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ORIGINAL ARTICLE

Cabergoline treatment promotes myocardial recovery in peripartum cardiomyopathy

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Abstract

Aims Peripartum cardiomyopathy (PPCM) is a rare heart disease, occurring in previously heart-healthy women during the last month of pregnancy or the first months after delivery due to left ventricular (LV) systolic dysfunction. A common pathomechanistic pathway of PPCM includes increased oxidative stress and the subsequent generation of a cleaved prolactin fragment (16 kDa PRL), which promotes the onset of heart failure (HF) in a microRNA (miR)-146a-dependent manner. Inhibition of prolactin secretion with the dopamine D2 receptor (D2R) agonist bromocriptine combined with standard HF therapy supports cardiac recovery. This study examined whether treatment with the more selective D2R agonist cabergoline prevents HF development in an experimental PPCM mouse model and might be used as an alternative treatment regime for PPCM.

Methods and results Postpartum (PP) female PPCM-prone mice with a cardiomyocyte restricted STAT3-deficiency (αMHC-Cre$^{tg/+}$; Stat3$^{fl/fl}$; CKO) were treated over two consecutive nursing periods with cabergoline (CKO Cab, 0.5 mg/kg/day) and were compared with bromocriptine treated CKO (CKO Br) and postpartum-matched WT and CKO mice. Cabergoline treatment in CKO PP mice preserved cardiac function [fractional shortening (FS): CKO Cab: 34.5 ± 9.4% vs. CKO: 22.1 ± 9%, $P < 0.05$] and prevented the development of cardiac hypertrophy, fibrosis, and inflammation as effective as bromocriptine therapy (FS: CKO Br: 33.4 ± 5.6%). The myocardial up-regulation of the PPCM biomarkers plasminogen inhibitor activator 1 (PAI-1) and miR-146a were prevented by both cabergoline and bromocriptine therapy.

A small cohort of three PPCM patients from the German PPCM Registry was treated with cabergoline (1 mg per week for 2 weeks, followed by 0.5 mg per week for another 6 weeks) due to a temporary unavailability of bromocriptine. All PPCM patients initially presented with a severely reduced LV ejection fraction (LVEF: 26 ± 2%). However, at 6 months of follow-up, LV function (LVEF: 56 ± 2%) fully recovered in all three PPCM patients, and no adverse events were detected.

Conclusions In the experimental PPCM mouse model, the selective D2R agonist cabergoline prevents the onset of postpartum HF similar to bromocriptine. In PPCM patients, cabergoline treatment was safe and effective as all patients fully recovered. Cabergoline might serve as a promising alternative to bromocriptine. However, these findings are based on experimental data and a small case series and thus have to be interpreted with caution and should be validated in a larger clinical trial.

Keywords Peripartum cardiomyopathy (PPCM); Dopamine D2 receptor agonist; Bromocriptine; Cabergoline; Heart failure

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Introduction

Peripartum cardiomyopathy (PPCM) is a rare heart disease in previously heart-healthy women presenting with heart failure (HF) secondary to left ventricular (LV) systolic dysfunction, which occurs during the last month of pregnancy or in the first months after delivery, where no other cause of HF can be identified. PPCM is characterized by HF due to LV dysfunction with an LV ejection fraction (LVEF) $< 45\%$.[1] Impairment of the vascular system is a major factor in the development of PPCM. A common pathomechanistic pathway of PPCM seems to include enhanced unbalanced oxidative stress and the subsequent generation of a cleaved prolactin fragment (16 kDa prolactin, 16 kDa PRL), which promotes in a nuclear factor kappa-B (NF- κB)-dependent manner the up-regulation of microRNA (miR)-146a in endothelial cells.[2,3] MiR-146a mediates vascular pro-apoptotic and anti-angiogenic effects of 16 kDa PRL and exerts adverse cardiac effects via exosomal transfer of miR-146a to cardiomyocytes associated with a reduced metabolism and an impaired cardiac ErbB4 signalling.[2,3] Female mice with a cardiomyocyte-specific deficiency of signal transducer and activator of transcription 3 (STAT3) (αMHC-Cre$^{tg/+}$; Stat3$^{fl/fl}$; CKO) develop HF after two consecutive pregnancies and nursing periods, a phenotype highly similar to PPCM, due to the described 16 kDa-PRL pathomechanism.[2,4,5] Decreased cardiac STAT3 expression was also observed in PPCM patients.[4,6]

Compared with patients suffering from other forms of cardiomyopathy (e.g. dilated cardiomyopathy), most PPCM patients have a high potential for cardiac recovery.[7,8] The inhibition of the prolactin secretion from the pituitary gland with the dopamine D2 receptor (D2R) agonist bromocriptine mediates beneficial effects on cardiac function in the experimental PPCM CKO mouse models and is associated with cardiac recovery in clinical studies.[4,7,9–11] The therapy recommendation for PPCM patients currently includes standard HF therapy with angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers/angiotensin receptor neprilysin inhibitors (ARNI), beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose co-transporter 2 (SGLT2) inhibitors in combination with bromocriptine (known as BOARD concept).[7,12,13] In addition, elevated circulating plasminogen activator and inhibitor 1 (PAI-1) and miR-146a levels act as biomarkers for detecting acute PPCM.[2,5,14]

Due to the global market situation and production shortage, bromocriptine was temporarily unavailable, making it necessary to treat PPCM patients with alternative D2R agonists. The various D2R agonists differ in their selectivity for D2 and D1 receptors and show different affinities for serotonin and adrenergic receptors. Therefore, it is unclear whether they have similar efficiency concerning the treatment of PPCM. Furthermore, they may also influence other signalling pathways, such as inflammation.

Here, we investigated the efficacy of the more selective D2R agonist cabergoline compared with the well-established bromocriptine treatment in the PPCM CKO mouse model. Furthermore, we present the first data regarding cabergoline treatment from a small cohort of PPCM patients from the PPCM German Registry.

Methods

Animal experiments

All animal studies were in accordance with the German animal welfare legislation and with the European Communities Council Directive 86/609/EEC and 2010/63/EU to protect animals used for experimental purposes under consideration of the ARRIVE guidelines. Furthermore, the experiments were approved by the local Institutional Animal Care and Research Advisory Committee and permitted by the local authority, application number 33.19-42502-04-16/2253.

Cardiomyocyte-specific STAT3 knockout mice

The generation of mice with cardiomyocyte-restricted deletion of STAT3 (*αMHC-Cre$^{tg/+}$*; *STAT3$^{fl/fl}$* mice, CKO) has been described previously.[4,15] As reported before, female CKO mice show a phenotype of postpartum HF after two pregnancies and nursing periods.[2,4,16] In the present study, the same established experimental set-up was used. Wild-type (STAT3$^{flox/flox}$, WT) and CKO mice were subjected to two consecutive pregnancies and were analysed postpartum after the second nursing period (PP). In addition, CKO females were randomized to either treatment with bromocriptine (4 mg/kg/day, in drinking water, Novartis) or cabergoline (0.5 mg/kg/day, in drinking water, Dostinex®, Pfizer Pharma PFE GmbH), starting 3 days before to 3 weeks after delivery for two consecutive pregnancies and nursing periods. In addition, echocardiography was performed in sedated mice (2% isoflurane inhalation, connected to a rodent ventilator) and determined in PP mice after the second nursing period (17–19 days after delivery) using a Vevo 770 and 3100 (Visual Sonics) as described[4,6] by an investigator, blinded for the randomization.

Histology and immunostaining

For cardiac morphological analyses, hearts were embedded in OCT Tissue-Tek and frozen at −80°C. Cardiac cryosections were stained with H&E as described.[15] Interstitial collagen was analysed in picro-Sirius red F3BA-stained LV cryosections.[15] Cardiomyocyte cross-sectional area (CSA) was determined in longitudinal 6-μm LV cryosections stained with

rhodamine-labelled wheat germ agglutinin (dilution 1:150; WGA, RL-1022, Vector Laboratories) and Hoechst 33258 (Sigma-Aldrich) for nuclear staining.[17] At least a minimum of 50 representative cardiomyocytes (three sections/heart) were measured per heart. Inflammation was stained in LV cryosections with antibodies recognizing the monocyte–macrophage marker CD68 (dilution 1:1000; abcam ab53444) counterstained with WGA and Hoechst 33258 as described.[18] Images were acquired by fluorescence and bright-field microscopy using Axio Observer 7 and Zen 2.6 pro software (Carl Zeiss Jena).

RNA isolation, cDNA synthesis, qRT-PCR, and miR-qRT-PCR

Total RNA from adult murine hearts was isolated with TRIzol® Reagent (Life Technologies) in accordance with the manufacturer's instructions. cDNA synthesis using Superscript III (Invitrogen), 2 μg of total RNA, and random hexamer primers (Sigma-Aldrich) was performed according to the manufacturer's protocols as previously described.[18] Semi-quantitative real-time PCR using the SYBR green dye method (SYBR Green qPCR 2X Master Mix Kit, Thermo Fisher Scientific) was performed with the AriaMX Real-Time PCR System (Agilent Technologies). Sequences of qRT-PCR primers used in this study are provided below. mRNA expression levels were normalized using the $2^{-\Delta\Delta CT}$ method relative to 18S.

Expression of mature miR-146a (Applied Biosystems) was determined using miR-qRT-PCR on an ABI7500 cycler (Applied Biosystems) and was normalized using the $2^{-\Delta\Delta CT}$ method relative to U6 as described.[2]

Sequences of qRT-PCR primers

mRNA	Sense primers (5′ to 3′)	Antisense primers (5′ to 3′)
mmu *18S*	GTAACCCGTTGAACCCCATT	CCATCCAATCGGTAGTAGCG
mmu *Adrge1*	GAGACATCCACTCTGGGCAC	GGGGCCCCTGTAGATACTGA
mmu *Ankrd1*	ATAAACGGACGGCACTCCAC	CATCTGCGTTTCCTCCACGA
mmu *Anp*	GCCGGTAGAAGATGAGGTCA	GGGCTCCAATCCTGTCAATC
mmu *Bnp*	ATCCGATCCGGTCTATCTTG	CCAGTCTCCAGAGCAATTCA
mmu *Col1a1*	ACAGACGAACAACCCAAACT	GGTTTTTGGTCACGTTCAGT
mmu *Il-6*	TTTCTCATTTCCACGATTTCC	CCATCCAGTTGCCTTCTTG
mmu *Pai-1*	AGTCAATGAGAAGGGCACAGC	GACAAAGATGGCATCCGCAG
mmu *Tgfß2*	CCCTCCGAAAATGCCATCCC	TGCTATCGATGTAGCGCTGG
mmu *Tnf-α*	GGTGCCTATGTCTCAGCCTCTT	GCCATAGAACTGATGAGAGGGAG
mmu *Vcam-1*	ACTTGTGGAAATGTGCCCGA	AGATGCGCAGTAGAGTGCAA

Protein isolation, SDS-PAGE, and western blot

Protein expression levels were determined by western blotting using SDS-PAGE as described.[18] In brief, total protein was isolated by lysing frozen LV tissue in RIPA buffer supplemented with 10 μM 1,4-dithiothreitol (Sigma-Aldrich) and protease/phosphatase inhibitor cocktail (Roche Diagnostics) on ice. For SDS-PAGE, 50 μg protein was loaded and blotted to a nitrocellulose membrane after separation. The following primary and secondary antibodies were used: ANKRD1 (dilution 1:1000; Santa Cruz Biotechnology, Inc., sc-365056), PAI-1 (dilution 1:1000; abcam, ab182973), and donkey anti-rabbit IgG, peroxidase-linked species-specific whole antibody NA934V (dilution 1:3000; GE Healthcare). Chemiluminescence detection was carried out after incubation with enhanced chemiluminescence reagents (PerkinElmer) using the ChemiDoc™ MP system (Bio-Rad). Image LabV5.0 software (Bio-Rad) was used for quantification.

Patients: Data collection

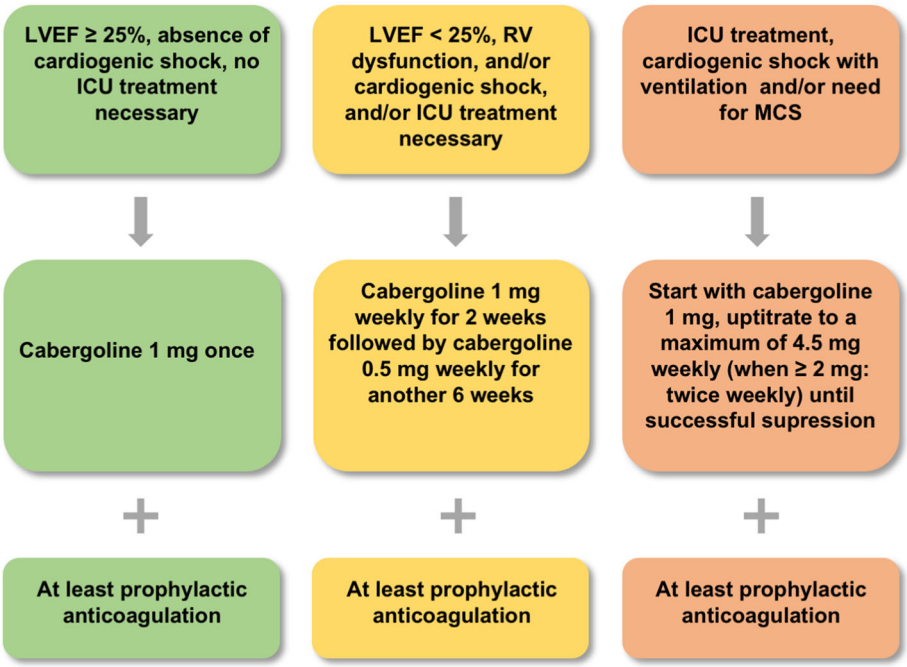
The local ethics committee of Hannover Medical School, Hannover, Germany, approved this study (approval number 10321_BO_K_2022). The study conforms to the principles outlined in the Declaration of Helsinki, and all patients provided written informed consent. Inclusion criteria were a diagnosis of PPCM, according to the definition provided in the position statement from the HF Association of the European Society of Cardiology (ESC) Study Group on PPCM[1,19] and treatment with the D2R agonist cabergoline. Cabergoline treatment has been carried out according to the cabergoline treatment regimen for PPCM patients from Hannover Medical School (*Figure 1*).

Clinical assessments such as the onset of symptoms and signs of HF, New York Heart Association (NYHA) functional class, ECG, echocardiographic analyses, cardiac magnetic resonance imaging (MRI), family history, and mode of delivery were obtained from the PPCM patients at diagnosis (baseline,BL) and at follow-up (FU) 3 and 6 months after diagnosis.

Blood tests

Blood samples were collected in S-Monovette® tubes containing ethylenediaminetetraacetic acid (EDTA, for plasma) or clot activator (for serum) at BL and at FU in all three PPCM patients. In addition, laboratory workup was performed as part of the routine analysis by hospital laboratories for N-terminal pro-brain natriuretic peptide (NT-proBNP) and prolactin at BL and at 3 M and 6 M FU and for troponin T (TNT), creatine kinase (CK) creatinine, and glomerular filtration rate (GFR) at BL.

Figure 1 Scheme for cabergoline treatment of acute PPCM at Hannover Medical School. Flow chart illustrating the cabergoline treatment regime used in the PPCM registry at Hannover Medical School. ICU, intensive care unit; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support, for example, extracorporeal membrane oxygenation, percutaneous micro axial pump; RV, right ventricle.



Statistical analyses

Statistical analysis was performed using GraphPad Prism version 7.0 or 8.0 for Mac OS X (GraphPad Software, San Diego, CA, USA). The Shapiro–Wilk test was used to test the data against the hypothesis of normal distribution. Continuous parametric data were expressed as mean ± SD, and in the case of non-parametric data, the median and (interquartile) range were reported. Between-group comparisons were analysed using a univariate one-way ANOVA, followed by post hoc tests. Multiple comparisons were adjusted with the Bonferroni criterion, and control-to-treatment contrasts were tested with Dunnett's test. In the case of non-parametric data, between-group comparisons were tested with the Kruskal–Wallis test, followed by Dunn's test for multiple comparisons. A P value of <0.05 was considered statistically significant.

Results

Treatment with cabergoline prevented the onset of PPCM in CKO postpartum mice

To investigate the efficacy of cabergoline in comparison with bromocriptine in the PPCM CKO mouse model, CKO PP mice were treated over two consecutive nursing periods (3 days before delivery until 21 days after delivery) with cabergoline (CKO Cab) or bromocriptine (CKO Br) compared with postpartum-matched WT and CKO females (*Figure 2A*). As previously shown, CKO PP mice developed HF after two pregnancies and nursing periods, characterized by a marked LV systolic dysfunction compared with WT PP mice, which could be prevented by bromocriptine treatment (*Table 1* and *Figure S1A–E*). Furthermore, cabergoline treatment was associated with comparable effects to bromocriptine treatment in terms of preventing HF in CKO PP mice (*Table 1* and *Figure S1A–E*). Survival was comparable between CKO PP mice treated with bromocriptine or cabergoline and WT PP (*Table 1*).

Treatment with cabergoline attenuated the development of cardiac hypertrophy in CKO postpartum mice

As previously shown, CKO PP mice develop cardiac hypertrophy characterized by an increased heart weight (HW), HW/body weight (BW) ratio, HW/tibia length (TL) ratio, an elevated mRNA expression of the hypertrophic and HF marker *atrial natriuretic peptide* (*Anp*) and *brain natriuretic peptide* (*Bnp*), and an increased cardiomyocyte size determined as cardiomyocyte CSA compared with WT PP mice (*Table 1* and *Figure 2B–F*; *Figure S1F–J*). Bromocriptine

Figure 2 Cabergoline treatment prevented cardiac hypertrophy in postpartum CKO mice. (A) Flow chart of the experimental protocol visualizes the mating and the treatment regime of Br or Cab in CKO PP mice. (B) Representative sections with haematoxylin and eosin staining visualizing cardiac morphology, and (C) with WGA (red) and nuclear Hoechst 33258 staining (blue) of LV cryosections from postpartum WT Ctrl, CKO Ctrl, CKO Br, or CKO Cab; scale bars indicate 50 μm. (D) Dot plot summarizing cardiomyocyte cross-sectional area (CSA) of WGA/Hoechst-stained cardiomyocytes of postpartum CKO Br (n = 7) and CKO Cab (n = 8) compared with CKO Ctrl (n = 10) and WT Ctrl (n = 6) LVs. (E) Dot plots summarizing *Anp* mRNA levels normalized to 18S RNA analysed by qRT-PCR in postpartum CKO Br (n = 7) and CKO Cab (n = 8) compared with CKO Ctrl (n = 8) and WT Ctrl (n = 7) LVs. (F) Dot plots summarizing *Bnp* mRNA levels normalized to 18S RNA analysed by qRT-PCR in postpartum CKO Br (n = 7) and CKO Cab (n = 7) compared with CKO Ctrl (n = 8) and WT Ctrl (n = 6) LVs. (G) Dot plots summarizing *Ankrd1* mRNA levels normalized to 18S RNA analysed by qRT-PCR in postpartum CKO Br (n = 7) and CKO Cab (n = 8) compared with CKO Ctrl (n = 8) and WT Ctrl (n = 7) LVs. (H) Representative ANKRD1 western blot and (I) dot plot summarizing quantification of ANKRD1 protein expression normalized to Ponceau S staining in cardiac tissue from postpartum CKO Br (n = 7) and CKO Cab (n = 8) compared with CKO Ctrl (n = 7) and WT Ctrl (n = 6) LVs. (D–G,I) Data are presented as mean ± SD, $^{*}P < 0.05$, $^{**}P < 0.01$ vs. WT Ctrl PP, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. CKO Ctrl PP, one-way ANOVA followed by post hoc tests with Bonferroni's correction.

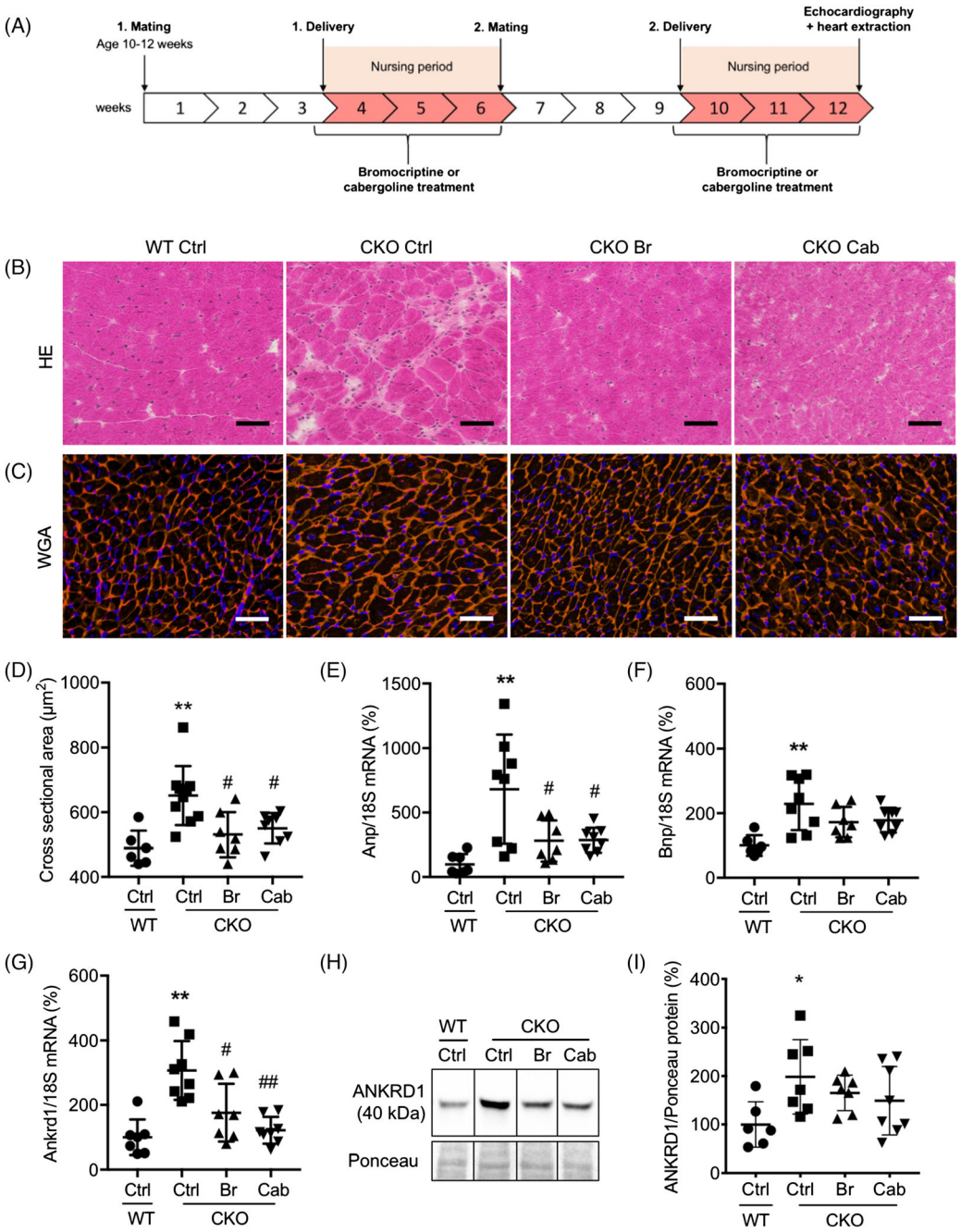


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Table 1 Cardiac function and dimension, body weight and mortality in CKO mice treated with Br or Cab compared to postpartum-matched WT and CKO mice

Parameters	WT Ctrl 2PP ($n = 8$)	CKO Ctrl 2PP ($n = 9$)	CKO Br 2PP ($n = 8$)	CKO Cab 2PP ($n = 8$)
FS (%)	37.2 ± 5.4	22.1 ± 9.0**	33.4 ± 5.6$^{\#}$	34.5 ± 9.4$^{\#}$
LVEDD (mm), median (IQR)	3.8 (3.6–4.3)	4.6 (4.2–5.1)	4.2 (4.0–4.2)	4.0 (3.7–4.3)
LVESD (mm)	2.5 ± 0.5	3.7 ± 0.9**	2.7 ± 0.3$^{\#}$	2.6 ± 0.3$^{\#\#}$
Heart rate (bpm)	550 ± 44	553 ± 46	558 ± 44	561 ± 48
HW (g)	0.13 ± 0.02	0.17 ± 0.03**	0.14 ± 0.01$^{\#}$	0.13 ± 0.01$^{\#\#}$
BW (g)	29.6 ± 1.8	30.0 ± 4.8	30.4 ± 2.9	26.6 ± 1.4
HW/BW ratio, median (IQR)	4.3 (4.0–4.5)	5.5 (4.9–6.7)**	4.6 (4.4–4.9)	5.0 (4.7–5.3)
Tibia length (TL, mm)	17.7 ± 0.3	17.7 ± 0.4	17.8 ± 0.4	17.5 ± 0.2
HW/TL ratio, median (IQR)	7.1 (6.6–7.7)	9.4 (8.4–10.6)**	8.1 (7.7–8.4)	7.6 (7.1–8.3)$^{\#}$
Mortality (%)	0% (0/8)	10% (1/10)	0% (0/8)	0% (0/8)

Fractional shortening (FS), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), heart rate (beats per minute, bpm), heart weight (HW), body weight (BW), HW/BW ratio, tibia length (TL), HW/TL ratio, and mortality determined in CKO PP mice treated with Br or Cab compared with postpartum-matched WT and CKO mice. Data are shown as mean ± SD or median (IQR), $^{**}P < 0.01$ vs. WT 2PP ctrl, $^{\#}P < 0.05$ $^{\#\#}P < 0.01$ vs. CKO 2PP ctrl using one-way ANOVA followed by post hoc tests with Bonferroni's correction or Kruskal–Wallis test followed by Dunn's test for multiple comparisons.

and cabergoline treatment attenuated the development of cardiac hypertrophy, as confirmed by the normalization of the cardiomyocyte size, the expression levels of *Anp*, and the additional cardiac-specific stress-response and hypertrophy marker *ankyrin repeat domain 1* (*Ankrd1*) (*Table 1* and *Figure 2B–I*). Cardiac *Bnp* mRNA expression is not increased in CKO PP mice treated with bromocriptine or cabergoline (*Figure 2F*).

Here, cabergoline treatment was as effective as bromocriptine in preventing cardiac hypertrophy in CKO PP hearts.

Treatment with cabergoline prevented fibrosis and infiltration of inflammatory cells in CKO postpartum hearts

As previously shown, CKO PP mice displayed enhanced cardiac fibrosis as demonstrated by elevated mRNA expression levels of *collagen type I alpha I* (*Col1a1*) and *transforming growth factor beta-2* (*Tgfß2*) and increased collagen content (determined by Sirius red staining) (*Figure 3A,C–E*). On the other hand, bromocriptine and, to a similar degree, cabergoline prevented the formation of LV fibrosis in CKO PP hearts (*Figure 3A,C–E*). In addition, both bromocriptine and cabergoline prevented the increase in inflammatory infiltrates in CKO PP LVs demonstrated by staining of the monocyte and macrophage marker CD68 and the mRNA expression levels of the macrophage marker Adgre1 (*Figure 3B,F,G*). Moreover, CKO PP LVs showed an increased mRNA expression of *vascular cell adhesion protein 1 (Vcam-1)*, a marker for endothelial dysfunction and endothelial activation through inflammatory cytokines, compared with WT PP, which could be normalized with bromocriptine or cabergoline treatment (*Figure 3H*). In addition, the elevated infiltration of inflammatory $CD68^{+}$ cells was associated with increased mRNA expression of the cytokines *tumour necrosis factor α* (*Tnf-α*) and *interleukin 6* (*Il-6*) in CKO PP LVs (*Figure 3I* and *J*), which could be prevented through the treatment with bromocriptine or cabergoline in CKO mice.

Cabergoline inhibited the up-regulation of PPCM biomarkers PAI-1 and miR-146a in the PPCM mouse model

To investigate whether the treatment with cabergoline can prevent the described pathomechanism mediated by 16 kDa PRL and miR-146a in the experimental PPCM CKO mouse model, the expression of the reported PPCM biomarkers PAI-1 and miR-146a[2,3,5,14] were evaluated. Indeed, CKO PP Ctrl mice showed an increased cardiac expression of PAI-1 and miR-146a compared with WT PP Ctrl LVs (*Figure 4A–D*). Furthermore, the up-regulation of PAI-1 and miR-146a in CKO LVs was attenuated by bromocriptine and cabergoline treatment of CKO PP mice, indicative of the prevention of HF onset (*Figure 4A–D*).

Cabergoline treatment in PPCM patients: Clinical characteristics, medication, and clinical course

Three PPCM patients were treated with cabergoline at Hannover Medical School as bromocriptine was not available. All patients were heart-healthy before pregnancy. However, all three patients reported pregnancy complications and/or pre-existing non-cardiac diseases. Before delivery, Patient 1 suffered from pre-eclampsia, gestational diabetes, and hypothyroidism. Patient 2 had no pre-existing diseases before pregnancy but needed surgical treatment after delivery due to uterine atony with massive bleeding. Patient 3 reported

Figure 3 Cabergoline treatment prevented the development of cardiac fibrosis and inflammation in postpartum CKO mice. (A) Representative images of Sirius red staining visualizing fibrosis and collagen deposits and (B) of $CD68^+$ monocytes and macrophages (green; indicated by yellow arrows) co-stained with WGA (red) and Hoechst 33258 (blue) in LV sections of postpartum WT Ctrl, CKO Ctrl, CKO Br, or CKO Cab mice; scale bars indicate 50 μm. (C) Quantification of fibrosis from postpartum WT Ctrl (n = 6), CKO Ctrl (n = 5), CKO Br (n = 5), or CKO Cab (n = 8) LVs in arbitrary units (a.u.). Dot plots summarizing (D) *Col1α1* and (E) *Tgfβ2* mRNA levels normalized to 18S RNA analysed by qRT-PCR in postpartum CKO Br (n = 7) and CKO Cab (n = 8) compared with CKO Ctrl (n = 8) and WT Ctrl (n = 7) LVs. (F) Quantification of $CD68^+$ monocytes and macrophages from postpartum WT Ctrl (n = 6), CKO Ctrl (n = 10), CKO Br (n = 7), or CKO Cab (n = 8) LVs in arbitrary units (a.u.). Dot blots summarizing (G) *Adgre1* and (H) *Vcam-1* mRNA levels normalized to 18S RNA analysed by qRT-PCR in postpartum CKO Br (n = 7) and CKO Cab (n = 8) compared with CKO Ctrl (n = 8) and WT Ctrl (n = 7) LVs. Dot blots summarizing (I) *Tnf-α* and (J) *Il-6* mRNA levels normalized to 18S RNA analysed by qRT-PCR in postpartum CKO Br (n = 7) and CKO Cab (n = 8) compared with CKO Ctrl (n = 8) and WT Ctrl (n = 6) LVs. (C–J) Data are presented as mean ± SD, $^*P < 0.05$, $^{**}P < 0.01$ vs. WT Ctrl PP, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. CKO Ctrl PP, one-way ANOVA followed by post hoc tests with Bonferroni's correction.

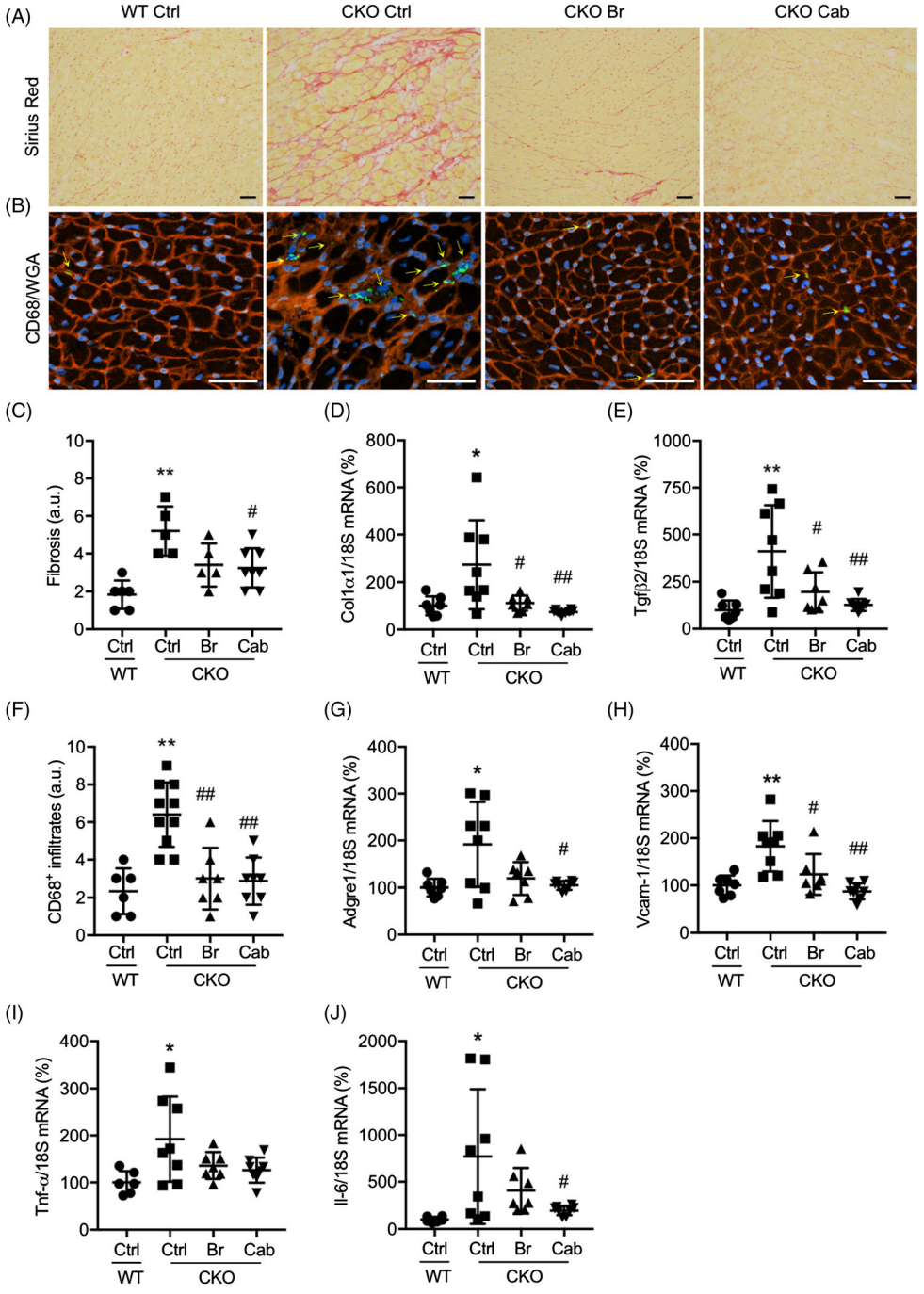
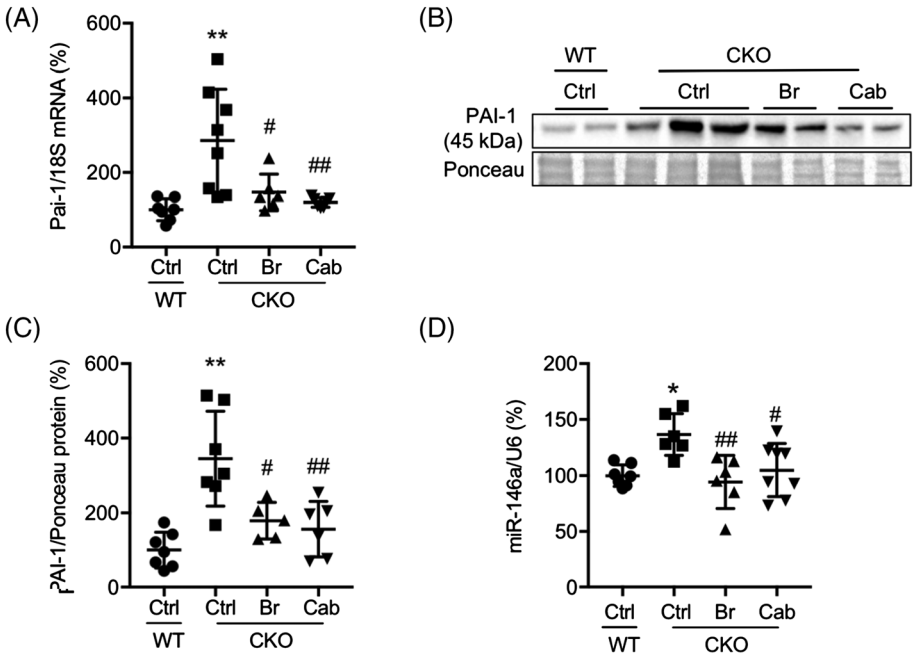


Figure 4 Cabergoline treatment prevented the up-regulation of PPCM biomarkers in postpartum CKO mice. (A) Dot plots summarizing *Pai-1* mRNA levels normalized to 18S RNA analysed by qRT-PCR in postpartum CKO Br (n = 7) and CKO Cab (n = 8) compared with CKO Ctrl (n = 8) and WT Ctrl (n = 7) LVs. (B) Representative PAI-1 western blot and (C) dot plot summarizing quantification of PAI-1 protein expression normalized to Ponceau S staining in cardiac tissue from postpartum CKO Br (n = 5) and CKO Cab (n = 7) compared with CKO Ctrl (n = 7) and WT Ctrl (n = 7) LVs. (D) Dot plot showing miR-146a levels (mean value) normalized to U6 of postpartum CKO Br (n = 6) and CKO Cab (n = 8) compared with CKO Ctrl (n = 6) and WT Ctrl (n = 7) LVs. (A,C,D) Data are presented as mean ± SD, $^{*}P < 0.05$, $^{**}P < 0.01$ vs. WT Ctrl PP, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. CKO Ctrl PP, one-way ANOVA followed by post hoc tests with Bonferroni's correction.



an uneventful pregnancy but suffered from epilepsy and a meningioma, which has been resected 6 years before diagnosis. However, before pregnancy, she was seizure free for many years without need for anticonvulsive drugs.

The BL characteristics of these patients are shown in *Table 2*, and individual values are presented in *Table S1* as well as representative BL images of echocardiography, cardiac MRI, and chest X-ray (*Figure 5A–C*). At diagnosis, all PPCM patients presented with a severely reduced LVEF (26 ± 2%), high NT-proBNP levels (8007 ± 2347 ng/L), and HF NYHA functional class IV (*Figure 6A–C*). At diagnosis, all PPCM patients showed pulmonary congestion and/or pleural effusion (*Figure 5C*).

Despite the severely reduced LV function, all PPCM patients were haemodynamically stable without signs of cardiac shock. Non-invasive ventilation was necessary in one case due to pulmonary oedema. Comparable with the bromocriptine treatment regime, all PPCM patients were treated with cabergoline 1 mg per week for 2 weeks, followed by 0.5 mg per week for another 6 weeks (*Figure 1*). Prolactin suppression was monitored via blood tests, showing sufficient suppression of prolactin levels at 3 (12 ± 9 ng/mL) and 6 (10 ± 1 ng/mL) months follow-up, compared with diagnosis (171 ± 206 ng/mL) (*Figure 6A*).

Furthermore, according to the current ESC guidelines, all patients received HF medication.[1] For prevention of sudden cardiac death, two patients received a wearable cardioverter-defibrillator (WCD). In one patient, LVEF already improved from initially 25% to 47% before discharge; therefore, WCD was not necessary.

Follow-up was conducted 3 and 6 months after diagnosis. LV function recovered in all patients with a mean LVEF of 51 ± 4% after 3-month and 56 ± 2% at 6-month follow-up (*Figure 6B*). In comparison with the time point of PPCM diagnosis, NT-proBNP levels decreased at 3 (213 ± 142 ng/L) and 6 (186 ± 106 ng/L) months' follow-up, and all three patients were classified with NYHA Class I or II at 3-month and 6-month follow-up (*Figure 6C* and *D*). No adverse events occurred during follow-up.

Discussion

Treatment of PPCM with the D2R agonist bromocriptine to inhibit prolactin secretion has proven an effective treatment regime in previous studies in the experimental PPCM mouse model and patients.[4,7,9,11,20] Bromocriptine is a D2R agonist with additional agonistic and antagonistic properties on various monoamine receptors, including the dopamine D1 and D2 family, adrenergic α, and serotonin receptors.[21–23] As a

Table 2 Baseline characteristics of all three included PPCM patients receiving cabergoline treatment

Parameters	PPCM patients (n = 3)
Age, years	30 ± 1
Median gravida (range)	1 (1–1)
Median parity (range)	1 (1–1)
Ethnic group: Caucasian, *n* (%)	3 (100)
Systolic blood pressure, mmHg	164 ± 11
Heart rate, beats per minute	135 ± 7
Body mass index (BMI)	28 ± 10
Clinical feature of HF	
Left ventricular ejection fraction (%)	26 ± 2
Mean NT-proBNP, ng/L	8007 ± 2347
Mean troponin T, ng/L	53 ± 43
Mean creatine kinase, U/L	85 ± 17
Mean creatinine, μmol/L	72 ± 15
Mean GFR, mL/min	99 ± 21
NYHA functional class, *n* (%)	
I	0 (0)
II	0 (0)
III	0 (0)
IV	3 (100)
HF medication at discharge, *n* (%)	
ACE inhibitor/angiotensin receptor blocker/ ARNI	3 (100)
Mineral receptor antagonist	3 (100)
Beta-blocker	3 (100)
Ivabradine	2 (67)
Diuretic	3 (100)
Treatment duration cabergoline, weeks	8
WCD, *n* (%)	2 (67)

WCD, wearable cardioverter defibrillator.
New York Heart Association (NYHA), left ventricular ejection fraction (LVEF), blood pressure (BP), body mass index (BMI), N-terminal pro-brain natriuretic peptide (NT-proBNP), troponin T (TNT) creatine kinase (CK), creatinine, and glomerular filtration rate (GFR) were analysed in routine clinical lab tests. Gaussian distributed data were presented as mean ± SD and not normally distributed data were presented as median and range. Categorical variables were presented as frequencies (percentage).

result of its activity for several receptors, bromocriptine therapy is associated with potential side effects such as mental disorders or thrombotic events,[24] which could be reduced by using more selective D2R agonists. In addition, due to the temporary unavailability of bromocriptine, it is necessary to test the effectiveness and safety of further approved D2R agonists, which differ in their affinities and efficacies at the D2R and other receptors compared with bromocriptine, to ensure the best possible therapy for PPCM patients.

The selective D2R agonist cabergoline shows a higher affinity for D2R than bromocriptine, which might be associated with an even better prolactin inhibition.[25]

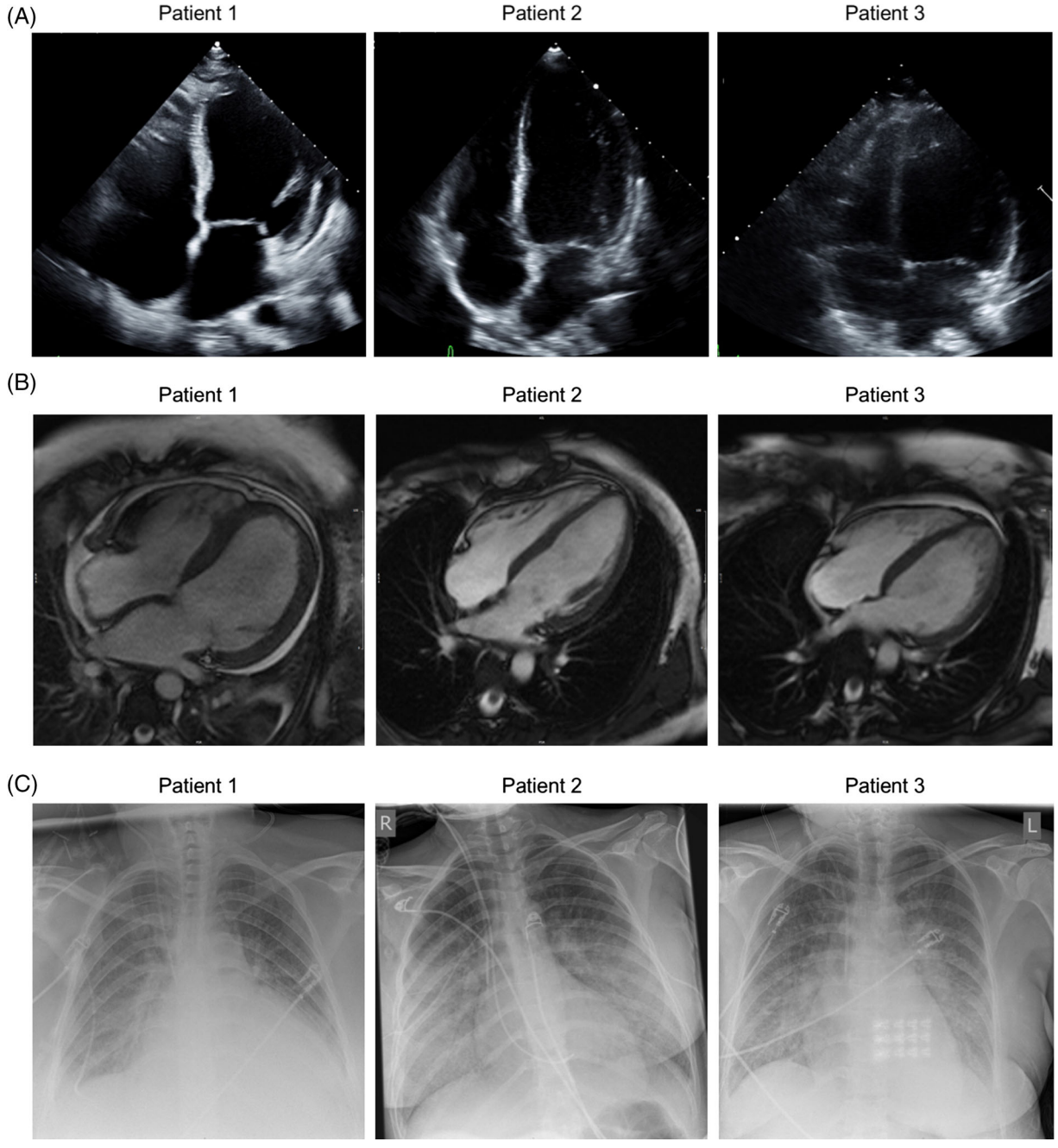
In the present study, we investigated the effectiveness of cabergoline compared with bromocriptine over two consecutive pregnancies and nursing periods in the established PPCM CKO mouse model. In line with our previously reported results, CKO mice showed a decreased cardiac function and developed HF postpartum with a phenotype highly similar to the human PPCM.[2,4–6,16] Cabergoline treatment was as effective as bromocriptine to prevent LV dysfunction and cardiac remodelling with regard to cardiac hypertrophy, fibrosis, and inflammation in CKO PP mice. The efficacy of cabergoline treatment was also confirmed by measuring the PPCM biomarkers PAI-1 and miR-146a, which were less expressed in the hearts of cabergoline and bromocriptine treated CKO PP mice compared with CKO PP controls. PAI-1 and miR-146a were identified as critical players in the 16 kDa PRL-related pathomechanism of PPCM. PAI-1 can form a complex with 16 kDa PRL and uPA that binds to the uPAR on endothelial cells and induces miR-146a expression in an NF-κB-dependent manner.[2,5] MiR-146a mediates anti-angiogenic properties in endothelial cells and impairs the cardioprotective ErbB4 signalling, leading to postpartum HF.[2] Recently, we have demonstrated that PAI-1 and miR-146a circulating levels are increased in acute PPCM and normalize after bromocriptine treatment at 6-month follow-up.[2,5] In the experimental PPCM CKO mouse model, we found a reduced expression of both markers verifying that the induction of the 16-kDa-PRL-mediated pathomechanisms could be prevented. Our results demonstrate that cabergoline treatment prevents the onset of postpartum HF in PPCM CKO mice as effective as bromocriptine.

Our clinical data support the relevance of our results, showing that treatment with cabergoline was also effective in PPCM patients. All PPCM patients treated with cabergoline showed suppressed prolactin levels, associated with full cardiac recovery at 3-month and 6-month follow-up, despite an initially severely reduced LV function. It is important to note that all patients received an optimized medical HF treatment, including ACE inhibitors/angiotensin II receptor blockers/ARNI, beta-blockers, and mineralocorticoid receptor antagonists, also underlining the importance of adapted HF treatment according to the BOARD concept.[7,12,13] Furthermore, no adverse events occurred during follow-up. Cabergoline treatment was well tolerated, and all patients completed the 8-week treatment duration without observed side effects. At this point, it is important to note that cabergoline treatment was accompanied by at least prophylactic anticoagulation (*Figure 1*).

Our data are supported by promising results in several single case reports of PPCM patients treated with cabergoline, showing similar positive effects on the clinical course without the occurrence of adverse events.[26–29] Furthermore, in a retrospective study including 24 Danish PPCM patients treated with cabergoline, the treatment was associated with an increased chance of full cardiac recovery,[30] further emphasizing the positive effects of cabergoline treatment in PPCM patients regarding the cardiac outcome.

Thus, concluding from our data, cabergoline seems to serve as a promising alternative to bromocriptine. Especially whenever bromocriptine is not available, cabergoline treatment should be considered as the first alternative. Furthermore, cabergoline has the advantage that compared with the daily application of bromocriptine, the weekly treatment

Figure 5 Representative images of (A) echocardiography, end-diastolic (B) cardiac-MRI, end-diastolic, and (C) chest X-ray at diagnosis in all three patients treated with cabergoline.



with cabergoline might increase treatment adherence. In other diseases with high prolactin levels, such as hyperprolactinaemia, cabergoline has positive effects on various metabolic and cardiovascular risk factors.[31,32] However, these patients were often treated with higher dosages or longer duration of cabergoline treatment than our PPCM patients. Therefore, it is unclear whether these additional effects could also apply to PPCM patients treated with cabergoline. Overall, fewer adverse effects were observed for cabergoline than for bromocriptine patients with hyperprolactinaemia.[32]

However, data regarding the effectiveness and safety of cabergoline treatment in PPCM are still sparse, especially compared with the well-examined D2R agonist bromocriptine. Therefore, when available, bromocriptine should still be preferred in PPCM patients due to the higher level of

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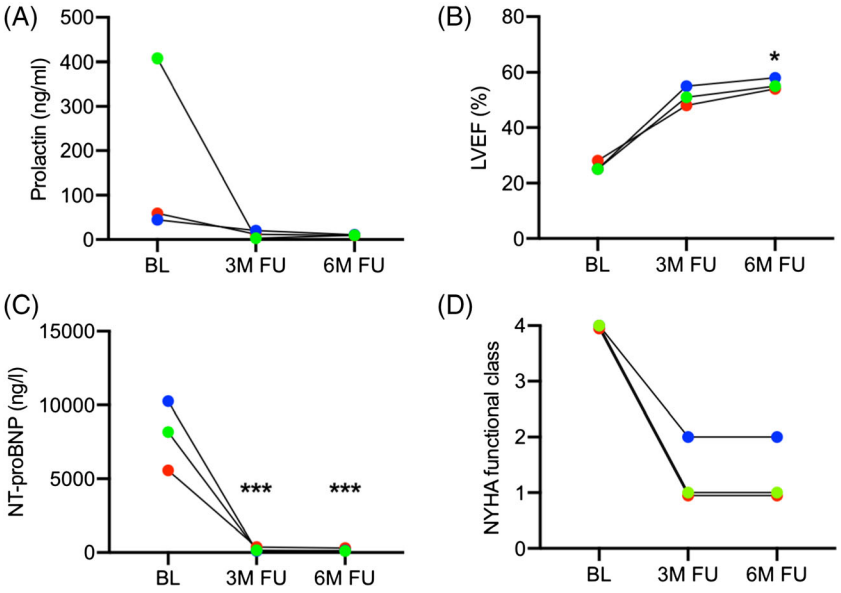
Figure 6 Cabergoline treatment is associated with improved cardiac outcomes in PPCM patients. (A–D) Changes in (A) prolactin, (B) LVEF, (C) NT-proBNP, and (D) NYHA class from baseline (BL) to 3 months (3 M) and 6 months (6 M) follow-up (FU) in three PPCM patients receiving cabergoline treatment from the German PPCM Registry. (B) *$P < 0.05$ vs. BL, Kruskal–Wallis test with Dunn's test for multiple comparisons, (A,C) ***$P < 0.001$ vs. BL, one-way ANOVA with Dunnett's test for multiple comparisons.



evidence. Further studies are required to validate our findings in a larger cohort of PPCM patients.

Limitations

Limitations of the study are the retrospective analysis of cabergoline treatment in PPCM patients and the small number of patients included in the study. Therefore, further studies are required to validate our findings in a larger cohort of PPCM patients.

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Conflict of interest

Tobias J Pfeffer, Julia H Mueller, Lea Haebel, Sergej Erschow, Kuebra C Yalman, Steven R Talbot, Tobias Koenig, Dominik Berliner, Carolin Zwadlo, Michaela Scherr, Denise Hilfiker-Kleiner, Johann Bauersachs, and Melanie Ricke-Hoch declare that they have no conflict of interest.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Cardiac function and dimension, body weight and mortality in CKO mice treated with Br or Cab compared to postpartum-matched WT and CKO mice. (A) Representative M-mode pictures of postpartum WT and CKO Ctrl mice and CKO mice treated with BR or Cab over two consecutive pregnancies and nursing periods. (B-E) Fractional shortening (FS), left ventricular end-diastolic diameter (LVEDD), left ventricu-

lar end-systolic diameter (LVESD), heart rate (HR) determined in B-mode from echocardiographic analyses of postpartum WT and CKO Ctrl mice and CKO mice treated with BR or Cab over two consecutive pregnancies and nursing periods. (F-J) Heart weight (HW), body weight (BW), HW/BW ratio, tibia length (TL) and HW/TL ratio of postpartum WT and CKO Ctrl mice and CKO mice treated with BR or Cab over two consecutive pregnancies and nursing periods. Data are shown as (B, D-G, I) mean ± SD or (C, H, J) median (IQR), $^{**}P < 0.01$ vs WT 2PP ctrl, $^{\#}P < 0.05$ $^{\#\#}P < 0.01$ vs CKO 2PP ctrl using one-way ANOVA followed by post-hoc tests with Bonferroni's correction or Kruskal-Wallis test followed by Dunn's test for multiple comparisons.

Table S1. Baseline characteristics of each included PPCM patients receiving cabergoline treatment.

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