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CASE REPORT
Heart failure

Fleckenstein's hypothesis revisited: excessive myocardial calcification after prolonged high dose catecholamine treatment: a case report

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Background Myocardial calcification after prolonged highly dosed catecholamine treatment has been described experimentally. Here, we demonstrate myocardial calcifications by high-dose catecholamine treatment leading to chronic heart failure in patients.

Case summary A 62-year-old Caucasian woman presented with central pulmonary embolism, developing acute heart failure, and cardiogenic shock. Twenty-six days of high-dose norepinephrine treatment had to be administered to maintain circulation. After 74 days of intensive care treatment, the patient fortunately recovered but was readmitted to emergency ward because of dyspnoea and congestion. Computed tomography pulmonary angiography ruled out recurrence of pulmonary embolism, but depicted massive intramural cardiac calcifications, which were not present before treatment. Coronary angiography showed normal coronary arteries, and myocardial biopsy excluded infectious myocarditis. There was no evidence for sarcoidosis, thyroid disease, tuberculosis, or hyperparathyroidism. Oral heart failure treatment was initiated and at the 7 week follow-up the patient remained symptomatic with New York Heart Association functional Class III, while right and left ventricular function had recovered.

Discussion Prolonged activation of the heart by catecholamines leading to myocardial calcifications has first been examined experimentally by Fleckenstein *et al*. Herein, we are able to show, that this can occur in clinical situations. Careful dosing of catecholamines and early use of non-catecholamine-based haemodynamic support is recommended to avoid consecutive impairment of heart function and heart failure.

Keywords Myocardial calcification • Congestive heart failure • Myocardium • Catecholamines • Case report

Learning points

- Significant myocardial calcification following ß-adrenergic overstimulation can also occur in patients, as shown experimentally in the animal model.
- Careful dosing of catecholamines and early use of non-catecholamine-based haemodynamic support should be taken into concern.

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Introduction

Experimentally, myocardial calcification was first described by Fleckenstein *et al.*,[1] the inventor of calcium-antagonists. Fleckenstein *et al.* hypothesized that a hyperadrenergic state can cause catecholamine-initiated excessive intracellular Ca^{2+} accumulation (EICA) through mitochondrial Ca^{2+} overloading, leading to dysfunction and structural degeneration of cardiac myocytes.[1,2] We report intramyocardial calcifications after high dose catecholamine treatment with norepinephrine.

Timeline

14 days prior to presentation	Traumatic fracture and pneumothorax after accidental stairs fall
At presentation	Dyspnoea, bilateral pulmonary embolism
Transfer to the intensive care unit	Cardiogenic shock with drop in oxygen saturation, blood pressure and centralization, ventricular fibrillation
26 days at intensive care unit	Catecholamine treatment, left ventricular ejection fraction (LVEF) 30%, ventricular fibrillation
Further 21 days at intensive care unit	Fulminant congestive liver failure and acute kidney failure, pneumonia
19 days in normal ward	Recompensation
72 days after cardiogenic shock	Readmission, in computed tomography and magnetic resonance imaging extensive hyperdense calcification of the myocardium were diagnosed
Follow up at 7 weeks	LVEF 59%, no signs for decompensation, stable heart failure Class III

Case summary

A 62-year-old woman presented 2 days after an accidental fall with traumatic rib fracture and pneumothorax to the emergency ward. Her comorbidities included arterial hypertension, glaucoma, treated normo-thyroid goitre, and postmenopausal disorder, for which she received hormonal replacement therapy. A chest drain was inserted and after successful treatment she could be discharged after 5 days. Seven days later, she presented again with dyspnoea. D-dimer result was 3.39 mg/L (normal range 0.17–0.55 mg/L), computed tomography angiography (CTA) of the chest detected bilateral central pulmonary embolisms accompanied by right ventricular enlargement, and absence of calcifications in the left ventricular (LV) wall. Troponin T value was 0.016 ng/mL (normal range ≤ 0.014 ng/mL). She was initially observed on the intensive care unit for 24 h where she was haemodynamically stable without hypoxaemia, and anticoagulation with 7.5 mg fondaparinux was initiated immediately. Subsequently, she was transferred to normal ward.

After 2 days, she suddenly deteriorated. Physical examination revealed cold sweat, hypotension (95/55 mmHg), tachycardia (110 b.p.m.), hyperventilation with orthopnoea, and cold extremity. The capillary blood gas analysis showed a respiratory alkalosis (pH 7.51; normal range 7.32–7.45), pO_2 60 mmHg (40–60 mmHg), pCO_2 22 mmHg (32–45 mmHg), HCO_3 17.6 mmol/L (normal range 25–28 mmol/L), and base excess -5.4 mmol/L (-3 till +2 mmol/L). She was retransferred to the intensive care unit, where she had to be ventilated mechanically immediately. Bedside transthoracic echocardiography showed right ventricular overload and a right to left septum shift. Left ventricular ejection fraction (LVEF) was 30%. Early after intubation she developed ventricular fibrillation and underwent cardiopulmonary resuscitation for 30 min, while 2 mg epinephrine, 300 mg amiodarone, defibrillation with 200 Joule and thrombolysis with 145 mg recombinant tissue plasminogen activator being administered. PESI-Score was 130 points. For cardiovascular support, high dose catecholamines were administered for 26 days (*Figure 1*).

Due to circulatory and rhythmic instability over 14 days she was kept in deep anaesthesia. After 8 days she had fulminant congestive liver failure with ascites. The liver functional test revealed a direct bilirubin of 6 mg/dL (<1.1 mg/dL), and the kidney functional test showed an acute kidney failure with a creatinine GFR value of 14 mL/min, and haemofiltration treatment was initiated. She spent 47 days at the intensive care unit and additional 19 days at normal ward until full recompensation and finally discharge. There was no presence of myocardial or perimyocardial infection, myocardial abscess, tuberculosis, echinococcal disease, hyperparathyroidism, or history of malignancy.

Within 6 days after discharge to a rehabilitation clinic, she was readmitted to the emergency ward because of congestion with pleural effusions. Medical history exhibit severe orthopnoea during the past days, with acute worsening at night. Auscultation of the chest revealed vesicular respiration with right basal crackles. No murmurs were present. Examination of the lower limbs showed no oedema or clinical signs of deep vein thrombosis. Transthoracic echocardiography disclosed bilateral pleural effusions, moderate mitral regurgitation II–III°, severe right ventricular dysfunction, a restrictive LV pattern *E/A* 2.2, and a reduced ejection fraction (LVEF 35%). NT-pro BNP was 6211 pg/mL (<247 pg/mL) and troponin T 0.028 pg/mL (≤0.014 ng/mL).

Due to d-dimer value was 1.63 mg/L another native and contrast enhanced CTA study of the chest with ECG synchronization was investigated, which excluded recurrence of pulmonary embolism, but showed right-side accentuated pleural effusion and depicted extensive hyperdense calcifications of the myocardium with subepicardial and intramural localization (*Figure 2*), which were not present before catecholamine treatment. Cardiac catheterization disclosed normal coronary arteries. In line with the computed tomography (CT) study, subepicardial and intramural late gadolinium enhancement was detected in cardiac magnetic resonance imaging (*Figure 3*), which was further investigated by myocardial biopsy without evidence of a chronic myocarditis, cardiotropic viruses, bacterial infection, endocardial fibrosis, or eosinophilic endocarditis (*Figure 4*). Culture of mycobacterium tuberculosis and tuberculosis specific testing of T-cells remained negative. Leucocyte count, differential blood count, and immunelectrophoresis were normal. Serological testing ruled

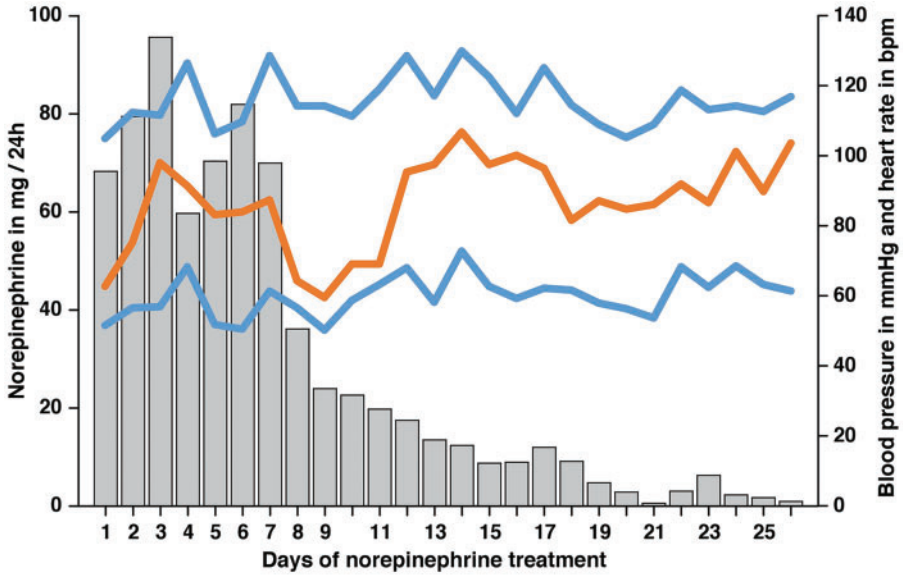

Figure 1 Total doses of norepinephrine in mg/24 h (bars) and course of systolic and diastolic blood pressure (blue lines) and heart rate (red line) over time.

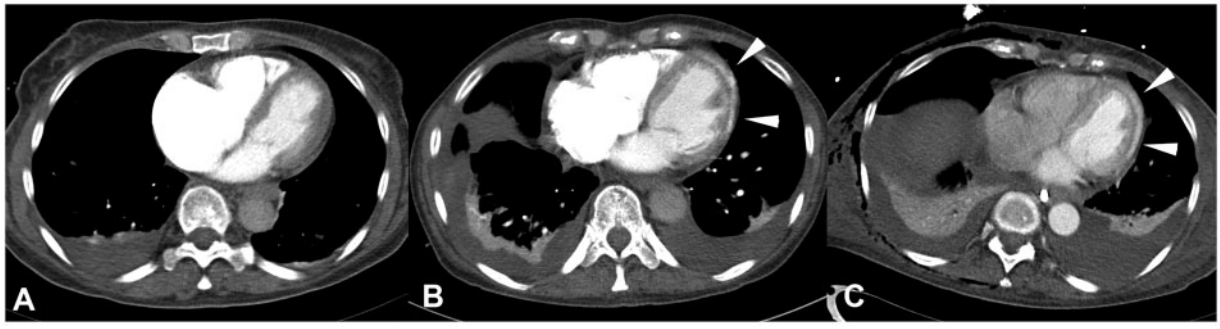

Figure 2 Initial contrast-enhanced computed tomography of the thorax (*A*) demonstrating a normal density of the left ventricular myocardium. At that time pulmonary embolism was demonstrated. On corresponding follow-up computed tomography scans 2 weeks (*B*) and 2 months later (*C*) the left ventricular myocardium depicts markedly hyperdense areas at the apex and the lateral wall suggestive of diffuse calcifications (arrowheads).

out an acute Hepatitis A, B, C, CMV, HSV 1 and HSV 2, VZV, rubella virus, measles, mumps, EBV, and Parvovirus B19 infection. ANA- and ANCA-Screenings were negative. There were normal values for calcium 2.3–2.5 mmol/L (normal range 2.2–2.6 mmol/L), PTH 31 pg/mL (normal range 15–65 pg/mL), and TSH 3.32 µIU/mL (normal range 0.27–4.20 µIU/mL), while she was substituted with L-thyroxin 25 µg per day after prolonged intensive care stay. Further, there was no evidence for malignancy.

The patient received loop diuretic treatment (torasemid 10 mg) and heart failure medication (5 mg bisoprolol, 2, 5 mg ramipril, 10 mg ivabradine, 25 mg eplerenone per day), was stabilized and followed up in our outpatient clinic. An improvement of the LVEF to 59% could be detected by echocardiography after about 7 weeks and the right ventricular function had recovered. She was physically weak, hypotonic and in New York Heart Association (NYHA) functional class III heart failure. To do strength training she was referred to the fitness centre. In the 2 years follow-up, she was free of malignancy development.

Discussion

About 50 years ago, Fleckenstein hypothesized that excessive catecholamine excess may lead to calcium overload.[1] To our knowledge, no direct report of such an effect is proven to be true in humans. Mechanistically, catecholamines induce excessive

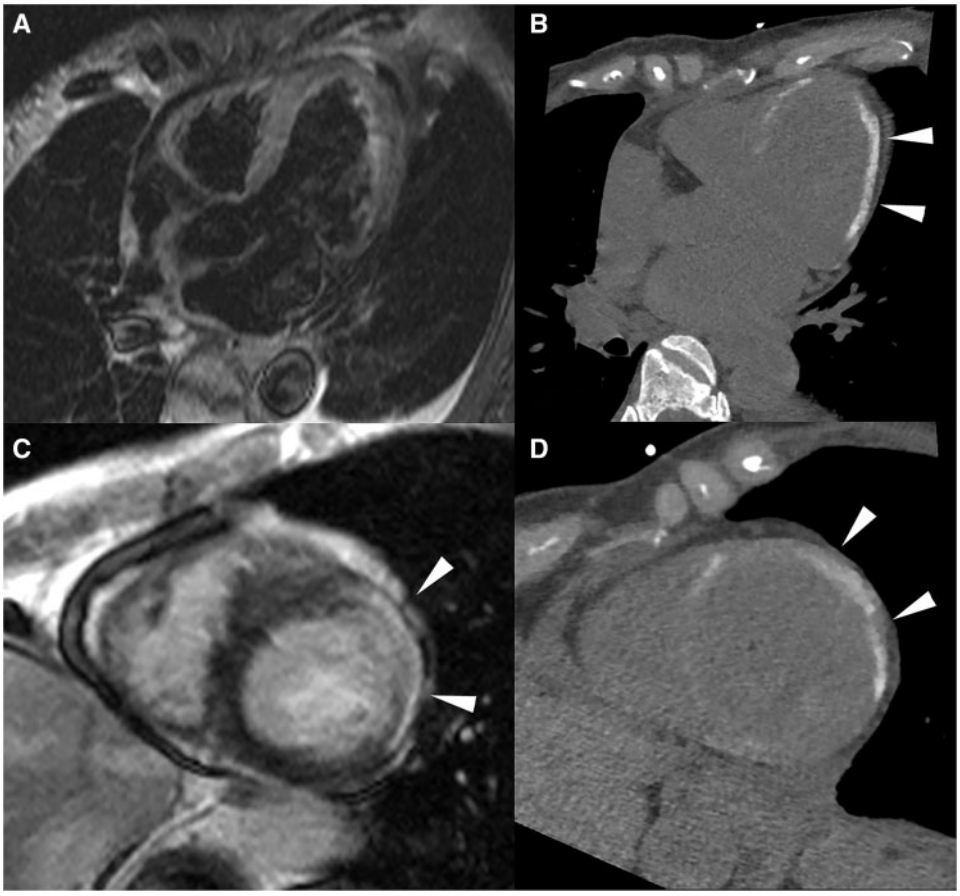

Figure 3 Cardiac magnetic resonance imaging (*A* and *C*) and computed tomography (*B* and *D*) acquired with ECG synchronization. On T2-weighted STIR images in three-chamber view (*B*) the left ventricular myocardium shows a normal signal intensity without signs of myocardial oedema. T1-weighted inversion-recovery sequences in short-axis orientation (*C*) after intravenous application of contrast show a marked late gadolinium enhancement of the anterior and anterolateral aspects of the left ventricular wall (arrowheads). *B* and *C* display corresponding multiplanar reconstructions in three-chamber view and short-axis orientation of the unenhanced cardiac computed tomography scan with ECG synchronization. Note again the markedly hyperdense depictions of the left ventricular wall corresponding to diffuse calcifications.

intracellular calcium accumulations via ß-adrenergic receptor stimulation, which will be followed by mitochondrial swelling and intracellular calcium overload.[2] Uncoupling of inhibitory G-proteins (Gi) with pertussis toxin resulting in unopposed beta-adrenergic stimulation has been shown to be accompanied by cellular calcium overload.[3] In a known form of catecholamine-related cardiomyopathy, namely Tako-Tsubo cardiomyopathy, activation of sympathetic nervous system enhances both, sarcoplasmic Ca^{2+} uptake through the long-term calcium channel and phosphorylation of phospholamban which increases intracellular Ca^{2+} storage.[4] Other causes can be metastatic myocardial calcification as in the case of hyperparathyroidism[5] or haemodialysis,[6] previous myocardial infarction with scarring, secondary calcification of myocardial fibrotic lesions, sarcoidosis, and infections such as viral, bacterial or fungal myo- and perimyocarditis, myocardial abscess, cardiac tuberculosis, and echinococcal disease.[7] An intensive search excluded these causalities. With the absence of pathological mediastinal lymph nodes and no granulomas on myocardial biopsy, cardiac sarcoidosis was excluded. No other organ calcifications were depicted.

In one case series, a link between hypothyroidism and calcifications in the brain was described. These individuals appeared to be normal in neonatal thyroid stimulating hormone screening, but developed various degrees of hypothyroidism in infancy accompanied by multiple calcifications of the basal ganglia and subcortical areas.[8] Hypothyroidism was also excluded in this case, because CT-scan before catecholamine treatment showed a calcification free left ventricle and the patient only had moderate hypothyroidism with normal TSH values, only occurring after prolonged intensive care treatment. Soft tissue calcifications as a consequence of hypoparathyroidism, as described previously,[9] were also excluded. Calcifications to an extent as described herein have not been reported in this condition.

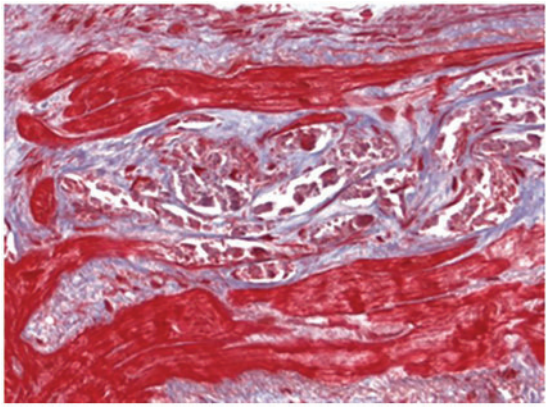

Figure 4 Histology in Masson Trichrome staining showing replacement of ventricular myocardium by calcificated components.

Conclusion

In summary, Ca^{2+}-overload, as suggested by Fleckenstein *et al.*,[1] with subsequent calcification appears to be of clinical relevance in patients requiring high-dose catecholamine treatment. This finding favours non-pharmacological approaches for haemodynamic stabilization.[10] Novel approaches to prevent catecholamine-induced calcifications appear to be warranted.[11]

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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