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SHORT COMMUNICATION

Perhexiline treatment improves toxic effects of β-adrenergic receptor stimulation in experimental peripartum cardiomyopathy

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Abstract

Aims Peripartum cardiomyopathy (PPCM) is a pregnancy-associated cardiomyopathy that occurs in previously heart-healthy women towards the end of pregnancy or in the first months after delivery and is characterized by heart failure due to systolic dysfunction. The clinical course of PPCM differs between mild symptoms and severe forms with acute heart failure complicated by cardiogenic shock (CS). Treatment of CS complicating PPCM is challenging, as β-adrenergic receptor (β-AR) stimulation seems to be associated with progression of heart failure and adverse outcome. This experimental study aims to examine whether postpartum treatment with the glucose uptake-promoting drug perhexiline alone or as co-treatment with β-AR stimulation prevents heart failure in the experimental PPCM mouse model.

Methods and results Postpartum (PP) female PPCM-prone mice with a cardiomyocyte-restricted STAT3-deficiency (αMHC-Cre$^{tg/+}$;Stat3$^{fl/fl}$; CKO) were treated with perhexiline over two to three pregnancies and nursing periods (2/3PP) or were co-treated with perhexiline after one pregnancy (1PP) under chronic β-AR stimulation using isoproterenol (Iso) infusion. Perhexiline was not able to prevent onset of PPCM in CKO mice (FS: CKO Pexsig-2/3PP: 25 ± 12% vs. CKO Ctrl-2/3PP: 24 ± 9%, n.s.) but attenuated worsening of left ventricular function in response to treatment with the β-AR agonist Iso (FS: CKO Pexsig-Iso-1PP: 19 ± 4% vs. CKO Ctrl-Iso-1PP: 11 ± 5%, $P < 0.05$).

Conclusions Treatment of PPCM patients with β-AR agonists should be avoided whenever possible. In cases with CS complicating PPCM, when treatment with β-AR agonists cannot be prevented, co-medication with perhexiline might help to reduce the cardiotoxic side effects of β-AR stimulation. Clinical data are necessary to further validate this therapeutic approach.

Keywords Peripartum cardiomyopathy (PPCM); Cardiogenic shock; Perhexiline; B-adrenergic receptor stimulation; ErbB4

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Background

Peripartum cardiomyopathy (PPCM) is a rare but life-threatening heart disease affecting heart-healthy women in the last months of pregnancy or in the first months after delivery. PPCM is characterized by heart failure due to left ventricular (LV) dysfunction with an LV ejection fraction (LVEF) <45%.[1] Better understanding of the pathophysiology of PPCM has led to specific therapeutic approaches including treatment with the dopamine receptor agonist bromocriptine (BOARD concept).[2–4] Although PPCM patients, treated according to the BOARD concept, show a high potential for

cardiac recovery the treatment of acute heart failure with cardiogenic shock (CS) complicating PPCM is still challenging.[5,6] Treatment with β-AR agonists is associated with an adverse cardiac outcome in PPCM patients.[7] Furthermore, treatment with the β-AR agonist isoproterenol (Iso) induced rapid onset of heart failure in cardiomyocyte-restricted knockout of STAT3 (αMHC-Cre$^{tg/+}$; STAT3$^{fl/fl}$, CKO) male mice due to reduced serum fatty acid levels and impaired fatty acid and glucose uptake.[7] The resulting metabolic deficit leads to a reduction of the Krebs cycle activity thereby impairing both, ATP production and with this contractility and detoxification of reactive oxygen species (ROS) causing enhanced oxidative stress and cardiomyocyte death.[7] This pathomechanism could be attenuated by treatment with the glucose-uptake-promoting drug perhexiline.[7] Perhexiline promoted glucose uptake by enhancing GLUT4 recruitment to the plasma membrane and thereby restored Krebs cycle activity, mitochondria energy production, and ROS detoxification perhexiline.[7,8]

As Iso also aggravated PPCM in CKO female mice, we tested whether perhexiline has beneficial effects on the development of PPCM per se and/or on the Iso-induced worsening of the condition in CKO female mice.[7]

Aims

This experimental study aims to examine whether postpartum perhexiline alone or as co-treatment with β-AR stimulation prevents heart failure in the experimental PPCM mouse model.

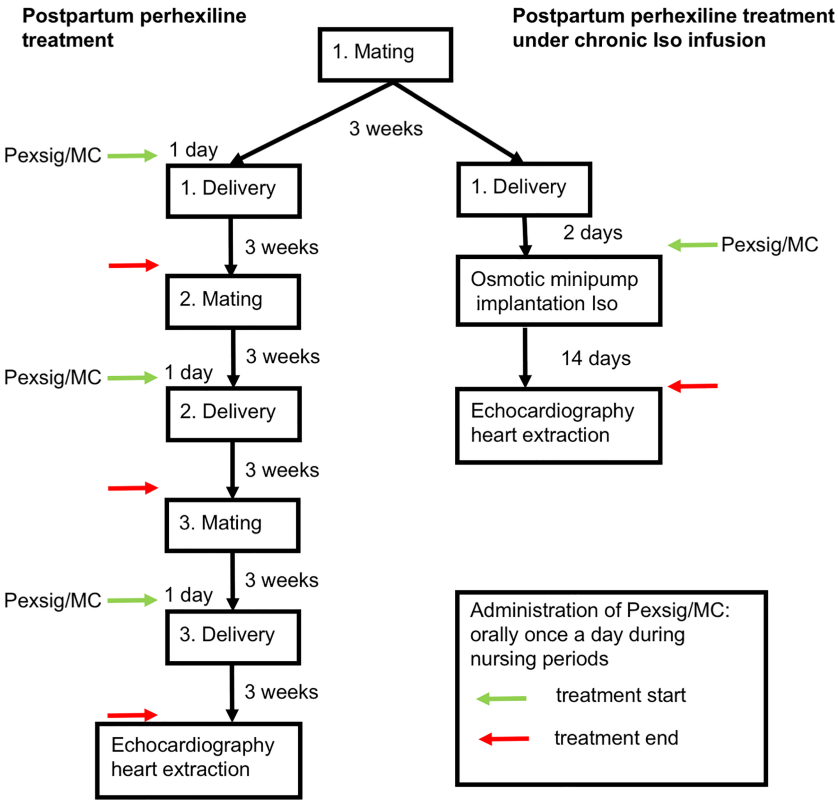
Methods

Animal experiments

Generation of CKO mice and WT littermates (STAT3$^{fl/fl}$) has been described previously.[4,9]

Osmotic minipumps were implanted subcutaneously under isoflurane anaesthesia to infuse isoproterenol (Iso 30 mg/kg/day) 2 days after the first delivery.[7] Echocardiography (Vevo 3100, Visual Sonics) was carried out in sedated mice (isoflurane inhalation 0.5%) after two to three nursing periods or 14 days after osmotic minipump implantation as described before (*Figure 1*).[4,7] Perhexiline malate (25 mg/kg/day, Sigma)

Figure 1 Flow chart of the experimental protocol visualizes the mating and perhexiline (Pexsig) treatment regime in CKO mice with and without chronic Iso infusion. Green arrows indicate the treatment start of the daily Pexsig or MC treatment, red arrows mark the end of the treatment. Iso, Isoproterenol; MC, methylcellulose.



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was dissolved in 0.5% methylcellulose (MC) and given orally once a day during nursing periods. Treatment started 1 day before delivery or immediately after implantation of osmotic minipumps. Animals treated with Iso alone received MC orally once a day (*Figure 1*).

All animal studies were in accordance with the German animal protection law and with the European Communities Council Directive 86/609/EEC and 2010/63/EU for the protection of animals used for experimental purposes and the ARRIVE guidelines. All experiments were approved by the local Institutional Animal Care and Research Advisory Committee and permitted by the local authority.

Histology and immunostaining

For cardiac morphological analyses, hearts were embedded in OCT and frozen at −80°C. Cardiac cryosections were stained with hematoxylin and eosin as described.[9] Interstitial collagen volume fraction was determined in picro-Sirius red-stained LV cryosections.[9] Inflammation was stained in LV cryosections with antibodies recognizing CD45 (BD Pharmingen, Clone 30-F11).[10,11]

qRT-PCR, miR-qRT-PCR, Western blot

Total RNA from adult murine hearts was isolated with Trizol (Invitrogen) and cDNA synthesis was performed as described.[10,11] Real-time PCR using the SYBR green dye method (Brilliant SYBR Green Mastermix-Kit, Thermo Fisher) was performed with the AriaMX Real-Time PCR System (Agilent Technologies) as described.[10,11] Sequences of quantitative real-time polymerase chain reaction (qRT-PCR) primers used in this study are provided below.

Expression of mature miR-199a-5p, miR-7a and miR-146a (Applied BioSystems) was determined using miR-qRT-PCR on an ABI7500 cycler (Applied Biosystems, Foster City, USA) and was normalized using the 2-ΔΔCT method relative to U6 as described.[12] Protein expression levels were determined by Western blotting, using SDS-PAGE as described.[9] The following antibody was used: anti-HER4/ErbB4 mAB (CST, 4795).

Sequences of qRT-PCR primers

mRNA	Sense primers (5′ to 3′)	Antisense primers (5′ to 3′)
mmu 18S	GTAACCCGTTG AACCCCATT	CCATCCAATCG GTAGTAGCG
mmu Adrge1	GAGACATCCAC TCTGGGCAC	GGGGCCCCTGT AGATACTGA
mmu ANP	GCCGGTAGAAG ATGAGGTCA	GGGCTCCAATC CTGTCAATC
mmu Col1a1	ACAGACGAACA ACCCAAACT	GGTTTTTGGTCA CGTTCAGT
mmu ErbB4	GTGCTATGGACC CTACGTTAGT	TCATTGAAGTTC ATGCAGGCAA
mmu GLUT4	AAACAAGATGC CGTCGGGT	ATAGCCAAACT GAAGGGAGCC
mmu VE-cadherin	CGTGGTGGAAA CACAAGATG	CGTTTGGGGTC TGTCTCAAT

Statistical analyses

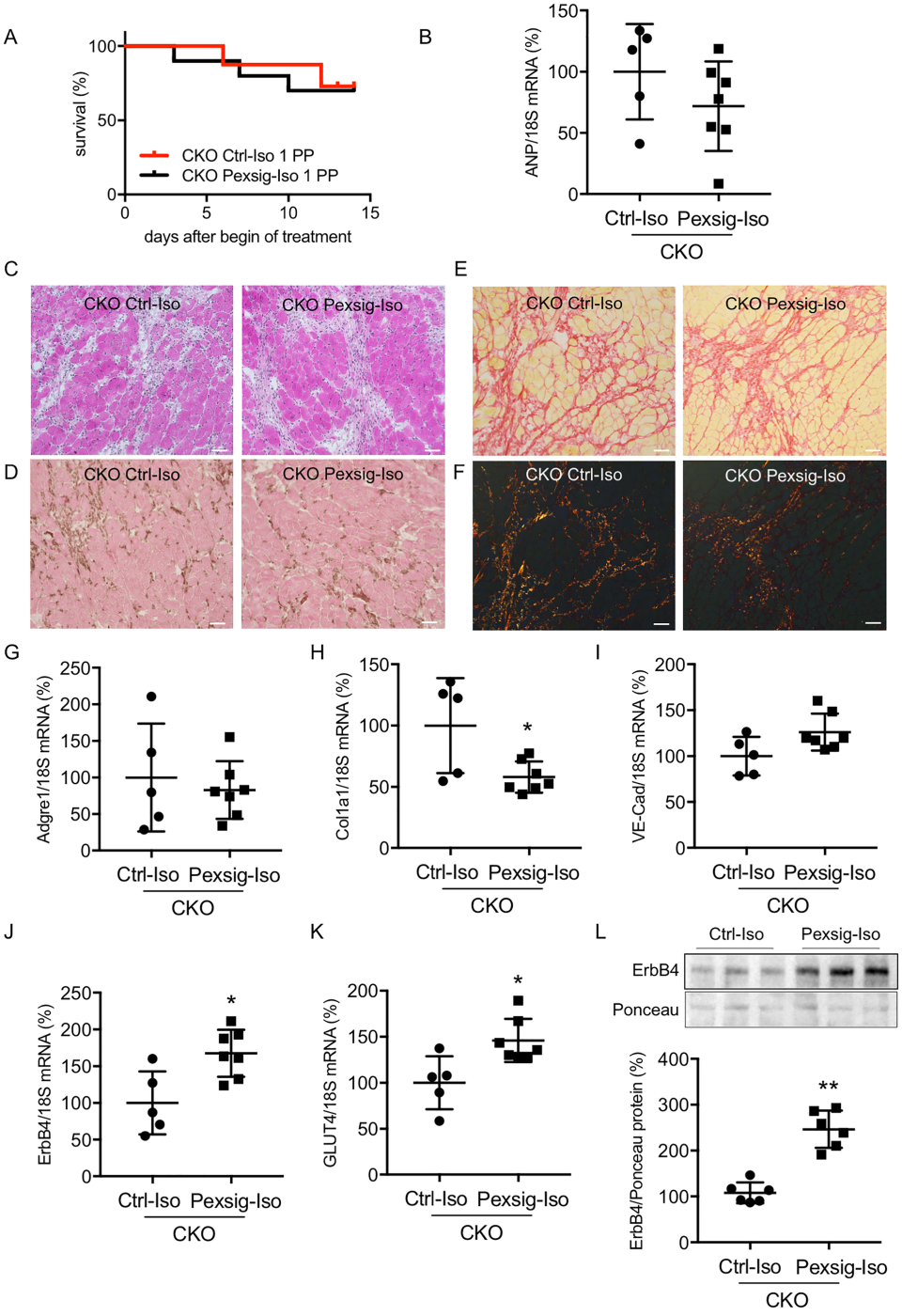
Data were analysed using GraphPad Prism version 7 or 8 for Mac (GraphPad Software, La Jolla California, USA).

Table 1 Cardiac function and dimension in CKO mice with and without chronic Iso infusion treated with perhexiline or methylcellulose after the first pregnancy and nursing period

Parameters	WT 2/3PP (n = 9)	CKO Ctrl 2/3PP (n = 10)	CKO Pexsig 2/3PP (n = 9)	CKO Ctrl-Iso 1PP (n = 6)	CKO Pexsig-Iso 1PP (n = 7)
FS (%)	40 ± 6	24 ± 9**	25 ± 12*	11 ± 5****	19 ± 4****,#
LVEDD (mm)	3.7 ± 0.5	4.8 ± 1.1*	4.4 ± 0.5	5.7 ± 0.2****	5.4 ± 0.3****
LVESD (mm)	2.2 ± 0.4	3.7 ± 1.1*	3.3 ± 0.9	5.1 ± 0.3****	4.4 ± 0.3****,##
Heart rate (bpm)	519 ± 45	497 ± 60	501 ± 84	514 ± 65	527 ± 72
HW (g)	0.139 ± 0.02	0.162 ± 0.03	0.15 ± 0.02	0.184 ± 0.03**	0.17 ± 0.02*
BW (g)	31.9 ± 4	34.3 ± 4	32.3 ± 2	25.5 ± 4**	28 ± 3
HW/BW ratio	4.5 ± 1.0	4.5 ± 0.4	4.6 ± 0.4	7.0 ± 1****	6.0 ± 0.5*,#
Tibia length (TL, mm)	18.0 ± 0.2	18.6 ± 0.3**	18.5 ± 0.3*	17.3 ± 0.3****	17.1 ± 0.2****
HW/TL ratio	0.008 ± 0.001	0.009 ± 0.001	0.008 ± 0.001	0.011 ± 0.001***	0.010 ± 0.001**
Mortality (%)	0% (0/9)	0% (0/10)	10% (1/10)	33% (3/9)**	22% (2/9)**

FS, fractional shortening; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter.
Heart rate (beats per minute, bpm), determined in WT and CKO mice after two to three (2/3 PP) pregnancies and nursing periods or in CKO 1PP mice after the first pregnancy and nursing period (14–17 days after osmotic minipump implantation). Data are mean ± SD.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.
****$P < 0.0001$ vs. WT PP.
#$P < 0.05$
##$P < 0.01$ vs. CKO Ctrl-Iso 1PP using one-way ANOVA followed by Bonferroni post hoc test and Fisher's exact test for discrete variables.

Figure 2 Chronic Iso infusion induces heart failure in CKO mice postpartum. Perhexiline improves cardiac ErbB4 signalling and glucose metabolism (A) Kaplan–Meier curve showing survival of CKO Pexsig-Iso 1PP (n = 9) and CKO Ctrl-Iso 1PP (n = 9) mice exposed to pregnancy. Survival data were analysed using the log-rank (Mantel–Cox) test, n.s.. (B) Dot blots summarizing ANP mRNA levels normalized to 18S RNA analysed by quantitative real-time PCR in CKO Pexsig-Iso 1PP (n = 7) and CKO Ctrl-Iso 1PP (n = 5) left ventricles (LVs). (C) Representative sections with hematoxylin and eosin staining visualizing cardiac morphology, (D) with the pan-inflammatory marker CD45 (brown, co-stained with eosin) showing inflammation and (E, F) with Sirius red staining in (E) bright field and (F) in polarized light visualizing fibrosis and collagen deposits in LV sections from CKO Pexsig-Iso 1PP (n = 7) and CKO Ctrl-Iso 1PP (n = 5) mice; scale bars indicate 50 μm. Dot blots summarizing (G) Adgre1, (H) Col1a1, (I) VE-Cadherin, (J) ErbB4 and (K) GLUT4 mRNA levels normalized to 18S RNA analysed by quantitative real-time PCR in CKO Pexsig-Iso 1PP (n = 7) and CKO Ctrl-Iso 1PP (n = 5) LVs. (L) Representative ErbB4 western blot and dot plot summarizing quantification of ErbB4 protein expression normalized to Ponceau S staining in cardiac tissue from CKO Pexsig-Iso 1PP (n = 6) and CKO Ctrl-Iso 1PP (n = 6) mice. (B, G–L) *$P < 0.05$, **$P < 0.01$ vs. CKO Ctrl-Iso, all data are mean ± SD, unpaired two-tailed t test.



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Continuous data are expressed as mean ± SD. Comparison between the groups was performed using Student's *t* test or one-way ANOVA followed by Bonferroni post hoc testing. Categorical variables are presented as frequencies (percentages) and compared using the Fisher's exact test. Survival data were analysed using the log-rank (Mantel–Cox) test. A two-tailed *P* value of <0.05 was considered statistically significant.

Results

Treatment with perhexiline does not prevent onset of PPCM in CKO PP. To investigate the effect of perhexiline in the PPCM mouse model per se, CKO PP mice were randomized after one pregnancy to either receive perhexiline (CKO Pexsig 2/3PP) or methylcellulose (MC, CKO Ctrl 2/3PP) for consecutive two to three pregnancies (*Figure 1*). Cardiac function was significantly reduced in both groups, without differences between the two treatment groups (*Table 1*). Survival was comparable between mice treated with perhexiline and mice receiving MC (*Table 1*).

Treatment with the β-AR agonist isoproterenol induces heart failure in the PPCM mouse model, which can be improved by co-treatment with perhexiline

To investigate whether the toxic effects of Iso can be prevented by co-treatment with perhexiline, osmotic minipumps containing Iso were implanted in CKO mice after delivery (*Figure 1*). Mice were randomized to receive either perhexiline (CKO Pexsig-Iso 1PP) or MC (CKO Ctrl-Iso 1PP). Cardiac function was severely reduced in both groups with significant improvement in CKO Iso mice treated with perhexiline compared to CKO Ctrl-Iso 1PP (*Table 1*). As previously reported,[7] chronic Iso infusion aggravated heart failure in CKO PP mice, associated with enhanced mortality and cardiac hypertrophy (increased ANP mRNA expression and HW/BW or HW/TL ratio; *Table 1*, *Figure 2A*). Moreover, decreased cardiac capillarization, increased collagen deposits, and elevated inflammation (increased CD45 positive infiltrates and mRNA expression of the macrophage marker EGF-like module-containing mucin-like hormone receptor-like 1, also known as F4/80 or Adgre1) were observed in CKO PP hearts.[4,7,13] Perhexiline treatment was not associated with significant changes in mortality, inflammation, fibrosis or VE-cadherin mRNA expression as a marker for capillarization. (*Table* 1, *Figure 2A–I*). However, Col1a1 mRNA expression was reduced in CKO Pexsig-Iso 1PP hearts (*Figure 2H*).

Perhexiline treatment improves cardiac ErbB4 signalling and glucose metabolism under chronic Iso infusion in CKO PP mice

Because we have previously shown that ErbB4 expression is reduced in CKO mice compared with WT mice and that ErbB4 expression is further decreased after Iso treatment, contributing to deteriorated glucose metabolism,[7] we investigated the influence of perhexiline treatment on cardiac ErbB4 and GLUT4 expression under chronic Iso infusion. CKO Pexsig-Iso 1PP hearts showed improved cardiac ErbB4 and GLUT4 expression (*Figure 2J–L*). However, miRNAs known to target ErbB4 or GLUT4, miR-7a, miR-199a-5p, and miR-146a[7,12] were not differently expressed in CKO Pexsig-Iso 1PP compared with CKO Ctrl-Iso 1PP hearts (data not shown).

Conclusions

Co-treatment with perhexiline attenuates β-AR agonist-induced heart failure in the PPCM mouse model. Mechanistically, perhexiline up-regulated the expression of the cardioprotective ErbB4 receptor and GLUT4, thereby preventing the β-AR agonist-induced mitochondrial impairment and subsequent cardiomyocyte dysfunction and death, features that otherwise lead to irreversible heart failure in PPCM.[7] The positive effect of perhexiline on ErbB4 seems independent from miRNAs (miR-199-5p and miR-146a) up-regulated in CKO mice with PPCM or specifically up-regulated by Iso treatment (miR-7a). However, perhexiline treatment did not improve mortality, heart failure, enhanced cardiac hypertrophy, elevated inflammation, and fibrosis in CKO mice treated with β-AR agonists. Therefore, further therapy strategies, aiming for reduction or replacement of β-AR agonists, for patients with CS complicating PPCM are necessary. Recent studies could show that mechanical circulatory support, using an intravascular microaxial blood pump, was associated with a favourable outcome in PPCM patients with CS.[14,15] In both studies, the dosage of β-AR agonists could be significantly reduced by the use of a microaxial blood pump.[14,15] Furthermore, the use of extracorporeal membrane oxygenation and left ventricular assist devices represent further therapeutic options in PPCM patients with CS.[16,17] Thus, perhexiline may reduce the risk for cardiac failure associated with catecholamine treatment in PPCM with CS, but it seems not to be able to completely prevent the cardiotoxic effects of these drugs. Therefore, as suggested by the ESC guidelines,[1] β-AR stimulation should be avoided whenever possible in PPCM patients, and other treatment options to stabilize the patients' haemodynamic situation such as mechanical circulatory support should be considered.

Limitations

As these are only experimental data, conclusions regarding the clinical significance should only be drawn with great caution. However, as perhexiline is not approved for treatment of CS, in our opinion, these data do not justify further clinical studies.

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Conflict of interest

Tobias J. Pfeffer, Manuel List, Julia H. Müller, Michaela Scherr, Denise Hilfiker-Kleiner and Melanie Ricke-Hoch declare that they have no conflict of interest.

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