Clinical profiling of patients with peripartum cardiomyopathy and its value for translational research

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ABSTRACT **Postpartum cardiomyopathy (PPCM) is a disease of unknown etiology and exposes women to high risk of mortality after delivery despite optimal medical therapy. Experimental data suggested that enhanced oxidative stress promotes the proteolytical processing of the lactation hormone prolactin into a biologically active derivative, the 16kDa prolactin, which appears to be a major cause for PPCM. We observed increased oxLDL levels in a subset of these PPCM patients, indicative of oxidative stress, enhanced Cathepsin D activity and substantial levels of the cleaved 16kDa form of prolactin. We therefore propose that the excessive generation of 16kDa prolactin mediates PPCM in humans and suggest that inhibition of prolactin release may represent a novel therapeutic strategy for PPCM.**

INTRODUCTION

Peripartum cardiomyopathy (PPCM) is a distinct entity of dilated cardiomyopathy that occurs in women between 1 month antepartum and 5 months postdelivery.[1, 2] The low incidence of PPCM in the northern hemisphere (1:15 000) as compared to countries like Nigeria, Haiti and South Africa with an incidence between 1:100 to 1:1 000,[3-7] is one of the reasons why numerous previous studies on PPCM relied on case reports, small numbers of patients or a review of medical records. One option was even a survey among 15 000 members of the American College of Cardiology by mail[8] in an effort to obtain basic information that totaled 123 patients.[9] Only patients in Haiti were studied prospectively by the same group of doctors, but given the political situation, researchers were faced with practical and logistical difficulties.

Many reports on PPCM were written before the advent of echocardiography, an essential investigation into the diagnosis of PPCM. As a result, previous reports and studies most likely included a significant percentage of patients with a non-PPCM cause of cardiac malfunction that clinically mimic heart failure. The criteria for PPCM were re-defined in 1997,[1] emphasizing the absence of other underlying cardiac conditions to help refine the diagnosis of human PPCM. This problem of inaccurate diagnosis is reflected by the fact that select studies of human PPCM included a high percentage of patients with other cardiac conditions, e.g. a history of hypertension during pregnancy in 43% of patients.[9] Furthermore, ACE-inhibitors or β-blockers were not available during many of the early studies, impacting negatively on outcome.

In view of the above, systematic data collection to study the aetiology and the potential pathogenic mechanisms of PPCM was deemed difficult. The high incidence of PPCM at a single tertiary centre in South Africa provided a unique opportunity to conduct a prospective study of the mechanism of the pathogenesis and clinical features of PPCM. This enabled us to perform a translational study and novel therapeutic approach to treat patients with a high risk for PPCM. Based on data obtained from an animal model of PPCM (mice with a cardiomyocyte-specific knock-out of signal transducer and activator of transcription (STAT)3, *alpha-MHC-cre*$^{+/o}$*; stat3*$^{flox/flox}$: STAT3-KO)[10] we emphasized that a biologically active degradation product of the nursing hormone prolactin might be a major cause of the development of PPCM. Treatment with bromocriptine, a drug widely used to stop lactation in women, prevented PPCM completely in our mouse model. Interestingly, we discovered striking parallels between the prolactin based pathomechanism in STAT3-KO mice and patients with PPCM.[10] Based on these experimental findings, a pilot trial with bromocriptine was started at our center, including 12 patients with a high risk for PPCM due to a PPCM in a previous pregnancy.

In summary, this review points out the systematic data collection and analysis of 100 patients with PPCM. In addition, we made use of our

genetic mouse model of PPCM to investigate potential underlying mechanisms, which may start and/or drive this disease and took a translational approach to investigate potential novel treatment strategies specifically addressing PPCM.

CLINICAL PROFILE OF 100 PATIENTS WITH PERIPARTUM CARDIOMYOPATHY

Study design and patient enrolment

The protocol was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand, Johannesburg, South Africa and complies with the Declaration of Helsinki. All patients and controls gave written informed consent before study entry. Clinical assessment, echocardiography, and blood analysis were done at baseline and after 6 months of standard therapy. Inflammatory markers were measured at baseline only. All patients received treatment with diuretics and the angiotensin-converting enzyme inhibitor accupril. Carvedilol was added after resolution of overt heart failure, and the dose was slowly titrated up to a target of 25 mg twice daily as long as SBP was ≥ 100 mmHg or symptoms such as dizziness did not occur. Patients attended the cardiac clinic at least once a month for routine follow-ups. Inclusion criteria, exclusion criteria, measurement of tumour-necrosis factor (TNF)-alpha and Fas/APO-1 levels, assessment of New York Heart Association (NYHA) functional class, echocardiography and details of the statistical analysis are described elsewhere.[11]

Clinical profile of 100 study patients with PPCM

Seventy-seven out of the 100 patients completed the follow-up period of six months - 15 patients had died and eight had moved to remote areas and were not available for follow-up. The mean age was 31.6±6.6 years and 23.2% had undergone caesarean section. The mean haemoglobin at time of presentation was 12.5±1.7 g/dl and mean body mass index (BMI) was 25.6±5.1. Patients were normotensive with a mean systolic blood pressure of 111.1±17.4 mmHg over 70.4±13.5 mmHg diastolic and tachycardic (93.5±18.5 b.p.m.). Although 91% of the study patients were diagnosed as PPCM patients for the first time, the remaining 9 PPCM patients had been diagnosed at a previous pregnancy. These nine patients had recovered their left ventricular (LV) function and experienced a subsequent episode of PPCM. None of the patients had identifiable causes for heart failure. There was no association between history of hypertension and eclampsia during pregnancy or use of tocolytic agents (9%). On presentation at the clinic (baseline), 26 patients were in NYHA FC II, 49 in functional class (FC) III and 25 in FC IV. Left ventricular thrombi were detected on echocardiography in 16% of the patients.

During the first months after enrolment, patients received standard therapy for heart failure, which included furosemide [n = 96, median daily dose 160 mg (80–250)], accupril [n = 96, median daily dose 10 mg (10–20)], and carvedilol [n = 95, median daily dose 25 mg (6.25–50)]. Carvedilol was uptitrated as long as SBP was > 100 mmHg or symptoms such as dizziness did not occur. After six months of treatment, surviving patients presented with lower heart rate (p=0.001), higher systolic (p=0.018) but unchanged diastolic blood pressure (p=0.37). Left ventricular diastolic dimensions improved from 61.2±7.1 mm to 55.6±8.9 mm (p<0.0001) and end-diastolic dimensions from 53.4±7.7 mm to 43.7±10.3 mm (p<0.0001). Left ventricular ejection fraction (LVEF) improved from 26.2±8.2% to 42.9±13.6% (p<0.0001) as determined by echocardiography and from 23.9±8.1% to 43.1±15.1% as measured by multiple gated acquisition scan (MUGA) (<0.0001). However, normalization of LVEF (>50%) was only observed in 18 (23%) of the patients. The median plasma level of C-reactive protein (CRP) for the 100 PPCM patients was 10.0 mg/L (range 1–90) with 45% of patients having values of .10 mg/L (Table 1). Only ten patients had a C-reactive protein level of 3 mg/L. Baseline plasma levels of C-reactive protein correlated positively with LV end-diastolic (rs = 0.33, P = 0.0026) and end-systolic dimensions (rs = 0.35, P = 0.0012), whereas the correlation with LVEF (rs = 20.27, P = 0.015) was inverse (Figure 1). Plasma C-reactive protein levels also correlated inversely

TABLE 1: Baseline characteristics of study population (n=100)

Parameter	Mean value
C-reactive protein (mg/l)	10.8±13.2
Glucose (mmol/L)	4.8±1.1
Total cholesterol (mmol/l)	4.2±0.8
Fas/Apo-1 (U/l)	6.3±4.1
TNF-alpha (pg/ml)	4.9±4.2

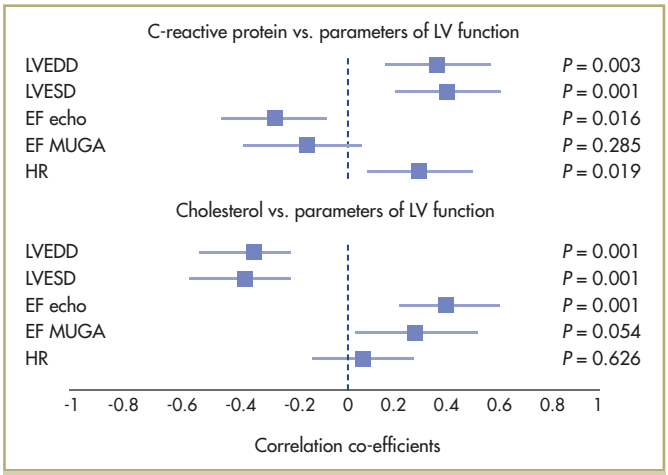

FIGURE 1: Correlation co-efficients of total cholesterol and C-reactive protein vs. parameters of LV dimensions and function.[11]

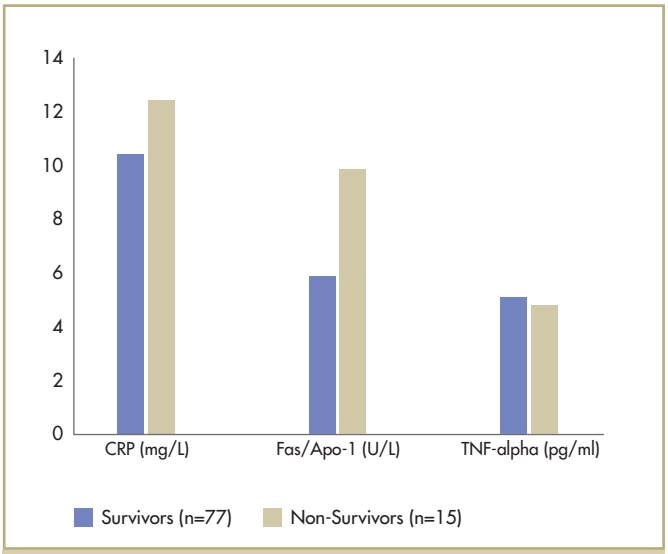

FIGURE 2: Baseline plasma inflammatory markers of deceased patients vs. survivors. Only differences in Fas/Apo-1 were statistically significant (p=0.002).

with levels of total cholesterol (rs = 20.29, P = 0.01). Baseline plasma levels of C-reactive protein, TNF-alpha, and Fas/Apo-1 were elevated in patients with PPCM when compared with 20 age, sex, body mass index, and parity comparable healthy volunteers (TNF-alpha 4.9±4.2 vs. 1.4±1.3 pg/mL, Fas/Apo-1 6.3±4.1 vs. 0.84±0.2 U/L, C-reactive protein 10.8±13.2 vs. 3.1±0.9 mg/L, P = 0.01). There was no correlation between baseline plasma levels of C-reactive protein, TNF-alpha, and Fas/Apo-1 among the PPCM patients.

In the population studied, mortality remained high (15%). Significant differences in the baseline data between deceased patients and survivors were seen in NYHA FC, values of systolic blood pressure (SBP), end-diastolic and end-systolic dimensions, LVEF, plasma aspartate aminotransferase (AST) and plasma levels of Fas/Apo-1 (Figure 2). Logistic regression analysis of NYHA FC, SBP, end-diastolic dimension (EDD), end-systolic dimension (ESD), EF, AST, and Fas/Apo-1 revealed that only the baseline plasma levels of Fas/Apo-1 (OR = 3.56, CI 95% = 1.35–9.42, p=0.01) and NYHA FC (OR = 2.67, CI 95% = 1.04–6.83, p=0.04) were independent predictors of death.

TRANSLATIONAL APPROACH FROM MOUSE TO (WO)MAN

A mouse model of PPCM

In studies by us and others it was shown that male mice with a cardiomyocyte-specific knock-out of STAT3, STAT3-KO spontaneously develop dilated cardiomyopathy with older age, associated with increased apoptosis of cardiomyocytes.[12, 13] We have demonstrated that an activated Fas/Fas ligand system promotes apoptosis of endothelial cells in the myocardium of STAT3-KO males.[13] Moreover, we noted that homozygotic STAT3-KO female mice and, to a lesser extent, heterozygotic (αMHC-cre+/o; stat3flox/+) female mice invariably develop PPCM, with a phenotype resembling that of STAT3-KO males including excessive apoptosis and impaired angiogenesis.[10] Furthermore, our study in Cell[10] describes the PPCM phenotype in STAT3-KO mice extensively. There we showed that the physiological stresses of pregnancy, labor, and/or nursing resulted in PPCM with a high mortality rate in virtually all STAT3-KO female mice studied. Death occurred always within the first 3 weeks after delivery. The postpartum phenotype of STAT3-KO mice included signs of overt heart failure, such as generalized edema and labored breathing, the hearts were characterized by four-chamber dilatation, often with thrombi in the atria, and extensive fibrosis. Echocardiography analysis revealed left ventricular dilatation and depressed fractional shortening in STAT3-KO female mice compared with postpartum wildtype sister mice. Molecular analysis of left ventricular tissue displayed up-regulation of the hypoxia inducible genes (hypoxia inducible factor-1α and BNIP3). Most strikingly, we observed a substantial loss of capillaries in ventricles from postpartum STAT3-KO females associated with increased cardiac apoptosis.

Enhanced cardiac oxidative stress and impaired oxidative defence mechanism in postpartum STAT3-KO

STAT3 is known to protect cardiomyocytes from oxidative stress by the up-regulation of the reactive oxygen species (ROS) scavenging enzyme manganese superoxide dismutase (MnSOD).[14] The important role of MnSOD in oxidative defense has been demonstrated in mice harboring only one functional MnSOD gene, where a 50% decrease in levels of MnSOD protein is associated with increased oxidative damage and cardiomyocyte death.[15] Indeed, the production of superoxide anions was enhanced in left ventricles from postpartum STAT3-KO mice compared with postpartum wildtype sisters.[10] In contrast, analysis of left ventricular tissue from postpartum wildtype female mice showed a marked increase in cardiac MnSOD protein levels compared to nulli-pari females.[10] This increase in MnSOD was blunted in postpartum STAT3-KO females. Taken together, this data suggested the presence of higher levels of oxidative stress due to an insufficient anti-oxidative defence system in postpartum STAT3-KO mice (Figure 3).[10]

Is prolactin the heart breaker in postpartum STAT3-KO mice?

Prolactin, a dominant hormone in pregnancy and early postpartum, has been suggested previously as a potential factor in the pathogenesis of PPCM.[16] Interestingly, prolactin can be cleaved by cathepsin D, a protease which is activated by oxidative stress in cardiomyocytes[17, 18]

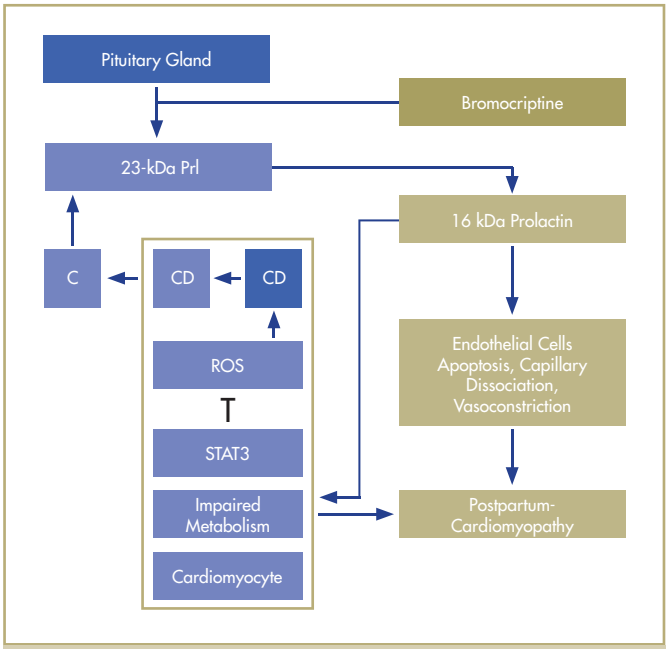

FIGURE 3: Schematic model for the development of PPCM. In absence of cardiomyocyte STAT3 activity, oxidative stress (indicated by increased production of reactive oxidant species, ROS) is increased, leading to the release of Cathepsin D (CD) from the lysosome into the cytoplasm and the interstitium. There it processes 23kDa prolactin (Prl) into its detrimental 16kDa form. Subsequently, the 16kDa Prl promotes vasoconstriction, apoptosis in endothelial cells, capillary dissociation and interferes with cardiomyocyte metabolic activity, all of which subsequently leads to heart failure. Consequently, bromocriptine (BR), a pharmacological inhibitor of prolactin release, prevents PPCM in mice by excluding prolactin from the circulation.

into a 16-kDa form of prolactin, which is known to exert strong anti-angiogenic effects such as endothelial cell dissociation and apoptosis.[19] We were able to demonstrate that left ventricular tissue displays a high cleavage activity for prolactin into its 16kDa form.[10] Furthermore, we showed that the 16kDa prolactin, even in the absence of the post-partum physiology, decreased cardiac capillary density and cardiac function, thereby mimicking at least in part the cardiac phenotype of PPCM in our mouse model (Figure 3).[10]

To obtain further proof of whether or not the generation of the 16-kDa form of prolactin is involved in the development of PPCM as well as to test a potential novel therapeutic strategy, we treated STAT3-KO female mice for two consecutive pregnancies with bromocriptine, a dopamine-D2-receptor agonist, which inhibits prolactin secretion (administered 5 days before delivery and continued 3 weeks postpartum). Indeed, bromocriptine treatment of STAT3-KO female mice prevented the entire PPCM phenotype concerning postpartum mortality, cardiac angiogenesis, cardiac function, cardiac dilatation, as well as cardiac fibrosis and apoptosis.[10] In Figure 3 we outline schematically the pathomechanism of prolactin cleavage and the proposed interference of bromocriptine in this pathway by blocking prolactin release from the pituitary glands in postpartum STAT3-KO mice.

Increased oxLDL, enhanced activation of Cathepsin D and augmented protein levels of the 16-kDa form of prolactin are present in the serum of lactating women with PPCM

We analyzed sera collected from PPCM patients and healthy peripartum controls for parallels of the pathomechanism of prolactin cleavage between our STAT3-mouse model and the human disease of PPCM. Indeed, the serum of lactating patients with PPCM contained increased levels of oxidized low density lipoprotein (oxLDL), a marker for oxidative stress[20] and increased Cathepsin D activity compared to healthy lactating women.[10] In addition, we were able to detect an antigen corresponding to the 16-kDa prolactin in the sera of 3 out of 5 lactating PPCM patients with obvious cardiac dysfunction at the time of serum sampling (mean %EF: 24±7), while no 16-kDa form of prolactin was detectable in healthy lactating women (n=5).[10]

Bromocriptine treatment may prevent PPCM in high-risk patients

PPCM occurs in previously healthy women who cannot be identified prospectively. However, women with PPCM who recover normal cardiac function have a high risk for reoccurring PPCM.[21] We therefore studied 12 patients who had recovered from a previous episode of PPCM and presented with a subsequent pregnancy.[10] In these women echocardiography was performed before delivery (8 months of pregnancy) and 3 months post-delivery. Six of these patients received bromocriptine 2.5 bd. after giving birth and subsequently for 2 months post-delivery in addition to standard heart failure therapy.[10] Controls for this preliminary study consisted of 6 patients with subsequent pregnancies after a previous episode of PPCM who presented similar pre-delivery cardiac function and dimensions (Table 2) and received standard heart failure treatment only.[10] In all patients who received additional bromocriptine post-delivery prolactin serum levels were returned to non-pregnant levels within 14 days of treatment as described previously.[22] Moreover, all bromocriptine treated patients presented normalization of LV function and dimensions (Table 2) and

TABLE 2: Cardiac function and NYHA stage in patients with subsequent pregnancies with (n=6) or without (n=6) BR treatment

	Peripartum control predelivery	Peripartum bromo-criptine predelivery	Postpartum control 1 month	Postpartum bromo-criptine 1 month	Postpartum control 3 months	Postpartum bromo-criptine 3 months
EF(%)	45±7	40±14	27±5	49±10	23±3	52±6**
NYHA	1.4±0.5	1.8±0.9	3±1	1.5±0.6	2.3±0.6	1±0*

*Ejection fraction (EF) was determined by echocardiography peripartum (before bromocriptine (BR) treatment was started) and 3 months postpartum. Mean age of control (standard heart failure therapy only) group: 32±6 and of BR group (standard heart failure and BR for 8 weeks): 33±4 (n.s). In the control group three patients died within 14 weeks postpartum, while all patients in the BR group survived. Data are presented as mean±SD, *p<0.05, **p< 0.01 BR group vs. corresponding control group.*

survived the 4-month observation period.[10] In the control group, three patients had died and the surviving showed deterioration of LV function and marked dilatation of the left ventricle (Table 2).[10]

DISCUSSION AND CONCLUSION

This review summarizes the clinical profile of 100 PPCM patients at a tertiary level hospital in South Africa and examined the role of plasma/serum pro-inflammatory markers at the time of diagnosis and clinical outcome after 6 months of treatment. In addition, it offers novel insights into the pathomechanism of PPCM by comparing a mouse model of PPCM with the clinical profile of human PPCM patients. Finally, it suggests that increased myocardial oxidative stress and enhanced cathepsin D activity induces a detrimental conversion of prolactin into its 16-kDa anti-angiogenic derivative. This 16kDa prolactin may induce and drive PPCM in mice and in patients. This highlights a novel specific treatment strategy for PPCM based on the inhibition of prolactin release by the well-established dopamine-D2-receptor agonist bromocriptine.

Despite appropriate and optimal clinical care including angeotensin converting enzyme (ACE)-inhibitors and carvedilol, 15% of patients died and only 23% of the studied population normalized their LVEF after 6 months of therapy. Prognosis of patients with PPCM seems to vary according to geographical region. Whereas Felker et al.[23] reported a 94% survival rate in 52 patients diagnosed at Johns Hopkins Hospital in the USA, 14% died in a prospectively studied population in Haiti and only 20% regained normal left ventricular function.[24] Poor socio-economic status, subtle yet undefined nutritional deficiencies, genetic factors and inadequate pre- and postnatal care could contribute to these geographical differences. The only options for patients who do not regain normal left ventricular function are the use of left ventricular assist devices and cardiac transplantation. However, such options are not available in resource-poor settings, such as in Haiti and South Africa. Patients that died had lower NYHA FC, LVEF and larger left ventricular dimensions at diagnosis compared to those who survived, whereas age, parity or onset of symptoms did not appear to play a role. Demakis et al. found that pathological findings in the myocardium of patients whose hearts had returned to normal size within six months of treatment and those whose hearts had not returned to normal size were indistinguishable.[25]

CRP is an acute-phase protein which recognizes a range of pathogenic targets, including membranes of apoptotic and reactive cells.[26] As this inflammatory marker is associated with adverse prognosis in patients with idiopathic dilated cardiomyopathy[27, 28] we investigated if levels of plasma CRP at baseline could predict outcome in patients with PPCM. Almost half of the population investigated had raised levels of CRP reflecting possibly the presence of a low-grade chronic inflammatory process due to the release of endotoxin or endotoxin-like substances and subsequent release of pro-inflammatory cytokines.[29] However, we did not find a correlation with NYHA FC or death. None of the patients with PPCM presented with symptoms during the antepartum period. This is in contrast to studies performed by others[30] and more in keeping with a study from Haiti[24] documenting that 96% of patients with PPCM developed heart failure in the postpartum period. Our failure to include PPCM patients during the prepartum period in the present study was not due to a lack of identifying such patients, since the cardiologists at Chris Hani Baragwanath Hospital are routinely involved in the care of pregnant patients presenting with symptoms and signs of congestive cardiac failure. The majority of cases developed symptoms in the first 4 weeks postpartum. Twenty per cent of patients studied were primiparous. We could not confirm factors mentioned by others[30] as multiparity, older age, or long-term use of tocolytic agents to be associated with the development of PPCM. At presentation, this group of patients had acute onset heart failure of short duration. There was no evidence of chronic disease or cardiac cachexia that could account for a low lipid profile being a marker of severe, chronic disease. Mean plasma levels of total cholesterol of the patient population studied was 4.2±0.8 mmol/L and low compared to that reported in other studies.[31-33] In a study by Rauchhaus and colleagues with an established plasma cholesterol cut-off level of < 5.2 mmol/L, low total cholesterol level was found to be predictive for impaired 1-year survival.[32] In line with findings by others[31, 32] demonstrating an increase in the rate of mortality with low serum total cholesterol levels, we found an association of low total cholesterol levels with larger left ventricular dimensions and lower EF. There was a trend, but no statistically significant association between the rate of mortality, which could possibly be explained by the short duration of the trial, the limited number of patients studied and the spontaneous recovery rate typical for patients with PPCM. Levels of low plasma cholesterol correlated positively with the levels of the inflammatory marker CRP. These findings are in support of the endotoxin-lipoprotein hypothesis[29] suggesting that lower plasma levels of total cholesterol provide lesser protection against endotoxins, making a susceptible group of patients more prone to severe heart failure. A recent trial by Albert and

colleagues[34] showed a significant variation in the distribution of plasma CRP levels among various ethnic groups living in the United States. Median plasma CRP levels were significantly higher among black women compared to their white, Hispanic or Asian counterparts. Since 40% of the variance of plasma CRP levels is genetically determined and PPCM is much more frequent in black patients, one could hypothesize that an increase in the intensity of an inflammatory response could be one of many factors contributing towards the development of PPCM. This is supported by our previous research in PPCM patients presenting with subsequent pregnancy, where we observed an exaggerated postpartum pro-inflammatory cytokine surge possibly playing a role in the development of PPCM.[21] Plasma levels of Fas/Apo-1 in the PPCM patients were significantly higher compared to healthy controls and a predictor of mortality, indicating that cardiac apoptosis may play a causal role in the pathogenesis of PPCM. Indeed, our mouse model of PPCM emphasizes increased cardiac apoptosis associated with the PPCM phenotype. However, most patients with acute PPCM have normal or only slightly increased troponin T or creatinine kinase (CK) serum levels, indicating that apoptosis may not affect primarily cardiomyocytes, but rather non-myocyte cells such as cardiac endothelial cells as suggested by our mouse model of PPCM.[10] In this regard, our experimental findings suggest a novel pathomechanism of heart failure, where a cleaved form of the pregnancy and nursing hormone prolactin, 16kDa prolactin, targets the endothelium, leading to impairment of the cardiac microcirculation and possibly thereby inducing and/or promoting progression of PPCM.[10] Our findings of increased cathepsin D activity and the presence of the 16-kDa form of prolactin in serum samples of nursing PPCM patients but not in pregnancy-matched controls,[10] point to striking similarities between our experimental mouse model of PPCM and support the concept of this pathomechanism in PPCM patients.

Clinical studies have determined that bromocriptine is safe during pregnancy.[35] Our encouraging preliminary results in patients treated with a combination of bromocriptine and standard heart-failure therapy compared to patients treated with standard heart-failure therapy only could further support the hypothesis that the 16-kDa form of prolactin may represent a causal factor for development of PPCM in patients.[10]

In conclusion, the well characterized profile of 100 PPCM patients, in combination with basic science, enables a unique concept of translational research, which provides new insights into the pathomechanisms behind heart failure and, more specifically, PPCM. In addition, this concept may have contributed to a novel and more specific therapeutic option to treat patients with PPCM or prevent the disease in patients who suffered and recovered from PPCM in a previous pregnancy. However, additional data, mainly a controlled randomized study, is needed in order to determine the true value of bromocriptine as a specific novel therapy for PPCM.

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