD plays a role in this phenomenon.

3.5. Effect of calcium on cardiac electrical stability during hemodialysis

An increase in QT interval and QT dispersion on a standard 12-lead ECG represents abnormal ventricular repolarization and hence an increased risk of ventricular
arrhythmias (Day et al. 1990, Elming et al. 1998). Recently, groups under Cupisti (1998) and Morris (1999) have demonstrated that both QT interval and QT dispersion increase during HD treatment, and a number of studies have in fact shown the incidence of ventricular arrhythmias to increase during HD (Ramirez et al. 1984, Gruppo Emodialisi 1988, Kimura et al. 1989, Strata et al. 1994).

The arrhythmogenic effect of HD treatment has been thought to result from pre-existing coronary artery disease (Wizemann et al. 1985), cardiac systolic dysfunction (Kimura et al. 1989), changes in plasma potassium during HD (Redaelli et al. 1996) and abnormalities in serum calcium and PTH metabolism (Ramirez et al. 1984, Gruppo Emodialisi 1988, Kimura et al. 1989, Strata et al. 1994). HD treatment induces substantial and acute changes in serum ionized calcium (Saha et al. 1996), and calcium is known to have a pivotal role in regulating the length of the QT interval and hence also cardiac electrical stability. In fact, findings on patients undergoing regular HD treatment would imply that a high predialysis serum calcium phosphate product or plasma PTH value are associated with an increased risk of cardiac arrhythmias during HD (Ramirez et al. 1984, Kimura et al. 1989, Strata et al. 1994).
4. Parathyroid hormone and cardiac function

PTH is of major importance in regulating the serum calcium concentration via its effects on kidney and bone. However, it is also known to have direct effects on many cell types; it raises the cytosolic calcium concentration at least in kidney cells (Filburn et al. 1990, Tanaka et al. 1993), hepatocytes (Mine et al. 1989) and thymocytes (Stojceva-Taneva et al. 1993). Groups under Urena (1993) and Tian (1993) have moreover demonstrated that the myocardium contains mRNA to produce PTH receptors. Indeed, in addition to its effect on serum calcium, PTH is known to modulate cardiac structure and function directly.

4.1. Direct effects of PTH on the myocardium

4.1.1. Cardiac metabolism

The effect of PTH on myocardial structure and function has been an object of intense investigation. Bogin and associates (1981) were the first to demonstrate that the heart is a target organ for PTH and may have receptors for the hormone. In their study, PTH increased the beating rate of rat heart cells and caused early death of cells. The effect of PTH required calcium, was mimicked by calcium ionophore and was prevented by the calcium antagonist verapamil. It has since been reported that PTH directly enhances myocardial calcium uptake with a subsequent increase in cardiac calcium content (Baczynski et al. 1985, Kondo et al. 1988, Wang et al. 1991). Finally, the PTH-induced rise in the cytosolic calcium of cardiac myocytes has been shown to be receptor-mediated and produced by activation of the L-type calcium channels after stimulation of cardiac G proteins (Smogorzewski 1995).

An increase in the intracellular calcium content of the myocardium has several unfavorable effects on cardiac energy production and utilization. Bogin and colleagues (1982) demonstrated that PTH inhibits oxidative phosphorylation of isolated heart mitochondrias. This effect was dose-dependent and occurred only in the presence of calcium. A later report by Baczynski and associates (1985) showed that PTH-induced myocardial calcification leads to a decrease in mitochondrial oxygen consumption and activities of mitochondrial and myofibrillar creatine phosphokinase, mitochondrial MgATPase and myofibrillar CaATPase. Similarly, studies on rats with uremic secondary
hyperparathyroidism have demonstrated that continuous PTH-mediated calcium entry into cardiac myocytes diminishes mitochondrial ATP production, with a subsequent decrease in the extrusion of calcium due to impaired activities of sarcolemmal Ca\(^{++}\)-ATPase, Na\(^+\)/K\(^+\)-ATPase and Na\(^+\)/Ca\(^{++}\) exchanger (El-Belbessi et al. 1986, Zhang et al. 1994).

In conclusion, PTH regulates the entry of calcium into cardiac myocytes and its intracellular concentration, as well as the exit of the ion out of the cell.

4.1.2. Effect of reduced energy production on cardiac function

During LV contraction, adequate cross-bridge cycling of the cardiac myofilaments actin and myosin is dependent on ATP produced by the cardiac mitochondria. Chronic excess of PTH may thus considerably impair the systolic performance of the myocardium. Treatment with 1-84 PTH for ten days has indeed been shown to reduce cardiac output in rats (Baczynski et al. 1985).

Myocardial relaxation, i.e. the active and energy-dependent phase of LV diastolic filling, begins as the energy-requiring calcium transport mechanisms in the SR and sarcolemma have reduced the cytosolic calcium concentration and the myofilaments become able to dissociate from each other (Opie 1997). Several studies have shown that a decrease in myocardial energy content impairs ventricular relaxation. In patients with end-stage heart failure, diminished capacity of SR and sarcolemma to restore low calcium levels during the diastole has been shown to delay myocardial relaxation (Morgan et al. 1990). Conversely, increased activity of the energy-dependent Ca\(^{++}\)ATPase of the SR is known to enhance intracellular calcium decline during the diastole and to result in improved relaxation of the myocytes (He et al. 1997). During cardiac ischemia decreased ATP production has been shown to lead to a persistence of the cross-bridges between the myofilaments, resulting in impaired relaxation (Pouleur 1990). A chronic excess of PTH may thus impair LV relaxation by reducing cardiac mitochondrial energy production and hence the activity of the energy-requiring calcium transport mechanisms in the SR and sarcolemma.
4.1.3. Myocardial compliance

A decrease in LV compliance – or an increase in diastolic stiffness – leads to an inappropriate upward shift of the ventricular pressure-volume relation curve, and hence to impairment of the passive late phase of diastolic filling (Brutsaert et al. 1997, Nishimura et al. 1997). Several factors may reduce LV chamber stiffness: pericardial restraint, multiple areas of infarction, infiltrative cardiomyopathies, interstitial fibrosis as well as increased LV wall thickness, cardiomyocyte size and myocardial collagen content (Weber et al. 1988, Nishimura et al. 1989, Lenihan et al. 1995, Cohen-Solal 1998).

A number of experimental studies have demonstrated that an excess of PTH causes derangements in myocardial morphology and configuration by inducing myocardial calcification (Bogin et al. 1981, Massry 1983 and 1984, Baczynski et al. 1985, Thompson et al. 1990, Smogorzewski et al. 1995). In addition, PTH has been shown to contribute to the pathogenesis of LV hypertrophy (LVH) in patients with hypertrophic cardiomyopathy (Symons et al. 1985) and primary or secondary hyperparathyroidism (Symons et al. 1985, Harnett et al. 1988, Parfrey et al. 1988). A direct relationship between LVM index and blood levels of PTH has also been found in patients with mild hypertension and normal renal function (Bowens et al. 1991). Amann and colleagues (1994) strengthened the hypothesis of PTH-induced cardiac hypertrophy by showing that in nephrectomized and parathyroidectomized rats PTH activates cardiac fibroblasts and promotes the genesis of intermyocardiocytic fibrosis. However, the pathogenetic process linking myocardial hypertrophy and PTH has not yet been clearly elucidated.

Consequently, while PTH-induced mitochondrial calcification may impair cardiac systolic function and relaxation due to a deficit in mitochondrial ATP production, PTH may also affect the passive filling characteristics of the LV.

4.2. Primary hyperparathyroidism

Patients operated on for PHPT carry an increased risk of death compared to age-and sex-matched controls (Palmer et al. 1987). The main sources of this increased mortality are cardiovascular, congestive heart failure and myocardial infarction accounting for the majority of premature deaths in these patients (Hedbäck et al. 1990 and 1991).
4.2.1. Calcium metabolism in primary hyperparathyroidism

In primary hyperparathyroidism, PTH is secreted inappropriately despite an elevation in serum ionized calcium. In most cases (85 %) PHPT results from the occurrence of single adenoma in a previously normal parathyroid gland, from hyperplasia of all four parathyroid glands (15 %) and more rarely from parathyroid carcinoma (Finkelstein et al. 1993). High plasma PTH levels cause excessive renal calcium reabsorption and phosphate excretion, as well as increased mobilization of calcium from the skeleton. Renal synthesis of 1,25(OH)2D3 is enhanced due to the effect of PTH on 1α-hydroxylase enzyme, resulting in increased intestinal calcium absorption. Eventually, serum calcium increases while phosphate decreases.

4.2.2. Systolic function

Several authors have sought to establish the effect of PHPT on cardiac systolic function. All these studies have consistently shown that PHPT does not affect LV systolic performance (Stefenelli et al. 1993 and 1997a, Ohara et al. 1995, Sato et al. 1995, Piovesan et al. 1999).

4.2.3. Cardiac structure and diastolic function

There are few studies and with contradictory results, concerning the effect of PHPT on LV diastolic function. Groups under Ohara (1995), Dalberg (1996) and Stefeneelli (1997a) have all reported a high incidence of impaired LV filling (decreased E/Amax ratio) in patients with PHPT. In contrast, more recent study by Piovesan and associates (1999) has suggested that patients with PHPT have normal Doppler indices of LV inflow.

Many potential factors may impair LV diastolic function in PHPT. PTH-induced deficit in mitochondrial energy production may reduce the early rapid filling of the LV, while the late phase of diastolic filling may be affected by myocardial calcification and LVH. In patients with PHPT, a chronic excess of PTH has been shown to induce calcification inside individual myocardial fibers (Roberts et al. 1981), heart valves (Niederle et al. 1990) and the media and intima of the coronary arteries (Roberts et al.
LVH is frequently observed in PHPT (Symons et al. 1985, Dominiczak et al. 1990, Stefenelli et al. 1993, 1997a and 1997b, Piovesan et al. 1999). The high incidence of LVH in these patients may result from the direct trophic effect of PTH on the myocardium (Bogin et al. 1981, Katoh et al. 1981, Pearce et al. 1985, Amann et al. 1994, Ogino et al. 1995, Hara et al. 1997), or it may also arise from hypertension, since PTH is known to increase blood pressure directly (Hulter et al. 1986, Fliser et al. 1997) and 40–50% of patients with PHPT have been reported to be hypertensive (Stefenelli et al. 1993, Chan et al. 1995, Piovesan et al. 1999).

4.2.4. Effect of parathyroidectomy

All studies assessing the effect of PTX on LV systolic function in patients with PHPT have been made with patients with initially normal LV systolic function. On the basis of the reports in question, PTX does not seem to affect the M-mode indices of LV systolic performance (Stefenelli et al. 1993, 1997a and 1997b, Ohara et al. 1995, Sato et al. 1995, Piovesan et al. 1999).

Several studies have shown that LV wall thicknesses diminish in PHPT patients after successful PTX (Stefenelli et al. 1993, 1997a and 1997b, Piovesan 1999). The reduction in LVH in PHPT seems to be a long-lasting process; in a study by Stefenelli and colleagues (1997b) no change occurred in septal and posterior wall thicknesses within one year after PTX, while a significant reduction was observed three years after an operation. The exact mechanism by which PTX diminishes LVH remains to be established, but several studies have shown that the decrease in LV wall thicknesses after PTX would be independent of changes in arterial blood pressure (Dominiczak et al. 1990, Stefenelli et al. 1993, Ohara et al. 1995, Sato et al. 1995, Piovesan et al. 1999).

Despite the considerable decreases in serum calcium and PTH levels after PTX, myocardial and valvular calcification appears to persist after an operation. Both Stefenelli and colleagues (1993 and 1997a) and Dalberg and colleagues (1996) report that after PTX and 12-41 months of normocalcemia and normal PTH concentrations, calcific deposits in the myocardium and in aortic and mitral valves persist without evidence of progression or regression.
The effect of PTX on LV diastolic function has remained unclear, since only two studies, with opposing results, have addressed the issue. Ohara and colleagues (1995) studied the effect of PTX in 14 PHPT patients with impaired LV relaxation at the baseline of the study. The Doppler indices of LV relaxation were significantly improved 1 month after PTX, and the change in E/Amax correlated strongly with that in serum PTH. In the above-mentioned study by Dalberg and group (1996), patients with PHPT had poorer indices of LV diastolic filling than the healthy control subjects at the outset, but no change was found in these indices 12 months after PTX.

4.3. Secondary hyperparathyroidism in chronic renal failure

Cardiovascular diseases occur frequently in patients with CRF (Raine et al. 1992, Foley et al. 1995, Parfrey and Foley 1999, Tsakiris et al. 1999, Foley et al. 2000), but the etiology of LV dysfunction in CRF has remained unclarified. The mechanisms underlying the genesis of cardiac dysfunction in CRF are many; hypertension, volume overload, hyperlipidemia, accelerated atherosclerosis, anemia, electrolyte disturbances, acidosis, malnutrition and glucose intolerance may all be implicated. Furthermore, there is evidence suggesting that disturbances in calcium and phosphate metabolism may play a role in uremic cardiomyopathy.

4.3.1. Calcium metabolism in secondary hyperparathyroidism

In secondary hyperparathyroidism plasma PTH is increased while the serum concentration of calcium is low. A variety of conditions may result in secondary hyperparathyroidism, the most significant being CRF.

The progressive nephron destruction in CRF impairs renal phosphate excretion and reduces the renal synthesis of 1,25(OH)2D3. High serum phosphate further impedes the renal production of 1,25(OH)2D3, stimulates the secretion of PTH and – probably via reduction of the release of calcium from bone - reduces serum Ca++ (Naveh-Many et al. 1995, Slatopolsky et al. 1996 and 1999). Low levels of 1,25(OH)2D3 result in increased PTH secretion and decreased intestinal calcium absorption. Consequently, serum ionized calcium is decreased, which further stimulates the secretion of PTH. Additionally, recent studies have shown that in patients with uremic secondary hyperparathyroidism the
abnormally high secretion of PTH may be, at least partly, due to down-regulation of the Ca$$^{++}$$-sensing receptors in parathyroid tissue (Gogusev et al. 1997, Brown et al. 1999). Eventually, a combination of simultaneous hyperparathyroidism, hypocalcemia and hyperphosphatemia evolves.

In contrast to PHPT, patients with secondary hyperparathyroidism are usually hypo- or normocalcemic. However, the cardiac effects of secondary hyperparathyroidism mimic those of PHPT, since the long-term adverse effects of secondary hyperparathyroidism on cardiac structure and function seem to be predominantly attributable to a chronic excess of PTH.

4.3.2. Myocardial metabolism

In 1978 Kraikipanitch and colleagues showed that the calcium content of the myocardium is increased in uremic dogs with intact parathyroid glands and that PTX prevents the accumulation of calcium. Subsequently, groups under El-Belbessi (1986) and Zhang (1994) revealed that in rats CRF is associated with increased uptake and intracellular concentration of calcium in the cardiac myocytes and decreased myocardial energy production, transfer and utilization. Normalization of the serum PTH concentration by PTX or by treatment with calcium antagonists blocks these adverse effects of uremia on heart cells. Both reports suggest a major role for excess PTH in the genesis of myocardial energy deficiency and, finally, LV dysfunction in CRF.

4.3.3. Systolic function

Studies hitherto to evaluating the effect of secondary hyperparathyroidism on cardiac systolic function have yielded contradictory results. Numerous authors have reported that LV systolic function may be normal in patients with CRF and secondary hyperparathyroidism (Drueke et al. 1980, McGonigle et al. 1984, Gafter et al. 1985, Huting et al. 1991, Fellner et al. 1991, Sato et al. 1995). Coratelli and associates (1984) obtained opposing results in showing that CRF reduces the cardiac contractile force. Similarly, groups under Harnett (1995) and Parfrey (1987 and 1988) report 18-33 % of CRF patients to have low-output LV failure and dilated LV.
In patients with CRF the occurrence of cardiac systolic dysfunction may be associated with secondary hyperparathyroidism (Parfrey et al. 1987 and 1988). Rostand and colleagues (1988) reported an inverse relationship between myocardial calcium content and LV systolic function in patients on HD therapy. In the same study, the myocardial calcium content was found to be associated with the serum calcium-phosphate product and advanced hyperparathyroidism. Furthermore, Hara and associates (1995) documented that LV systolic function correlates negatively with plasma PTH only in HD patients with profound secondary hyperparathyroidism. These reports strongly imply an inverse correlation between cardiac systolic function and the severity of secondary hyperparathyroidism in patients with CRF.

PTH has been shown to acutely increase the force and frequency of contraction of cardiac myocytes (Bogin et al. 1981, Katoh et al. 1981, Smogorzewski 1995). In contrast, a chronic excess of PTH is known to have an adverse effect on cardiac contractile function (Baczynski et al. 1985). Secondary hyperparathyroidism may also impair LV systolic function by inducing calcific deposits in heart valves (Maher et al. 1987, Raine et al. 1994) and myocardium (Thompson et al. 1990), and by causing myocardial fibrosis (Mall et al. 1990, Ritz et al. 1990) and hypertrophy (Mall et al. 1988, Lubbecke et al. 1994). Additionally, a PTH-induced intracellular calcium load with a subsequent reduction in mitochondrial energy production may potentially impair the cardiac contractile force.

4.3.4. Left ventricular hypertrophy

LVH is particularly common in patients with CRF, occurring in over 50-70 % of them (Harnett et al. 1988, Huting et al. 1988, Covic et al. 1996, Foley et al. 2000). A number of factors may contribute to this, including hypertension, decreased aortic and large artery compliance, volume overload, age, anemia and secondary hyperparathyroidism (Smogorzewski and Massry 1997, Parfrey and Foley 1999).

In essential hypertension, the LVM index correlates directly with nocturnal and daytime blood pressure (Verdecchia et al. 1990). Arterial hypertension, and especially systolic hypertension, is notably frequent in patients with CRF (Cheigh et al. 1992). Groups under Harnett (1988 and 1994) and Foley (1996a) have suggested that the
occurrence of LVH correlates directly with blood pressure in these patients. To the contrary, Huting and associates (1988) showed that in patients with CRF LV wall thicknesses may increase significantly with time without a simultaneous increase in arterial blood pressure. In a study by Facchin and colleagues (1995), LVM correlated with blood pressure in patients on HD, but morphological changes in LVH were also present in normotensive uremic patients. Experimental studies have shown, moreover, that uremia increases the heart weight and deposition of collagen fibers in the rat myocardium by mechanisms independent of hypertension (Rambausek et al. 1985, Mall et al. 1988). Consequently, although hypertension may worsen myocardial hypertrophy in CRF, LVH is probably not solely due to arterial hypertension in these patients.

The intima-media thickness of the major central arteries is increased in patients with CRF (London et al. 1996). The increased thickness of the aortic intima and media results in lowered aortic distensibility, increased aortic pulse wave velocity (PWV) and, eventually, hypertrophied LV (London et al. 1996). Similarly to the general population, in patients with CRF arterial wall thickness increases with age and blood pressure (London et al. 1990). These same two studies show, however, that the aortic PWV and the LV wall thicknesses are significantly increased in HD patients when compared to non-uremic control subjects of the same age and blood pressure. Additionally, Guerin and colleagues (2000) have shown that in CRF patients arterial calcification increases with the duration of dialysis therapy and the use of calcium-based phosphate binders.

Anemia is a nearly universal finding in patients with CRF, the primary cause being a deficiency of erythropoietin. Anemia induces compensatory increase in cardiac wall thicknesses, and several studies have shown that anemia may contribute to the development of LVH and heart failure in patients with CRF (Huting et al 1990, Harnett et al. 1995, Foley et al. 1996b and 1998, Tucker et al. 1999). The study by Murphy and colleagues (1998) demonstrated that correction of anemia with erythropoietin decreases, but does not normalize, LVM and volume in these patients.

Groups under Harnett (1988) and Parfrey (1988) observed that in patients with CRF the prevalence of LVH correlates with the severity of secondary hyperparathyroidism. Similarly, London and associates (1987a) had previously reported that in HD patients without hypertension or other cardiovascular risk factors, LVH and
dilated cardiomyopathy are related to the occurrence of secondary hyperparathyroidism. In secondary hyperparathyroidism, excess PTH may induce LVH indirectly by increasing blood pressure (Pizzarelli et al. 1993, Raine et al. 1993) and by inducing calcification of the arterial wall and the aortic valve (Maher et al. 1987, Guerin et al. 2000) with a subsequent increase in the systolic workload of the LV. In addition, secondary hyperparathyroidism may favor LVH directly by stimulating intramyocytic protein synthesis and activating cardiac fibroblasts (Schluter and Piper 1992, Amann et al. 1994).

4.3.5. Diastolic function

The Doppler indices of LV filling have been shown to be impaired in HD patients compared to healthy controls (Ruffmann et al. 1990). Abnormal diastolic function has also been described in patients on continuous ambulatory peritoneal dialysis (CAPD) and in kidney-transplant patients (Wizemann et al. 1994). The prevalence of LV diastolic dysfunction in patients with CRF appears to be in the range of 30-60 % (Wizemann et al. 1994, Kunz et al. 1998).

It is well established that the hypertrophied myocardium exhibits impaired ventricular relaxation and diastolic distensibility (Grossman 1991, Lenihan et al. 1995). However, both Facchin and associates (1995) and Covic and associates (1996) have documented that in CRF Doppler indices of LV diastolic filling do not correlate with blood pressure and the occurrence of LVH. Similarly, Huting and colleagues (1991) showed that LV filling is impaired in patients on CAPD with either normal or a hypertrophied myocardium. These reports suggest the additional factors contributing to the impairment of diastolic function in CRF.

Myocardial calcification reduces LV chamber compliance and hence impairs the late phase of diastolic filling. Numerous investigators have reported widespread cardiovascular calcification in patients with CRF (Maher et al. 1987, Rostand et al. 1988, Milliner et al. 1990, Michel 1998, Rostand et al. 1999). In the general population, age and hypertension are both known to favor the deposition of calcium in the myocardium (Mazzaferro et al. 1993, Braun et al. 1996), but in patients with CRF myocardial calcification seems to correlate primarily with the degree of secondary hyperparathyroidism. Groups under Maher (1987) and Huting (1994) have presented a
correlation between valvular calcification and serum calcium-phosphorus product in patients with CRF. Huting (1993) demonstrated a relation between mitral valve calcification and plasma PTH level in patients on CAPD. Rostand and colleagues (1988), in turn, found a strong correlation between cardiac calcification and serum calcium-phosphorus product as well as advanced secondary hyperparathyroidism.


4.3.6. Effect of parathyroidectomy and vitamin D treatment

Drueke and associates (1980) were the first to suggest that PTX improves cardiac contractile function in HD patients with secondary hyperparathyroidism. A group under Hara (1995) obtained similar results when examining the effect of PTX on HD patients with impaired LV systolic function at the start of their study. In addition, Coratelli and colleagues (1984) reported an improvement in LV dimensions and McGonigle and colleagues (1984) in cardiac systolic function after long-term vitamin D therapy in patients with CRF and secondary hyperparathyroidism. In contrast, a number of investigators report that PTX does not affect cardiac dimensions or contractile function in CRF patients with normal LV systolic function (Gafter et al. 1985, Fellner et al. 1991, Rostand et al. 1994, Sato et al. 1995). Consequently, it may be that vitamin D treatment and PTX enhance LV systolic performance only in patients with pre-existing cardiac systolic dysfunction.

Reversal of secondary hyperparathyroidism by PTX or vitamin D treatment has been shown to cause a regression in myocardial hypertrophy, detectable within 4 to 12 months after the operation or start of therapy (Sato et al. 1995, Park et al. 1999). Some
studies, however, have failed to demonstrate a decrease in LV wall thicknesses 1-6 months after PTX (Hara et al. 1995, Gafter et al. 1985). These discrepancies may arise from the length of the follow-up period; as in PHPT, the reduction in LVH in secondary hyperparathyroidism may be a time-taking process.

There is no agreement as to the mechanisms by which PTX might reduce LVH in patients with CRF. It is possible that PTX reduces myocardial hypertrophy by lowering blood pressure (Pizzarelli et al. 1993, Hara et al. 1995). However, numerous studies have proved that a reduction in plasma PTH level does not affect blood pressure in these patients (Sato et al. 1995, Ifudu et al. 1998, Park et al. 1999). Additionally, Park and colleagues (1999) showed that treatment of secondary hyperparathyroidism with vitamin D decreases LVH without a simultaneous change in arterial blood pressure. Indeed, in the same study the improvement in LVH was strongly correlated with the change in plasma PTH.

Few studies have assessed the effect of PTX or vitamin D treatment on cardiac diastolic function. Rostand and colleagues (1994) evaluated LV diastolic function in 10 HD patients before and 6-12 months after PTX. No improvement was found in the Doppler indices of LV diastolic filling, and myocardial calcium content was similarly unaffected.
5. Vitamin D and cardiac function

The mechanisms by which vitamin D regulates the serum calcium concentration have been well characterized and involve actions of its active metabolite 1,25(OH)2D3 on bone, intestine and parathyroid glands (Brinthurst et al. 1998). Specific receptors for 1,25(OH)2D3 have been identified in a number of tissues not previously thought to be responsive to vitamin D (Walters 1992, Bouillon et al. 1995), and increasing evidence exist for the presence of 1,25(OH)2D3 receptors also in the myocardium (Walters et al. 1986 and 1991, Bidmon et al. 1991). Therefore, similarly to PTH, vitamin D may affect myocardial structure and function both indirectly by modulating serum calcium concentration and directly by its actions on the myocardial cells themselves.

5.1. Myocardial vitamin D receptors

Simpson and associates (1983) were the first to report the existence of a specific intracellular receptor protein for vitamin D in cytosols prepared from cultured rat heart cells. Subsequently, a group under Walters (1986) showed that cardiac vitamin D receptors are functional receptors and may modulate the intracellular calcium homeostasis. Similarly to other tissues, the direct effects of vitamin D on the heart may occur via a genomic mechanism, i.e. activation of intracellular mRNA and protein synthesis or through nongenomic actions of the hormone (Walters 1992, Bouillon et al. 1995). Walters and colleagues (1987) provided evidence for the genomic action of vitamin D on the heart; vitamin D was shown to stimulate calcium uptake by cardiac myocytes in a concentration-dependent and steroid-specific manner after a prolonged exposure time, suggesting a requirement for protein and nucleic acid synthesis. Subsequently, Selles and associates (1991) showed that vitamin D increases the intracellular calcium concentration also by non-genomic rapid actions involving stimulation of sarcolemmal calcium channels.

5.2. Direct effects of vitamin D on cardiac structure and function

Studies by groups under Weishaar (1987b and 1990) and O`Connell (1995) have demonstrated that rats maintained on a vitamin D-deficient but calcium supplemented diet for several weeks show an increase in myocardial collagen content and heart to body
weight ratio. This finding suggests a direct role for vitamin D in the regulation of cardiac structure. The optimal range of serum vitamin D concentration seems to be narrow, since an excess of the hormone has also been shown to have a trophic effect on rat myocardial cells (Takeo et al. 1991). Additionally, vitamin D is known to induce calcific deposits inside the myocardium (Walters et al. 1987, Selles et al. 1991, Takeo et al. 1991) and to cause calcification and swelling of cardiac mitochondrias (Takeo et al. 1991).

The acute and chronic effects of vitamin D on cardiac function seem to be quite different. Jahn and associates (1991) showed that an acute infusion of 1,25(OH)2D3 enhances the contractile state of the dog myocardium within 30-60 minutes. The improvement in contractile force was mimicked by a calcium ionophore and blocked by a calcium antagonist, suggesting a direct activation of sarcolemmal calcium channels. Takeo and group (1991) documented that a 3-day massive hypervitaminosis D produces excessive myocardial and mitochondrial calcium accumulation, impairment of mitochondrial energy production and, finally, impaired LV systolic and diastolic function. Conversely, studies on vitamin D-depleted rats have shown cardiac systolic and diastolic performance to be indirectly correlated to the serum concentration of vitamin 1,25(OH)2D3, irrespective of the serum calcium level (Weishaar et al. 1987a, O’Connell et al. 1994).

Consequently, a chronic excess of vitamin D may impair cardiac systolic function and relaxation by inducing mitochondrial calcification with a subsequent decrease in myocardial energy content. A continuous excess of the hormone has also been found to cause disorientation and degeneration of cardiac contractile fibrils (Takeo et al. 1991) and to reduce total myosin levels in rat ventricular myocytes (O’Connell et al. 1994).

5.3. Vitamin D deficiency

Clinical studies evaluating the effect of vitamin D depletion on the heart are restricted to a few case reports concerning nutritional osteomalacia. Avery and colleagues (1992) described a female patients with hypovitaminosis D, hypocalcemia, secondary hyperparathyroidism and LV systolic dysfunction. Cardiac failure improved promptly when the hypocalcemia was corrected with vitamin D supplementation. Similarly, a group under Brunvand (1995) reported a dramatic improvement in LV systolic function after
initiation of vitamin D therapy in a child with severe vitamin D deficiency, hypocalcemia and hyperparathyroidism. It may in any case be assumed that in these studies the enhancement of cardiac systolic performance was due primarily to the correction of hypocalcemia rather than to a direct effect of vitamin D on the myocardium.

5.4. Vitamin D and treatment of secondary hyperparathyroidism

Treatment of patients with CRF and secondary hyperparathyroidism with vitamin D has been reported to improve the echocardiographic indices of LV systolic function (Coratelli et al. 1984, McGonigle et al. 1984). Furthermore, a recent study by Park and associates (1999) has shown that 1,25(OH)2D3 treatment reduces cardiac wall thicknesses and LVM index in HD patients with secondary hyperparathyroidism. However, in all of the studies in question vitamin D treatment resulted in a significant lowering of plasma PTH level. The beneficial effect of vitamin D on cardiac structure and function in secondary hyperparathyroidism may thus be due either to a direct effect of vitamin D on the myocardium or to suppression of PTH secretion, or both.

In short, although experimental studies have shown that the heart is a target organ for vitamin D, the specific cellular mechanisms by which vitamin D exerts its direct effects on the heart remain obscure. There is an obvious lack of clinical studies evaluating the cardiac effects of vitamin D. The few reports available on patients with nutritional vitamin D deficiency and secondary hyperparathyroidism attest that vitamin D affects LV systolic function and structure at least indirectly via changes in blood calcium and PTH.
AIMS OF THE PRESENT STUDY

The purpose of the present study was

1. To examine left ventricular structure and function in patients with primary hyperparathyroidism

2. To examine left ventricular structure and function in chronic renal failure patients with secondary hyperparathyroidism

3. To evaluate the influence of the treatment of primary and secondary hyperparathyroidism on left ventricular structure and function

4. To study the effect of hemodialysis-induced acute changes in serum calcium on
   a) left ventricular systolic and diastolic function
   b) cardiac electrical stability
   in patients with chronic renal insufficiency.
SUBJECTS

Studies I-IV involved a total of 48 subjects. All gave informed consent and the studies were approved by the Ethics Committee of Tampere University Hospital. The clinical characteristics of these subjects are shown in Table 1. The patients in studies I-III had CRF and were on regular HD treatment. The duration of this therapy ranged from 1-90 months in study I, from 1-41 months in study II and from 1-108 months in study III. The reference range for plasma intact PTH was 0.8-6.0 pmol/l in study I and 1.0-6.8 in studies II-IV.

In study I the patients had moderate to severe secondary hyperparathyroidism. The mean plasma intact PTH was 41.4±10.7 pmol/l (range 7.8-111.0 pmol/l) and mean serum ionized calcium 1.23±0.04 mmol/l. Eight patients were hypertensive and two had congestive heart failure.

The subjects in study II had moderate secondary hyperparathyroidism. The median plasma intact PTH was 7.2 pmol/l (range <0.8–70.1 pmol/l) and mean serum ionized calcium 1.22±0.10 mmol/l. Two patients had congestive heart disease, eight were hypertensive and four had myocardial infarction in their medical history.

In study III the median plasma intact PTH was 10.7 pmol/l (range 1.2-138.0 pmol/l) and mean serum ionized calcium 1.24±0.10 mmol/l, indicating moderate to severe secondary hyperparathyroidism in the patients involved. Nineteen were hypertensive, three had congestive heart disease and three a myocardial infarction in their medical history.

The subjects involved in study IV had PHPT. The mean plasma intact PTH was 10.9±3.0 pmol/l (range 7.6-191 pmol/l) and mean serum total calcium 2.79±0.13 mmol/l. Eight of them were hypertensive, one had congestive heart disease and one a myocardial infarction in their medical history.

In the study settings of I,II and IV each patient had an age- and sex-matched control subject. The controls were healthy volunteers and they had no abnormalities in standard medical history, physical examination, electrocardiography or two-dimensional echocardiography.
Table 1. Clinical characteristics of the 48 patients and the controls involved in studies I-IV.

<table>
<thead>
<tr>
<th>Study number</th>
<th>Number of subjects</th>
<th>Sex female/male</th>
<th>Age, years mean±SD (range)</th>
<th>Clinical setting</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>10</td>
<td>6/4</td>
<td>49±12 (30-69)</td>
<td>Chronic renal failure, HD Moderate to severe secondary hyperparathyroidism</td>
<td>female/male 6/4 age 51±14 (mean±SD) 32-71 (range)</td>
</tr>
<tr>
<td>II</td>
<td>12</td>
<td>2/10</td>
<td>54±18 (24-76)</td>
<td>Chronic renal failure, HD Moderate secondary hyperparathyroidism</td>
<td>female/male 2/10 age 56±8 (mean±SD) 23-74 (range)</td>
</tr>
<tr>
<td>III *</td>
<td>23</td>
<td>3/20</td>
<td>53±17 (24-84)</td>
<td>Chronic renal failure, HD Moderate to severe secondary hyperparathyroidism</td>
<td>-</td>
</tr>
<tr>
<td>IV</td>
<td>15</td>
<td>11/4</td>
<td>61±14 (31-81)</td>
<td>Primary hyperparathyroidism</td>
<td>female/male 11/4 age 62±8 (mean±SD) 34-81 (range)</td>
</tr>
</tbody>
</table>

HD = hemodialysis
*) includes patients of study II

METHODS

1. Study protocol

In study I LV systolic function and diastolic filling in patients on chronic HD were compared with those in healthy controls. Thereafter, the effect of long-term calcitriol therapy on LV systolic function and diastolic filling was evaluated in the patients. All patients received intravenous calcitriol (Calcijex®; Abbott Laboratories, USA) at the end of their dialysis sessions, 1-2 µg 1-3 times a week (mean 2.8±0.1 µg/week). The duration of calcitriol therapy ranged from 3 to 4.5 months (mean 3.8±0.2 months). Cardiac function was studied by Doppler and M-mode echocardiography before and after calcitriol therapy, always immediately prior to the HD session. Blood samples were collected at the beginning of the sessions.
**Study II** assessed the effect of acute changes in serum ionized calcium on cardiac function during HD treatment. All patients underwent three study HD sessions with dialysate Ca\(^{++}\) (dCa\(^{++}\)) concentrations of 1.25 mmol/l (dCa\(^{++}\)1.25), 1.50 mmol/l (dCa\(^{++}\)1.5) and 1.75 mmol/l (dCa\(^{++}\)1.75). Before and immediately after these sessions each patient was studied by Doppler and M-mode echocardiography, blood pressure was measured and blood samples were collected. The healthy controls were also examined echocardiographically.

**Study III** was designed to evaluate the effect of dialysate Ca\(^{++}\) concentration on cardiac electrical stability during HD treatment. Three study HD sessions were arranged for each patient with the same dialysate Ca\(^{++}\) concentrations as in study II. At the beginning and end of the study sessions standard 12-lead ECG was used to define the QT interval and QT dispersion. Before and after each HD session blood pressure and heart rate were measured and blood samples collected.

In **study IV** the role of PHPT and the effect of PTX on LV wall thicknesses and systolic and diastolic function were studied. Patients with untreated PHPT were examined by Doppler and M-mode echocardiography before and 2-3 months after PTX. Patients’ echocardiographic indices were compared with those in healthy control subjects.

2. Echocardiographic examinations

All echocardiographic examinations were made by one investigator (Vesa K. Virtanen MD, PhD) in blinded fashion. The examinations were made with a Hewlett Packard 77020A ultrasound system (Hewlett Packard Inc., USA) or a System FiVe 1.3 ultrasound system (Vingmed Sound AIS, Norway) equipped with a 2.5 MHz transducer together with the lead II electrocardiogram.

All examinations were carried on in resting state during quiet respiration. The patient was supine and tilted about 30° to the left lateral position. Standard M-mode measurements of the LV were obtained from the parasternal long-axis view, the cursor being placed immediately below the mitral valve tips. Five representative consecutive or near consecutive cardiac cycles with clearly identifiable left septal and posterior wall endocardial echoes were analysed and averaged. Left ventricular posterior wall endocardium, septal wall endocardium and posterior wall epicardium were measured.
from the R wave of the ECG to the R wave of the subsequent beat. Left ventricular end diastolic dimension (LVEDD), thickness of interventricular septum (IVST) and posterior wall (PWT) were measured at the onset of the electrocardiographic Q wave. The left ventricular end-systolic dimension (LVESD) was measured at the time of the smallest left ventricular diameter. Left ventricular fractional shortening (FS) was defined as (LVEDD-LVESD)x100/LVEDD and the ejection fraction (EF) as (LVEDD^3-LVESD^3)x100/LVEDD^3. The left ventricular mass (LVM) was calculated as 1.04x(LVEDD+PWT+IVST)^3-LVEDD^3 (Devereaux 1986). The M-mode echocardiography measurements were interpreted according to the standards of the American Society of Echocardiography (Sahn et al. 1978).

The mitral inflow velocity was measured in the apical four-chamber view. The sample volume was placed at the tips of the mitral valve leaflets, whereby the pulsed-wave Doppler beam direction was aligned parallel to the expected direction of the ventricular inflow. The following indices were measured: peak early diastolic velocity (Emax), peak late diastolic velocity (Amax), the E/Amax ratio was calculated and the isovolumic relaxation time (IVRT) was measured as the time from closure of the aortic valve to the onset of mitral valve opening, deceleration time (DT) as the time from the peak to the end of the E-wave.

The reproducibility of the M-mode and Doppler echocardiography in Tampere University Hospital has been studied blindly by two independent observers using 17 healthy volunteers (Virtanen 1996). The coefficients of repeatability were calculated using the principles recommended by Bland and Altman (1986) and represent the 95% confidence intervals. The interobserver and intraobserver coefficients of repeatability of LVEDD were 3.2 mm and 2.2 mm, of IVST 1.4 mm and 1.0 mm, of PWT 2.2 mm and 1.4 mm, of Emax 0.108 m/s and 0.122 m/s, of Amax 0.084 m/s and 0.084 m/s, of E/Amax 0.428 and 0.624, and of IVRT 10 ms and 44 ms.

3. Electrocardiographic examinations

Standard 12-lead ECG was carried on at a paper speed of 50 mm/s (Sicard 440, Siemens). QT intervals were measured manually by a single observer (S.E.N) in blinded fashion. Three consecutive complexes were analysed for each lead. The end of the T
wave was defined as the intersection of the tangent to the descending limb of the T wave
with the isoelectric line (Browne et al. 1983). If the T wave was flat or could not be
properly determined, the lead in question was excluded from analysis. QT intervals were
corrected for heart rate with Bazett’s formula $QT_c = QT/(RR)^{1/2}$. QT dispersion was
defined as the difference between maximum and minimum QT interval, and $QT_c$
dispersion was computed.

To evaluate intraobserver variability in QT interval and QT dispersion
measurements in study III, the ECGs of 15 HD patients were analysed by a single
observer (S.E.N) on two different occasions. There were no significant differences in
$QT_c$ interval (404 ± 26 vs. 404 ± 28 ms, NS) or $QT_c$ dispersion (42 ± 21 vs. 45 ± 18 ms,
NS) between the two recordings. According to the method of Bland and Altman (1986),
the mean of the differences was 0.0 ± 7 ms for the $QT_c$ interval and –3.0 ± 27 ms for $QT_c$
dispersion, the corresponding 95 % confidence intervals ranging from –3.9 to +3.9 ms
and from –18.0 to 12.0 ms.

4. Biochemical methods

Analysis of total calcium, phosphate, magnesium, sodium, potassium, chloride,
creatinine, urea, hemoglobin, alkaline phosphatase and thyroxin was made by routine
automatic methods. The concentration of ionized serum calcium was measured with a
Radiometer ICA-1 Analyzer (Radiometer A/S, Copenhagen, Denmark) and that of intact
parathyroid hormone in the plasma by two-site immunoradiometry (N-tact® PTH IRMA;
Incstar Corp., Stillwater, Minn., USA). Samples for assessment of 1,25-(OH)2D3 were
prepurified with an acetonitrile-C 18 Sep-Pak® procedure followed by separation of
1,25-(OH)2D3 by high-performance liquid chromatography. 1,25-(OH)2D3 was
quantified by radioreceptor assay (Reinharth et al. 1984).

5. Statistical methods

The means and standard deviations (SD) of all variables were calculated, except
for the calculation of the median for plasma intact PTH in studies II and III. When the
distribution of the data was normal, Student’s t-test for paired or unpaired samples was
used. If the data did not follow a normal distribution the Wilcoxon signed-ranks test for paired samples and the Mann-Whitney U test for unpaired samples were used.

Interrelations between variables were described by Pearson’s correlation coefficients and multiple regression analysis with forward variable selection. In study III the coefficients of repeatability were calculated using the principles recommended by Bland and Altman (1986) and the coefficients represent the 95 % confidence intervals. P values < 0.05 were considered significant. The Statgraphics® (version 7.0) statistical package was used in studies I-III and the SPSS® (version 7.0) statistical package in study IV.
SUMMARY OF RESULTS

Summary of the major findings on cardiac structure and function in different clinical settings is given in Table 2.

1. Cardiac structure and function in primary hyperparathyroidism

The patients with PHPT in study IV had significantly increased LVM (250±102 vs. 189±46 g, p<0.05) and interventricular septum (10.6±2.1 vs. 8.8±2.0 mm, p< 0.05) in comparison to the healthy controls. FS (41.2±5.2 vs. 44.9±4.5 %, p<0.05) and EF (71.4±6.3 vs. 76.4±4.3 %, p<0.05) were slightly smaller in the patients. As an indicator of impaired LV diastolic filling, Amax (0.607±0.122 vs. 0.489±0.101 m/s, p<0.01) and IVRT (110±25 vs. 80±17 ms, p<0.01) were greater and E/Amax slightly (1.028±0.373 vs. 1.341±0.484, p=0.064) smaller in patients than in controls. A significant correlation emerged between serum total calcium and LVM (r=0.63, p<0.05), while no associations were found between plasma PTH and LV structure or function.

2. Cardiac structure and function in secondary hyperparathyroidism

The HD patients with secondary hyperparathyroidism had significantly thicker LV posterior wall (8.9±0.4 vs. 7.1±0.4mm, p<0.05 I, 11.3±1.5 vs. 8.0±1.5 mm, p<0.01 II) and interventricular septum (10.6±0.5 vs. 7.6±0.5mm, p<0.01 I, 13.4 ± 2.1 vs. 8.9 ± 1.5 mm, p<0.01 II) compared to the healthy control subjects. Plasma intact PTH correlated strongly with PWT in study I (r=0.70, p=0.01). LV systolic function was impaired when compared to the controls (FS 33±2 vs. 41±1 %, p<0.05 I, 31±8 vs. 43±5 %, p<0.01 II). Amax (0.732±0.046 vs. 0.431±0.037 m/s, p<0.01 I, 0.669±0.235 vs. 0.430±0.072 m/s, p<0.01 II) and IVRT (112±9 vs. 74±4 ms, p<0.01 I, 125±26 vs. 78±16 ms, p<0.01 II) were increased and the E/Amax ratio decreased (0.887±0.094 vs. 1.551±0.152, p<0.01 I, 1.278±0.514 vs. 1.448±0.329, p=0.25 II) in patients with secondary hyperparathyroidism when compared to controls, indicating impaired LV diastolic filling.
3. Effect of parathyroidectomy on cardiac function in primary hyperparathyroidism

In patients with PHPT, PTX resulted in a decrease in mean serum total calcium (2.79±0.13 vs. 2.39±0.09 mmol/liter, p<0.001) and an increase in mean plasma phosphate (0.79±0.11 vs. 0.96±0.11 mmol/liter, p<0.01) (IV). IVST, PWT and LVM tended to be reduced 2-3 months after PTX, but the changes were not significant. However, the PTX-induced change in serum total calcium was related to the change in LVM (r = 0.59, p < 0.05). PTX induced no significant changes in the Doppler or M-mode indices of LV systolic function or diastolic filling in these patients.

4. Effect of vitamin D treatment on cardiac function in secondary hyperparathyroidism

Three to 4.5 months of intravenous calcitriol therapy reduced plasma intact PTH in 9 of the 10 patients with CRF (I). Serum Ca++ increased from 1.23±0.04 to 1.33±0.04 mmol/l (p<0.01). The serum concentration of 1,25-(OH)2D3 did not increase in all patients, probably due to the pulsed periodical administration of intravenous calcitriol 1 to 3 times a week.

Calcitriol therapy caused no significant changes in cardiac function in the whole patient group. However, in a subgroup of HD patients with severe but controllable secondary hyperparathyroidism (PTH >3 times upper normal margin) the LV dimensions (LVESD 39.0±4.0 vs. 31.3±2.9mm, p=0.03; LVEDD 57.7±3.1 vs. 53.4±3.0mm, p=0.06) and systolic function (FS 33±4 vs. 42±3%, p=0.03) improved. No changes were found in IVST or PWT. The echocardiographic indices of LV diastolic filling tended to improve, but the change was not significant.

5. Effects of acute changes in serum ionized calcium on cardiac function during hemodialysis

In patients with CRF, dCa++1.25 HD induced a decrease in serum Ca++ and a slight increase in plasma intact PTH (II,III). During dCa++1.5 and dCa++1.75 HD treatments serum Ca++ increased and plasma intact PTH decreased (II,III). The HD-induced changes in arterial blood pressure, heart rate, body weight and total ultrafiltration were equal in the three sessions.
None of the three dialysis treatments with different concentrations of dialysate calcium in study II induced changes in LV systolic function or wall thicknesses. A slight decrease in Emax was seen during all sessions, while Amax remained unchanged (II). The changes in E/Amax and IVRT suggested impairment of LV relaxation on each occasion, but only during the dCa++ 1.75 HD was the impairment statistically significant (E/Amax 1.153±0.437 vs. 0.943±0.352, p<0.05; IVRT 147±29 vs. 175±50 ms, p<0.05) (II). Emax (r=-0.30, p<0.05), E/Amax (r=-0.25, p<0.05) and IVRT (r=0.25, p<0.05) correlated with serum Ca++, while no correlation was found between the echocardiographic indices and plasma intact PTH (II).

As a result of a decrease in serum Ca++, the QTc interval was prolonged during the dCa++ 1.25 HD (403±27 vs. 419±33 ms, p<0.05) (III). With dCa++ 1.5 HD the QTc interval remained stable and with dCa++ 1.75 HD it was curtailed (III). QTc dispersion tended to increase during all three HD treatments, but the dCa++ 1.25 HD was the only procedure to induce a significant increase in QTc dispersion (from 38±19 to 49±18 ms, p<0.05) (III). The change in QTc interval induced in the three study sessions with different concentrations of dialysate Ca++ correlated inversely with the change in serum Ca++ (r=-0.68, p<0.0001).
Table 2. Main findings in left ventricular structure and function in different clinical settings

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>LV structure</th>
<th>LV systolic function</th>
<th>LV diastolic filling</th>
</tr>
</thead>
<tbody>
<tr>
<td>(study IV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary hyperparathyroidism</td>
<td>LVH</td>
<td>Slightly impaired (compared to healthy controls)</td>
<td>Impaired</td>
</tr>
<tr>
<td>-effect of PTX (study IV)</td>
<td>slight decrease in LVH</td>
<td>Not affected</td>
<td>Not affected</td>
</tr>
<tr>
<td>(studies I-II)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary hyperparathyroidism</td>
<td>LVH</td>
<td>Impaired</td>
<td>Impaired</td>
</tr>
<tr>
<td>-effect of 3-4.5 months of intravenous calcitriol (study I)</td>
<td>Not affected</td>
<td>Not affected</td>
<td>Slight improvement</td>
</tr>
<tr>
<td>-effect of 3-4.5 months of intravenous calcitriol in patients with severe secondary hyperparathyroidism (study I)</td>
<td>Not affected</td>
<td>Improved</td>
<td>Slight improvement</td>
</tr>
<tr>
<td>Hemodialysis (study II)</td>
<td>Not affected</td>
<td>Not affected</td>
<td>Not affected</td>
</tr>
<tr>
<td>-dialysate Ca(^{++})1.25mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-dialysate Ca(^{++})1.50mmol/l</td>
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<td>-dialysate Ca(^{++})1.75mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemodialysis (study III)</td>
<td>Prolonged</td>
<td>Increased</td>
<td>Not affected</td>
</tr>
<tr>
<td>-dialysate Ca(^{++})1.25mmol/l</td>
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<td></td>
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<td>Stable</td>
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<td></td>
</tr>
<tr>
<td>-dialysate Ca(^{++})1.75mmol/l</td>
<td>Curtailed</td>
<td>Not affected</td>
<td></td>
</tr>
</tbody>
</table>

LV=left ventricle, LVH=left ventricular hypertrophy, PTX=parathyroidectomy
DISCUSSION

Abnormalities in LV structure and function are frequent findings in patients with primary and secondary hyperparathyroidism. However, studies evaluating the effect of calcium, PTH and vitamin D on cardiac function in these patients have yielded conflicting results. The acute changes in serum calcium which take place during HD treatment may adversely affect cardiac function, but data on this issue are limited. In the present study the roles of calcium, PTH and vitamin D in these different clinical settings were studied.

1. Cardiac structure and function in primary and secondary hyperparathyroidism

In this series LV wall thicknesses were seen to be increased in PHPT patients (IV) and in CRF patients with secondary hyperparathyroidism (I,II). This is in agreement with a number of previous reports (Stefenelli et al. 1993 and 1997a, Harnett et al. 1988, Huting et al. 1988). Hypertension is a frequent finding in these patients (Stefenelli et al. 1993 and 1997a, Parfrey et al. 1987, Harnett et al. 1988) and may account for the genesis of LVH. Eight of the 15 PHPT patients (IV) and 16 of the 22 CRF patients (I,II) had hypertension in their medical history. However, experimental studies (Mall et al. 1988) and studies on patients with PHPT (Stefenelli et al. 1997b, Piovesan et al. 1999) and CRF (Sato et al. 1995) have shown that LVH may be independent of blood pressure in these patients and may result, at least partly, from high plasma PTH concentrations (Harnett et al. 1988, Hara et al. 1995). This conception is compatible with the finding of a strong correlation between plasma PTH and LV posterior wall thickness in study I. Consequently, although hypertension seems to have a permissive role in the genesis of LVH in primary and secondary hyperparathyroidism, the increase in LV wall thicknesses may be at least partly dependent on the direct trophic effect of excess PTH on the myocardium in these patients.

The patients with primary (IV) and secondary (I,II) hyperparathyroidism evinced impairment of LV diastolic filling, which is in accord with previous findings (Ruffmann et al. 1990, Facchin et al. 1995, Ohara et al. 1995, Stefenelli et al. 1997a). Many potential factors may affect LV diastolic filling in these patients. LVH is frequently observed in both primary and secondary hyperparathyroidism and an excess of PTH is known to
induce deposition of calcium inside the myocardium (Roberts et al. 1981). These processes modulate the passive compliance of the myocardium and thus impair the late phase of LV diastolic filling. However, in CRF cardiac diastolic function does not necessarily correlate with the degree of LVH (Huting et al. 1991, Facchin et al. 1995). Similarly, in the present study no correlation was found between cardiac wall thickness and Doppler echocardiographic indices of LV diastolic filling (I). The early phase of LV filling, i.e. relaxation, is dependent on myocardial energy content and a PTH-induced increase in intracellular calcium has been shown to reduce cardiac mitochondrial energy production (Baczynski et al. 1985, Zhang et al. 1994). The impairment of LV relaxation in patients with primary or secondary hyperparathyroidism may thus also be due to this adverse effect of PTH on myocardial metabolism.

Although the M-mode echocardiography indices of LV systolic function were slightly smaller in the patients with PHPT compared to healthy control subjects, they were still within the normal ranges (IV). This finding accords with those in previous studies showing that PHPT does not affect cardiac systolic performance (Stefenelli et al. 1993 and 1997a, Ohara et al. 1995, Sato et al. 1995). Findings on the effect of secondary hyperparathyroidism on cardiac systolic function have been contradictory (Coratelli et al. 1984, Fellner et al. 1991, Huting et al. 1991, Harnett et al. 1995, Sato et al. 1995). Convincing evidence nonetheless indicates that in CRF there is an inverse relationship between LV systolic function and the severity of secondary hyperparathyroidism (Parfrey et al. 1987 and 1988, Rostand et al. 1988, Hara et al. 1995). In the present studies LV systolic function was poorer and LV dimensions greater in CRF patients with secondary hyperparathyroidism than in the healthy control subjects (I,II). As in the case of LV diastolic dysfunction, a chronic excess of PTH may impair cardiac systolic function by inducing cardiac hypertrophy and calcification with a subsequent reduction in mitochondrial energy production.

Myocardial relaxation is more sensitive to a deficiency in intracellular ATP content than is myocardial contraction (Brutsaert et al. 1984, Katz 1988). This may explain our finding that in PHPT and CRF patients with secondary hyperparathyroidism LV systolic function may be completely normal, the principal functional disorder being impaired LV diastolic filling. Accordingly, in patients with primary or secondary
hyperparathyroidism impaired LV filling may precede the impairment of cardiac systolic performance.

2. Reversibility of cardiac dysfunction in primary and secondary hyperparathyroidism

A number of studies have shown that in PHPT patients PTX and in patients with secondary hyperparathyroidism PTX or vitamin D treatment result in a reduction in LVH, which is detectable after 6-45 months of normocalcemia (Stefenelli et al. 1993 and 1997a, Sato et al. 1995, Park et al. 1999, Piovesan 1999). In other studies, however, no decrease in LV wall thicknesses has been found 1-12 months after PTX (Gafter et al. 1985, Hara et al. 1995, Stefenelli et al. 1997b). Therefore, the reduction in LVH in primary and secondary hyperparathyroidism would seem to be a protracted process. In the present series, 3-4.5 months of calcitriol therapy had no effect on LV wall thicknesses in patients with secondary hyperparathyroidism (I). In patients with PHPT there was a tendency for LVM to decrease 2-3 months after PTX (IV). It may be that the follow-up time was not long enough for more manifest structural changes to develop.

There is no agreement regarding the mechanisms by which treatment of primary or secondary hyperparathyroidism reduces LVH. Increased plasma PTH and calcium are known to have a blood pressure-increasing effect in humans. However, several authors have demonstrated that PTX or vitamin D treatment reduces LVH in these patients without lowering arterial blood pressure (Stefenelli et al. 1993, 1997a and 1997b, Park et al. 1999, Piovesan 1999). PTH has been shown to activate cardiac fibroblasts (Amann et al. 1994) and a continuous excess of intracellular calcium is known to induce myocardial disarray and hypertrophy (Pearce et al. 1985). Moreover, in CRF patients the decrease in LVM has been shown to correlate with the change in plasma PTH (Park et al. 1999). It is thus conceivable that treatment of primary or secondary hyperparathyroidism reduces LVH by abolishing the direct trophic effect of PTH on the myocardium.

The effect of PTX on LV diastolic filling in patients with primary or secondary hyperparathyroidism has been evaluated in only a few studies, and the results have been contradictory. Ohara and colleagues (1995) proposed that in patients with PHPT cardiac diastolic dysfunction is reversed 1 month after PTX. In contrast, other studies have
demonstrated no improvement after PTX and 6-12 months of normocalcemia in patients with primary (Dalberg et al. 1996, Piovesan et al. 1999) or secondary (Rostand et al. 1994) hyperparathyroidism. In the present case Doppler indices of LV inflow were not substantially altered after PTX and 2-3 months of normocalcemia in patients with PHPT (IV). In study I 3-4.5 months of calcitriol therapy induced a slight, but not significant, improvement in LV diastolic function in CRF patients with secondary hyperparathyroidism. It may be that, as in the case of LVH, longer follow-up periods are needed to obtain more conspicuous improvement in cardiac diastolic function.

The indices of LV systolic function in the patients with PHPT were within the normal ranges both before and after PTX (IV). This confirmed the earlier finding that LV systolic performance is not affected by PTX in these patients (Stefenelli et al. 1993, 1997a and 1997b, Ohara et al. 1995, Sato et al. 1995, Piovesan et al. 1999). The studies available on the effect of PTX or vitamin D treatment on LV systolic function in patients with secondary hyperparathyroidism are limited in number and have yielded contradictory results (Drueke et al. 1980, McGonigle et al. 1984, Gafter et al. 1985, Fellner et al. 1991, Hara et al. 1995). However, to judge from these reports, PTX and vitamin D treatment would appear to enhance cardiac contractile function at least in patients with pre-existing LV systolic dysfunction (Drueke et al. 1980, Coratelli et al. 1984, Hara et al. 1995). Additionally, in CRF cardiac systolic function seems to correlate inversely with the severity of secondary hyperparathyroidism (Parfrey et al. 1987 and 1988, Rostand et al. 1988, Hara et al. 1995). The results of the present series support these findings. In HD patients with pre-existing LV systolic dysfunction treatment of secondary hyperparathyroidism with intravenous calcitriol improved cardiac systolic function only in those patients with the highest levels of plasma PTH (I). PTH may thus be toxic to LV function only at relatively high plasma concentrations and, consequently, only in patients with severe hyperparathyroidism can positive effects of the therapy be expected.

3. Cardiac function during hemodialysis

Earlier studies have suggested that an increase in serum calcium during HD treatment improves cardiac systolic function (Henrich et al. 1984, Wizemann et al. 1986), while later studies have shown that HD treatment with a rise in serum calcium does not
affect LV systolic performance (Rozich et al. 1991, Sztajzel et al. 1993). This discrepancy may arise from the fact that the patients in the earlier studies were hypocalcemic prior to the HD session, while those in the later studies were already normocalcemic at the start of the dialysis treatment. In study II the HD patients, like most patients undergoing regular HD nowadays, were normocalcemic. This is probably why none of the three HD treatments in study II, with different concentrations of dialysate calcium, not even the high-calcium dialyses during which serum calcium increased to high normal (dCa\(^{++}\)1.5 HD) or hypercalcemic (dCa\(^{++}\)1.75 HD) level, induced any changes in LV systolic function. It would seem conceivable that HD, with a rise in serum calcium, improves LV systolic function only in those patients who are significantly hypocalcemic at the start of the dialysis session.

During HD fluid removal reduces cardiac preload, with subsequent changes in the indices of Doppler echocardiography (Stoddard et al. 1989, Sadler et al. 1992, Chakko et al. 1997). Accordingly, several studies have demonstrated a deterioration in LV diastolic indices during HD (Stoddard et al. 1989, Rozich et al. 1991, Chakko et al. 1997). However, acute hypercalcemia is known to impair LV relaxation (Virtanen et al. 1998) and in all of these previous studies the serum concentration of calcium increased significantly during dialysis. It has not hitherto been possible to distinguish whether the changes in serum calcium concentration, per se, have a separate and independent effect on LV relaxation properties during an HD procedure.

In the present series (II) the changes in E/Amax and IVRT suggested impairment of LV relaxation during all three HD sessions with different concentrations of dialysate calcium, but only during the dCa\(^{++}\)1.75 HD, i.e. when serum ionized calcium increased significantly, was the impairment statistically significant. Thus, the results of study II would indicate that although the Doppler indices of LV inflow decrease during HD treatment as a reflection of reduced cardiac preload, a significant deterioration in LV relaxation during an HD procedure takes place only if there is a simultaneous and marked increase in serum Ca\(^{++}\) to hypercalcemic level. In the early days of renal replacement therapy, high-calcium dialysates (1.65-1.75 mmol/l) were used in order to prevent negative calcium balance and the development of secondary hyperparathyroidism (Johnson 1976). Since the introduction of calcium salts to replace aluminium hydroxide
as phosphate binder in the 1980, there has been a tendency to lower dialysate calcium concentrations (even as low as 1.00 mmol/l) to avoid hypercalcemia (Mactier et al. 1987, Sawyer et al. 1989). However, many authors still recommend the use of high-calcium dialysates (Argiles 1995, Cunningham 2000). Judging from the findings in study II, the use of high-calcium dialysate (dCa++ 1.75) impairs cardiac relaxation and should perhaps be avoided at least when treating patients with a compromised cardiovascular system. A slightly lower dialysate calcium concentration of 1.5 mmol/l did not worsen cardiac function but nonetheless ensured a positive calcium balance by increasing serum ionized calcium to upper normal range (II).

Since changes in serum Ca++ induce suppression or stimulation of PTH secretion, it is not easy to judge the separate effects of serum calcium and PTH on cardiac function during HD. Nevertheless, in the present series (II) only serum Ca++, but not plasma PTH, correlated inversely with LV relaxation. A corresponding relationship between LV relaxation and an acute change in serum ionized calcium, but not plasma PTH, was found in a study by Virtanen and colleagues (1998). Thus, while the long-term adverse effects of CRF on cardiac structure and function may be at least partly due to a chronic excess of PTH, the acute changes in LV relaxation which occur e.g. during HD treatment may be due predominantly to changes in serum Ca++.

4. Cardiac electrical stability during hemodialysis

The arrhythmogenic effect of HD treatment is well-known (Kimura et al. 1989, Ramirez et al. 1984, Strata et al. 1994) and recent studies have shown QT dispersion, an indicator of cardiac electrical stability, to increase during the treatment (Cupisti et al. 1998, Morris et al. 1999). These arrhythmias are most probably multifactorial in origin. However, HD-induced changes in serum calcium may be involved, since the serum concentration of calcium is known to affect the electrical stability of the myocardium.

The present series was the first to evaluate the effect of dialysate Ca++ concentration on QT interval and QT dispersion (III). As expected, the changes in the QTc interval during the three HD sessions with different concentrations of dialysate calcium were inversely related to the changes in serum ionized calcium. Furthermore, the study demonstrated that the use of low-calcium dialysate (dCa++ 1.25) induces a
significant increase in QT dispersion. This finding may also have clinical consequences, as an increase in QT dispersion is known to predispose subjects to ventricular arrhythmias. During recent years there has been a tendency to reduce the dialysate calcium concentration in order to avoid hypercalcemia caused by the use of calcium-containing phosphate binders or vitamin D therapy (Mactier et al. 1987, Sawyer et al. 1989). However, the present results indicate that low-calcium dialysate (dCa$^{++}$1.25 or less) should not perhaps be used routinely due to its adverse effects on cardiac electrical stability.
SUMMARY AND CONCLUSIONS

The present studies were designed to examine the effects of calcium, parathyroid hormone and vitamin D on cardiac structure and function in various clinical situations. The studies were made on patients with primary hyperparathyroidism, secondary hyperparathyroidism due to CRF and during hemodialysis treatment.

The patients with primary hyperparathyroidism had hypertrophied LV, impaired LV diastolic filling and, when compared to the healthy controls, slightly impaired LV systolic function. A significant positive correlation was observed between serum total calcium and LVM. In spite of a decrease in serum calcium after parathyroidectomy, no improvement was found in LV function during the follow-up of 2-3 months. However, LV wall thicknesses tended to be reduced after PTX and correlated with the PTX-induced change in serum calcium. This suggests a beneficial role for PTX in the treatment of LVH in these patients, but a longer follow-up period may be needed for more obvious functional changes.

LV wall thicknesses were consistently increased in the HD patients with secondary hyperparathyroidism, and a strong correlation was found between plasma PTH and LV posterior wall thickness. M-mode and Doppler echocardiography showed marked impairment of LV systolic function and diastolic filling in these patients. Although LVH is known to induce cardiac diastolic dysfunction, no correlation was found between cardiac wall thicknesses and LV diastolic filling, while a significant inverse correlation was found between LV diastolic filling and serum calcium. Treatment of secondary hyperparathyroidism with intravenous calcitriol for 3-4.5 months reduced plasma PTH and increased serum calcium. Probably due to the relatively short duration of the calcitriol therapy, no changes were found in LV wall thicknesses. The beneficial effect of calcitriol on LV function was seen in patients with profound secondary hyperparathyroidism, in whom LV dimensions, systolic function and - to a minor extent - diastolic filling improved. Therefore, although uremic cardiomyopathy is apparently multifactorial in origin, these findings underline the role of excess PTH in the development and treatment of LV dysfunction in patients with CRF.
The effects of acute changes in serum Ca\(^{++}\) on cardiac function were studied in CRF patients on regular HD treatment. It was found that acute induction of hypercalcemia by HD with a high-calcium dialysate impairs LV relaxation. On the other hand, it was shown that the use of a low-calcium dialysate increases the QT interval and dispersion and hence may predispose HD patients to ventricular arrhythmias during treatment. Many factors contribute to the decision on dialysate calcium concentration used in a given case; the use of a phosphate binder (calcium salt or calcium-free drug), vitamin D therapy and the patient’s tendency to develop hypo- or hypercalcemia. Additionally, judging from the present findings the patient’s cardiovascular state should perhaps be taken into account. The use of the dCa\(^{++}\) 1.5 mmol/l might be advocated at least in treating patients with an unstable cardiovascular system, since it does not impair LV relaxation as does the higher calcium dialysate, and it does not increase the QT dispersion as does the lower calcium dialysate.

The present results would assign a major role for calcium, parathyroid hormone and vitamin D in regulating cardiac structure, electrical stability and systolic as well as diastolic function. The findings may be of clinical importance when treating patients with abnormal calcium metabolism, and especially patients who have pre-existing cardiac diseases.
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