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CASE REPORT

Complete recovery of fulminant peripartum cardiomyopathy on mechanical circulatory support combined with high-dose bromocriptine therapy

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Abstract

Peripartum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy presenting with heart failure due to left ventricular systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found. We report a case of a woman with PPCM who developed a critical cardiogenic shock with repeated cardiopulmonary resuscitation. We show for the first time that mechanical circulatory support combined with high-dose bromocriptine therapy to suppress systemic prolactin levels may serve as an effective therapeutic option in patients with fulminant PPCM and cardiogenic shock. Myocardial cathepsin D was overexpressed in our patient underscoring a potential role of cathepsin D-induced cleavage of prolactin in the pathophysiology of PPCM.

Keywords Peripartum cardiomyopathy; ECLS; Bromocriptine; Prolactin; Cathepsin D

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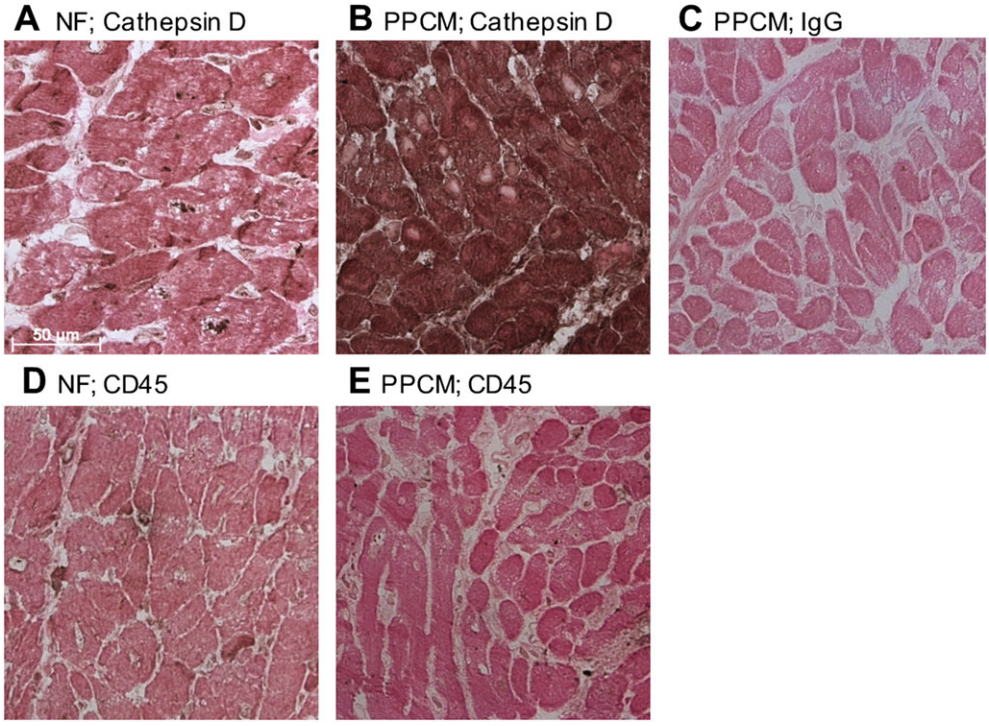
Introduction

Peripartum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy presenting with heart failure due to left ventricular (LV) systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found.[1,2] A cleaved 16 kDa fragment of the nursing hormone prolactin is considered as crucial in the pathophysiology of PPCM.[1,2] Feasibility of prolactin suppression by bromocriptine is currently investigated in women with PPCM in a multicentre prospective randomized trial.[3] Mechanical circulatory support (MCS) may bridge patients with fulminant cardiogenic shock to recovery or to heart transplantation.

Case report

A 30-year-old woman—4 months after uncomplicated delivery—developed critical cardiogenic shock with repeated cardiopulmonary resuscitation in a peripheral hospital. Initially, the patient had complained about dyspnoea and was treated for suspected postpartum depression by her gynaecologist. The patient remained in critical cardiogenic shock with severely reduced LV function and profound LV dilation. Therefore, remote implantation of an arterio-venous femoro-femoral extracorporeal life support was performed on an emergency basis by our mobile MCS service as bridge-to-decision strategy, and the patient was transferred to our university heart centre.[4] Administration of inotropes could be stopped on MCS. Coronary artery disease was excluded by coronary angiography. Endomyocardial biopsy during MCS revealed no active inflammation but enhanced expression of cathepsin D compared with non-failing heart samples (*Figure 1*). Cerebral computer tomography showed no pathologies after prolonged resuscitation. On admission, a prolactin value of 36.6 ng/mL was measured representing normal range for a lactating mother months after delivery. The patient received 5 mg/day bromocriptine administered by gavage (according to the PPCM study protocol). Prolactin value decreased to 10.1 ng/mL at day 1. Effective prolactin

Figure 1 Representative immunohistochemical staining of endomyocardial samples from a patient with non-failing heart compared with biopsy sample from the patient with peripartum cardiomyopathy (PPCM) and cardiogenic shock. Cathepsin D expression in myocardial tissue is enhanced in the patient with PPCM (B) compared with non-failing hearts (A) or myocardial sample stained with isotype control (C). Inflammation level as indicated by staining for the pan-inflammatory marker CD45 (brown; counterstaining with eosin, pink) did not differ between a non-failing heart (D) and the patient with PPCM (E).



suppression (1.5–3.5 ng/mL) was finally achieved by administration of 10 mg/day of bromocriptine. LV function improved gradually and weaning from MCS was accomplished at day 4. Bromocriptine therapy was continued for 8 weeks. Following 1 month of optimal medical heart failure therapy, we documented complete recovery of LV function and normalizing of left ventricular cavity after 3 months assessed by magnetic resonance tomography. At 12 months follow-up, the LV function remained normal and the patient was free from heart failure symptoms and without neurological deficits (Cerebral Performance Category Scale 1).

Discussion

We show for the first time that (i) MCS combined with high-dose bromocriptine therapy may serve as an effective therapeutic option in patients with fulminant PPCM and cardiogenic shock, (ii) higher bromocriptine dosing may be required for effective suppression of systemic prolactin levels in a critically ill patient, and (iii) cathepsin D is overexpressed in myocardial samples of a patient with PPCM, thus underscoring a potential role of cathepsin D-induced cleavage of prolactin in the pathophysiology of PPCM.

In severe cases of PPCM, where progressive LV failure leads to critical cardiogenic shock, MCS may serve as ultimate rescue therapy to gain some time until specific therapy (e.g. bromocriptine) unfolds its therapeutic effects (bridge to recovery) or until implantation of long-term left ventricular assist device (LVAD) or heart transplantation is pursued (bridge to LVAD/bridge to transplantation).[5,6] In contrast, high-dose inotropes were recently considered to be detrimental in PPCM,[7] and therefore, MCS should be considered in patients with cardiogenic shock due to PPCM.[1,6,8] However, here, clinical experience is particularly limited. In the present case, MCS implantation was performed successfully to bridge fulminant shock without inotropes and to initiate bromocriptine therapy.

Experimental and clinical data suggest that a cascade involving oxidative stress, the prolactin-cleaving protease cathepsin D, and 16 kDa prolactin play a crucial role in the development and progression of PPCM. Oxidative stress appears to trigger induction of cathepsin D in cardiomyocytes. Cathepsin D subsequently cleaves prolactin into an angiostatic and pro-apoptotic subfragment. Patients with acute PPCM reveal enhanced systemic markers of

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oxidative stress, as well as increased serum levels of activated cathepsin D, total prolactin, and the cleaved prolactin fragment.[9] Here, we were able to demonstrate by endomyocardial biopsy that cathepsin D expression in myocardial tissue is enhanced in a patient with PPCM compared with non-failing hearts corroborating a role of cathepsin D-mediated cleavage in the pathopyhsiology of PPCM (*Figure 1*). CD45-positive inflammatory cells did not differ between PPCM and non-failing hearts.

Adressing the cathepsin D–prolactin cascade could be a reasonable approach in the management of PPCM. Although evidence-based data from randomized clinical trials are limited, preliminary studies demonstrated that bromocriptine in addition to standard therapy of heart failure may serve as the first disease-specific treatment in PPCM. In rodents, suppression of prolactin production via the D_2 receptor agonist bromocriptine prevented the onset of PPCM.[9] In a small proof-of-concept trial, patients receiving bromocriptine in addition to standard heart failure therapy revealed greater recovery of LV function compared with patients on standard therapy only.[10] We can only speculate about the clinical course in the case of MCS alone without bromocriptine administration in our patient. Currently, a randomized clinical study evaluates the efficacy of prolactin blockade by bromocriptine in addition to standard therapy for heart failure.[3]

We show for the first time that bromocriptine administration and resorption by gavage is feasible and effective in decreasing the prolactin levels in a critically ill patient. Here, higher bromocriptine dosing was required for effective suppression of systemic prolactin levels that may mirror altered absorption of the drug or even altered pharmacokinetics compared with stable patients. Although the data about target prolactin level are limited, the acute suppression of prolactin levels after starting bromocriptine therapy in our study might indicate suppression of the 16 kDa prolactin and its deleterious effects on the myocardium. As a limitation, levels of 16 kDa prolactin have not been quantified separately in this study. As thromboembolic events have been reported during the use of bromocriptine, treatment should always be accompanied by at least prophylactic anticoagulation with heparin.[6] In our case, the LV function improved and weaning from MCS was achieved within 4 days. Normalizing of left ventricular cavity at follow-up indicated physiologic LV remodelling.

Conclusions

Mechanical circulatory support combined with high-dose bromocriptine therapy may serve as an effective therapeutic option in patients with fulminant PPCM. During MCS, the bromocriptine effect on prolactin is not impaired, but potentially higher drug dosage may be required.

Conflict of interest

None declared.

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