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CASE REPORT

# Use of recombinant human parathyroid hormone in hypocalcemic cardiomyopathy

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## Abstract

Hypocalcemia secondary to hypoparathyroidism is a rare cause of congestive heart failure. However, its early recognition and treatment lead to significant improvement in cardiac function. We report a middle-aged woman presenting with symptoms of heart failure with a serum calcium level of 3.7 mg/dl and a serum inorganic phosphate level of 17.6 mg/dl 22 years after subtotal thyroidectomy. Besides calcium and calcitriol supplementation, she was the first patient with severe hypocalcemic cardiomyopathy to be given off-label recombinant human parathyroid hormone (PTH) because of an elevated serum calcium–phosphate product. We discuss the management and outcome of the patient and then present a brief review of similar previously reported cases. We also describe the pivotal role of calcium ion and the potential role of PTH in maintaining myocardial contractility, effective natriuresis, and possible pathogenic mechanisms contributing to heart failure secondary to hypocalcemia and hypoparathyroidism.

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## Introduction

Congestive heart failure (CHF) is a rare yet reversible complication of chronic hypocalcemia. It was first reported in 1939 in a 51-year-old lady with long-standing hypoparathyroidism (1). The exact mechanisms underlying this relationship are not completely elucidated despite the well-described role of calcium ion in cardiomyocyte excitation–contraction coupling (2). We describe the first case of hypocalcemia-induced cardiomyopathy in whom recombinant human parathyroid hormone (rhPTH) was administered, off-label, in addition to calcium and calcitriol. We then review possible mechanisms involved in the pathogenesis of this form of heart failure.

## Case report

A 56-year-old woman presented from a neighboring country on December 3, 2010, to our emergency department with a 1-month history of progressive dyspnea, orthopnea and paroxysmal nocturnal dyspnea. Work-up done in her home country 1 week before presentation revealed a left ventricular ejection fraction (LVEF) of 38%, serum creatinine of 0.9 mg/dl, and total serum calcium ($Ca^{2+}$) of 5.0 mg/dl; consequently, the patient was started on aggressive diuresis with both a loop diuretic (bumetanide) and a potassium-sparing diuretic (spironolactone), after which she reported a rapid deterioration in her symptoms.

The patient had no known cardiovascular risk factors and was not receiving any chronic medication. She denied previous tobacco or alcohol consumption. Surgical history included bilateral cataract surgery in 2009 and subtotal thyroidectomy in 1989. Since that time she had complained of diffuse muscle twitches and parasthesias along with recurrent episodes of carpopedal spasms. These symptoms were, however, not severe enough to prompt medical attention, access to which was limited in her home country, and the patient had no calcium levels measured since her thyroidectomy. Upon further questioning, the patient reported episodes of choking on both solids and liquids associated with anorexia and subjective weight loss that started a few weeks before presentation.

On examination, it was found that she had a blood pressure of 100/70 mmHg, a heart rate of 74 bpm, and a body temperature of 36.5 °C. Diffuse wheezing was noted on chest examination, her cardiac examination was unremarkable and Chvostek's and Trousseau's signs were positive.



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**Table 1** Laboratory results upon admission and before discharge with our lab's reference values.

| | Day 1 | Day 8 | 9-month follow-up | Reference values |
|---|---|---|---|---|
| Total serum calcium (mg/dl) | 3.7 | 7.5 | 7.4 | 8.5–10.5 |
| Inorganic phosphate (mg/dl) | 17.6 | 5.6 | 5.5 | 2.7–4.8 |
| Albumin (g/l) | 46 | | | 36–53 |
| Magnesium (mg/dl) | 1.7 | 1.6 | 1.9 | 1.6–2.5 |
| Creatinine (mg/dl) | 1.8 | 0.9 | 0.8 | 0.5–1.0 |
| Ionized calcium (mmol/l) | 0.54 | 1.09 | 0.96 | 1.13–1.40 |
| PTH (pg/dl) | 8.6 | | | 15.0–76.0 |
| 25-OH-vitamin D (ng/ml) | 22.2 | | 49.4 | 30.0–74.0 |
| $1,25(OH)_2$-vitamin D (pg/ml) | 46.90 | | | 20.00–46.20 |
| Troponin T (ng/ml) | 0.022 | 0.007 | | 0.000–0.030 |
| CK-MB (μg/l) | | 3.0 | | 0.0–5.0 |
| TSH (μIU/ml) | 2.460 | | | 0.27–4.20 |
| CPK (IU/l) | 7137 | 95 | | 20–165 |
| LDH (IU/l) | 634 | | | 110–265 |

CK-MB, MB isoenzyme of creatine kinase; CPK, creatine phosphokinase; LDH, lactate dehydrogenase.

Relevant laboratory findings (Table 1) included total serum calcium level of 3.7 mg/dl, albumin of 46 g/l, inorganic phosphate of 17.6 mg/dl (no evidence of *in vitro* hemolysis), creatinine of 1.8 mg/dl, and PTH of 8.6 pg/ml (normal 15.0–76.0 pg/ml; by electrochemiluminescence immunoassay on the cobas 6000, Roche Diagnostics). Initial electrocardiogram (ECG) revealed (Fig. 1A) a prolonged $QT_c$ interval of 0.65 s (normal $\leq$0.44 s) along with diffuse *T*-wave inversions; these findings are consistent with underlying hypocalcemia. On chest radiography it was observed that the cardiac silhouette was at the upper limit of normal with no radiological signs of pulmonary edema. Echocardiography revealed mild left ventricular (LV) and left atrial dilatation with severely depressed LV function (LVEF = 25–29%) and a systolic pulmonary artery pressure (PAP) of 47 mmHg. There was no evidence of valvular disease or pericardial effusion. A brain computed tomography scan was done after the patient experienced a brief convulsive episode within a few hours after presentation. It revealed calcifications of the basal ganglia bilaterally as well as both hippocampi, the cerebellum and the left peritrigonal white matter.

The patient was immediately started on i.v. calcium gluconate (initially 6 g/day), oral calcitriol at 2 μg/day, and calcium carbonate at initially 3.6 g/day shifted on day 4 to 2.4 g/day. The serum calcium level increased promptly and consistently within the first 24 h (Fig. 2B), but the serum inorganic phosphate level remained elevated despite steady improvement in renal function. Consequently, the initial calcium–phosphate product of 65.12 kept on increasing over the first 24 h averaging at 69.59 (SD 9.2); it was thus decided on the second day of admission to start the patient on s.c. rhPTH (teriparatide, Forsteo by Lilly France SAS, Fegersheim, France), at a dose of 20 μg twice daily, as an off-label use. The product dropped to 37.52 (SD 7.2) in the 24 h following the treatment. Her serum inorganic phosphate level also dropped by half after the first injection and her serum calcium level continued to rise steadily (Fig. 2A). The patient, who initially presented *in extremis*, showed marked clinical improvement with resolution of her spasms by day 2 and she was able to ambulate within 72 h. On day 8 her ECG showed normalization of the QT interval, and *T*-wave inversions were limited to the inferior leads (Fig. 1B). A cardiac catheterization revealed normal coronary arteries. Repeat echocardiography 3 days post-admission showed marked qualitative improvement of global and segmental wall motion and a decrease in systolic PAP to 24 mmHg, despite an unchanged ejection fraction of 30%. In addition, the ratio of peak early diastolic flow (*E*) to peak atrial systolic flow (*A*), known as *E*/*A* ratio, decreased from 1.26 on day 1 to 0.8 on day 3, reflecting an improvement of relaxation properties of the left ventricle.

The patient received a total of 14 g of i.v. calcium gluconate over 4 days (which corresponds to 1.26 g elemental calcium): 6 g on day 1 then tapered gradually reaching 2 g on day 4 after which she remained on oral replacement only. She was discharged on day 8 on s.c. rhPTH injections for 1 week, in addition to long-term supplementation with oral calcium carbonate (total of 2.4 g/day), calcitriol (2 μg/day) and cholecalciferol (10 000 IU/week). On the day of discharge, serum electrolytes included calcium of 7.5 mg/dl, inorganic phosphate of 5.6 mg/dl, and creatinine of 0.9 mg/dl. Similar values were obtained 9 months later when the patient came back for follow-up (Table 1), with normalization of her 25-(OH)-vitamin D level. She reported stable exercise tolerance since her discharge and her echocardiogram remained unchanged.

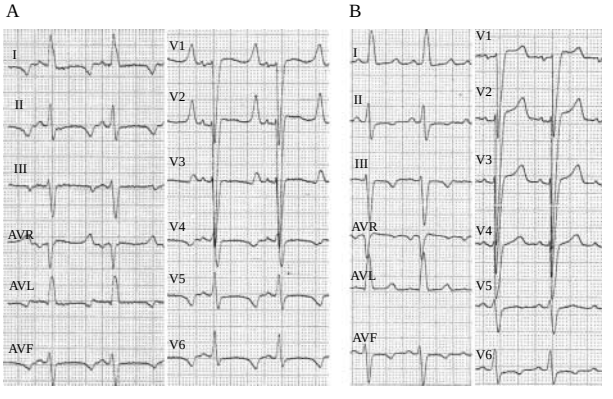


**Figure 1** (A) ECG on day 1 (Dec. 3, 2010). (B) ECG on day 8 (Dec. 10, 2010).

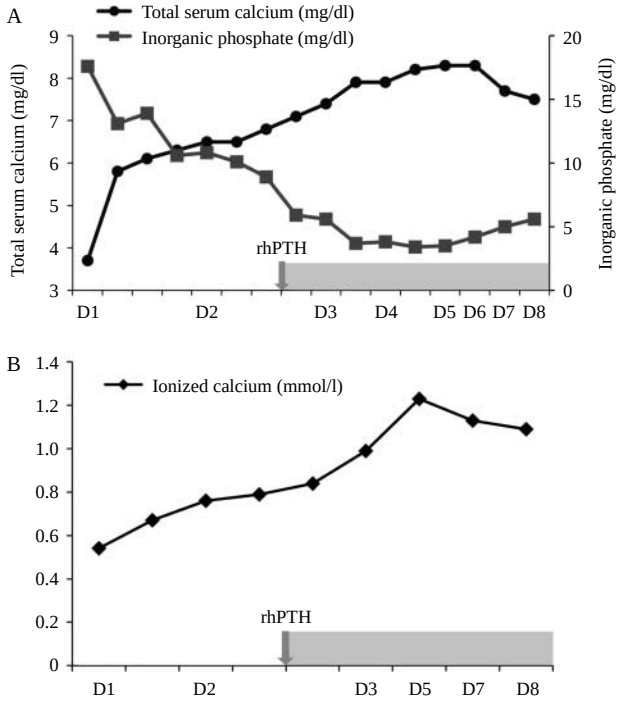


**Figure 2** (A) Total serum calcium and inorganic phosphate trends during the inpatient stay. (B) Ionized calcium trend during the inpatient stay. The patient received a total of 1.26 g of i.v. elemental calcium over 4 days: day 1: 0.54 g; day 2: 0.27 g; day 3: 0.27 g; day 4: 0.18 g. On admission she was treated with oral calcium carbonate 2.4 g/day and calcitriol 2 μg/day; and on day 2 she was started on s.c. rhPTH 20 μg twice daily.

## Discussion

Hypocalcemic cardiomyopathy has been described in more than 25 reports in the literature and in all age groups (3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33). We conducted a search in Pubmed using keywords 'hypocalcemia (all fields) AND heart failure (all fields)' yielding 221 entries. We retrieved all case reports of hypocalcemia-related heart failure written in English. In addition, references mentioned in the retrieved papers were also used.

Table 2 mentions 25 adult cases with hypocalcemic heart failure secondary to hypoparathyroidism. Unlike infants and children in whom the main cause of hypocalcemia is vitamin D deficiency (28, 32), most adult cases were secondary to either idiopathic or surgical hypoparathyroidism. There was no gender predominance and patients presented at a mean age of 49 years, with mean duration of hypocalcemia of 6.9 years (median of 3 years). The median serum calcium at presentation was 5.0 mg/dl (range 2.1–7.08 mg/dl) and serum inorganic phosphate was 7.85 mg/dl (4.7–11.61 mg/dl).

Our patient had one of the lowest serum calcium levels (3.7 mg/dl) and one of the longest durations of presumed hypocalcemia (22 years) reported till date. Moreover, she had the highest serum inorganic phosphate level reported (17.6 mg/dl). Her long-standing hypoparathyroidism was probably not the sole factor responsible for this extremely elevated inorganic phosphate level; in view of the elevated CPK and clinical presentation with severe tetany, rhabdomyolysis could have also contributed to the acute biochemical changes. In order to acutely correct these values, it was decided to treat her with rhPTH.

rhPTH treatment at a daily dose of 20 μg is only approved for adults with osteoporosis. However, two trials have investigated its use in adults with chronic hypoparathyroidism, not complicated by CHF, over periods of 20 weeks and 3 years respectively (34, 35). In both trials, treatment with rhPTH maintained serum calcium levels in the normal range, and more importantly reduced urinary calcium excretion compared with calcitriol treatment. These results were also achieved in an adult patient with postsurgical hypoparathyroidism refractory to calcitriol treated with multipulse s.c. rhPTH titrated to a total dose of 80 μg/day (36). Moreover, twice daily dosing has been shown to be more effective than once daily regimen in reducing the variation in serum calcium levels at a lower total daily PTH dose: mean of $0.62 \pm 0.45$ vs $1.48 \pm 1.29$ μg/kg per day respectively (37). Based on this trial our patient received a twice daily regimen at 0.6 μg/kg per day (20 μg twice daily). To our knowledge this is the first report in which rhPTH has been used off-label in the setting of hypocalcemic cardiomyopathy.

Our patient received a total dose of i.v. elemental $Ca^{2+}$ of 1.26 g over 4 days and did not receive any diuretic therapy or inotropes during her hospital stay; none of the previously described cases reported the total dose of i.v. $Ca^{2+}$ used and only two cases did not receive diuretics or inotropes: one of them was a young female (13) and the other had an asymptomatic decrease in his LVEF (21). We purposefully avoided diuretics to avoid further lowering of the serum-ionized calcium and exacerbation of her symptoms, as we suspected that her convulsion on presentation may have been precipitated by the loop diuretic initiated a few days before presentation to our care. It is likely that rhPTH not only decreased tubular phosphate reabsorption but also contributed to/promoted the clinical improvement by decreasing the need for i.v. $Ca^{2+}$ and avoiding the use of diuretics and inotropes. Similar to other reports, evidence for a probable causal relationship between hypocalcemia and heart failure was provided in our case by the marked improvement of cardiac function after correction of serum calcium concentration and the absence of any diagnosed etiology of heart failure.

The central role of calcium cycling in myocardial contractility was described as early as 1883 (38). L-type voltage-gated calcium channels distributed along the sarcolemmal membrane allow a transient influx of extracellular calcium into the cardiomyocyte in

**Table 2** Previously reported cases of heart failure in adult patients with hypoparathyroidism.

| Reference | Publication date | Age/ gender | Cause of hypocalcemia | Serum calcium (mg/dl) | Serum phosphorus (mg/dl) | Duration of hypocalcemia | Treatment | Time to clinical improvement | Time to symptom resolution | Change in LVEF |
|---|---|---|---|---|---|---|---|---|---|---|
| (1) | 1939 | 51/F | Surgical HPT | 5.8 | | 21 years | – | – | – | – |
| (4) | 1978 | 35/M | Idiopathic HPT | 4.0 | 11.3 | – | $Ca^{2+}$<br>DHT<br>Digoxin<br>Furosemide | – | – | – |
| (6) | 1980 | 35/F | – | 4.1 | 8.5 | 7 years | $Ca^{2+}$ and $1,25(OH)_2$ D<br>Digoxin<br>Diuretics | Few days | 6 weeks | NA |
| (7) | 1981 | 47/F | Surgical HPT | 5.6 | 7.6 | 10 years | $Ca^{2+}$ and $1,25(OH)_2$ D<br>$Mg^{2+}$<br>Diuretics | 3 days | 6 days | Poor to normal in 5 months |
| (9) | 1982 | 76/F | Surgical HPT | 5.1 | 7.2 | 11 months | $Ca^{2+}$ and $1,25(OH)_2$ D<br>Digoxin<br>Furosemide | 2 weeks | No resolution | No change in 2 weeks |
| (10) | 1985 | 39/F | Surgical HPT | 6.2 | 7.1 | 10 years | $Ca^{2+}$ and $1,25(OH)_2$ D<br>Digoxin<br>Furosemide | 3 days | 10 days | 25–50% in 10 days |
| (11) | 1985 | 61/M | Idiopathic HPT | 6 | 7.5 | – | $Ca^{2+}$ and $1,25(OH)_2$ D<br>Digoxin<br>Diuretics | – | 10 days | NA |
| (13) | 1990 | 25/F | Idiopathic HPT | 2.1 | 10 | 5 years | $Ca^{2+}$ and $1,25(OH)_2$ D | Shortly after treatment | 70 days | 17–50% in 70 days |
| (14) | 1990 | 65/F | Idiopathic HPT | 4.8 | 4.7 | – | $Ca^{2+}$ and $1,25(OH)_2$ D<br>Glucocorticoids<br>Furosemide | – | 11 days | 54–80% in 11 days |
| (15) | 1992 | 46/M | Idiopathic HPT | 5.2 | 5.5 | 20 years | – | 6 weeks | – | 33–47% in 6 weeks |
| (17) | 1997 | 46/F | Idiopathic HPT | 3.8 | 10.3 | 2 years | $Ca^{2+}$ and $1,25(OH)_2$ D<br>Inotropes<br>Diuretics | 1 day | 15 days | Severely impaired to normal in 5 months |
| (18) | 1998 | 53/F | Idiopathic HPT | 3.6 | – | – | – | – | 18 days | 23–47% in 3 months |
| (19) | 1999 | 25/F | Idiopathic HPT | 3.4 | 7.8 | 1.5 years | $Ca^{2+}$ and $1,25(OH)_2$ D<br>Furosemide | Few days | Few days | Impaired to moderately diminished |
| (20) | 2001 | 55/M | Idiopathic HPT | 3.7 | 8.4 | 3 years | $Ca^{2+}$ $Mg^{2+}$<br>ACEI<br>HCTZ | 3 days | 7 days | 20–50% in 1 week |
| (21) | 2001 | 38/M | Surgical HPT | 4 | – | 3 weeks | $Ca^{2+}$ and $1,25(OH)_2$ D | – | 3 weeks | 39–57% in 3 months |
| (23) | 2003 | 55/M | Surgical HPT | 2.8 | 10.1 | 19 years | $Ca^{2+}$ and $1,25(OH)_2$ D<br>Digoxin<br>ACEI | 2 weeks | – | NA |
| | | 46/F | Surgical HPT | 5.6 | 9.2 | 3 years | $Ca^{2+}$ and $1,25(OH)_2$ D<br>Digoxin<br>ACEI | 3 weeks | – | NA |

**Table 2** *Continued*

| Reference | Publication date | Age/ gender | Cause of hypocalcemia | Serum calcium (mg/dl) | Serum phosphorus (mg/dl) | Duration of hypocalcemia | Treatment | Time to clinical improvement | Time to symptom resolution | Change in LVEF |
|---|---|---|---|---|---|---|---|---|---|---|
| (24) | 2004 | 40/F | Surgical HPT | 3.5 | 5.7 | 3 years | $Ca^{2+}$ and $1,25(OH)_2$ D<br>Dopamine<br>Furosemide | 3 days | 8 days | 25–55% in 9 months |
| (25) | 2004 | 73/M | Idiopathic HPT | 5.36 | 9.44 | 2 months | $Ca^{2+}$<br>Inotropes | Few days | NA | Global hypokinesia to normal in 6 days |
| (26) | 2007 | 18/M | Idiopathic HPT | 7.08 | 11.61 | – | $Ca^{2+}$<br>$Mg^{2+}$<br>Inotropes<br>Digoxin | – | 16 days | 24.4–67% in 2 weeks |
| (27) | 2007 | 71/M | Surgical HPT | 6.2 | 7.4 | 4 months | $Ca^{2+}$ and $1,25(OH)_2$ D<br>Dobutamine<br>Diuretics | – | 10 days | 30–45% in 10 days |
| (29) | 2010 | 39/M | Idiopathic HPT | 5 | 7.8 | $>$3 years | $Ca^{2+}$<br>Inotropes<br>Diuretics | – | No resolution | 25–30% in 27 months |
| (30) | 2010 | 57/F | Surgical HPT | 5.1 | – | 6 months | $Ca^{2+}$ and $1,25(OH)_2$ D<br>ARB<br>Furosemide | – | – | 37–61% in 6 months |
| (31) | 2010 | 61/M | Surgical HPT | 4.2 | 7.9 | 6 months | $Ca^{2+}$ and $1,25(OH)_2$ D<br>Furosemide | – | 14 days | 32–75% in 4 weeks |
| (33) | 2011 | 76/F | Surgical HPT | 5.08 | – | 25 years | $Ca^{2+}$<br>Diuretics<br>ACEI and β-blocker | – | 2 months | 36% to normal in 2 months |

LVEF, left ventricular ejection fraction; HPT, hypoparathyroidism; DHT, dihydrotachysterol; ACEI, angiotensin converting enzyme inhibitor; HCTZ, hydrochlorothiazide; ARB, angiotensin II receptor blocker.

response to membrane depolarization. This influx triggers a massive release of calcium from the sarcoplasmic reticulum (SR) (2, 39). Calcium then binds to the troponin–tropomyosin complex allowing cross-linkage between actin and myosin and thus leads to muscle contraction (2, 39). Relaxation requires calcium dissociation and removal from the cytoplasm, back to the SR, into the mitochondria, or to the extracellular space. Based on these calcium dynamics, a dysfunction in cardiomyocyte contractility might be expected as a result of even a subtle change of extracellular calcium levels.

Although the pathophysiology of hypocalcemic cardiomyopathy is rare and only briefly mentioned in textbooks (40, 41, 42), several mechanisms based mainly on the physiologic role of calcium ion – and rarely on experimental models – have been proposed. These include the inotropic role of calcium ion acting through $Ca^{2+}$ channels and the calcium-sensing receptor (CaSR), the possible inotropic role of PTH, the effect of hypoparathyroidism on natriuresis through the tubular action of $Ca^{2+}$ and PTH, and digoxin resistance in this setting.

In contrast to skeletal muscle fibers where exchange of calcium with the extracellular space is minimal (43), contraction of cardiac muscle depends on calcium availability in the extracellular fluid as well as its release from the SR. Furthermore, the duration and amplitude of the calcium influx have been shown to affect the strength of cardiomyocyte contraction (6, 21). Experimental studies demonstrated reduced cardiac contractility in hypocalcemic states, as evidenced by decreased LV performance and cardiac index (44, 45), and suggested an increase in myocardial contractility and cardiac output with calcium correction (46, 47). However, clinical heart failure in patients with hypocalcemia is rare, probably because it is a late complication, most commonly following the onset of neuromuscular irritability (15). Also, in chronic hypocalcemic states poorly defined mechanisms may initially attempt to maintain adequate cardiomyocyte contraction, mechanisms that no longer operate effectively in severe hypocalcemia (20). Thus, myocardial dysfunction appears to be influenced not only by serum calcium concentration but also by the duration and rapidity of the change in serum calcium (19). In addition to its well-described role mediated by influx through $Ca^{2+}$ channels, the calcium ion has been recently shown to act through CaSRs in cardiac tissue and may be involved in cell cycle regulation (48, 49). Activation of the receptor has been shown to induce an increase in intracellular $Ca^{2+}$ concentration independent from extracellular $Ca^{2+}$ entry through voltage-gated channels (48). During hypoxia, this mechanism has been linked to apoptosis induced by $Ca^{2+}$ overload (50); however, in the physiological state it may contribute to myocyte contractility; thus, hypocalcemia could lead to decreased activation of the receptor and decreased myocardial contractility.

Another potential mechanism may be derived from the direct action of PTH on the heart. PTH was shown to exert a potent chronotropic effect on neonatal cardiomyocytes via activation of L-type calcium channels (51). In the adult myocardium, it increases calcium influx into the cells with no direct contractile effect (52, 53). It can, however, activate protein kinase C and increase intracellular protein synthesis. At high levels, such as those seen in end-stage renal disease, this trophic effect is deleterious and contributes to the genesis of LV hypertrophy in these patients (54, 55). At normal levels, however, this effect might be essential to maintain normal myocardial contractility.

The action of calcium and PTH on renal tubular cells and their effects on natriuresis may also be implicated in the development of hypocalcemia-induced cardiomyopathy. Previous reports suggested that activation of the CaSR in the kidney tubules reduces not only calcium but also sodium reabsorption in the thick ascending limb as well as water reabsorption in the collecting ducts (56), thereby decreasing urinary concentrating ability. In the setting of hypocalcemia we can hypothesize that the kidney would tend to retain sodium and excrete inappropriately concentrated urine, resulting in overall volume retention. However, this aberrancy in sodium and water handling is not traditionally seen in patients with hypoparathyroidism suggesting that the osmotic control of water economy by vasopressin would be more powerful and would overcome the contribution of the CaSR. PTH, on the other hand, is known to stimulate renal calcium reabsorption. A low PTH level leads to a low free cytosolic calcium concentration in the distal tubular cells, which, in turn, will increase renal sodium reabsorption through a $Na^{+}$–$Ca^{2+}$ exchange mechanism (57, 58); this phenomenon was observed in parathyroidectomized rats in which PTH infusion normalized the associated 40% reduction in renal $Na^{+}$–$Ca^{2+}$ exchange (59). Water and sodium retention may thus exacerbate heart failure in the setting of hypocalcemia (6). In our patient, rhPTH was given mainly to induce phosphaturia because of the very high serum inorganic phosphate level. However, it could have also contributed to the rapid symptomatic improvement through its effect on natriuresis.

Hypocalcemia is also known to cause resistance to the inotropic action of digitalis that usually resolves with calcium supplementation (60). However, nowadays digoxin is not used in the acute management of CHF; thus this effect did not play a role in the clinical improvement of our patient.

## Conclusion

Chronic hypocalcemia and low PTH were established as the only factors precipitating severe CHF in our patient,

potentially through multiple mechanisms. Moreover, the patient did not improve and even worsened on diuretic therapy, and, most importantly, the patient's dramatic clinical improvement and qualitative improvement in global ventricular function paralleled the restoration of serum calcium levels to low normal levels. History, work-up, and clinical course of the patient could not identify any valvular, ischemic, inflammatory, infectious, or other metabolic etiologies for the cardiac dysfunction. The direct effect of PTH on myocardial contractility and on natriuresis needs to be further elucidated, as it may have major clinical implications for the treatment of patients with hypoparathyroidism.

## Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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