16-kDa Prolactin and Bromocriptine in Postpartum Cardiomyopathy

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Abstract

Peripartum cardiomyopathy (PPCM) is a potentially life-threatening heart disease emerging towards the end of pregnancy or in the first postpartal months in previously healthy women. Recent data suggest a central role of unbalanced peri/postpartum oxidative stress that triggers the proteolytic cleavage of the nursing hormone Prolactin (PRL) into a potent anti-angiogenic, pro-apoptotic and pro-inflammatory 16-kDa PRL fragment. This notion is supported by the observation that inhibition of PRL secretion by bromocriptine, a dopamine D2 receptor agonist, prevented the onset of disease in an animal model of PPCM and by first clinical experiences where bromocriptine seem to exert positive effects with respect to prevention or treatment of PPCM patients. Here we highlight the current state of knowledge on diagnosis of PPCM, provide insights into the biology and pathophysiology of 16-kDa PRL and bromocriptine and outline potential consequences for the clinical management and treatment options for PPCM patients.

Introduction

Peripartum cardiomyopathy (PPCM) is the major cause of pregnancy-induced heart failure (HF) and it's often unpredictable course leads to a high morbidity and mortality [1]. PPCM is an idiopathic cardiomyopathy, characterized by left ventricular (LV) systolic dysfunction and symptoms of heart failure appearing in previously healthy women mainly towards the end of pregnancy, during delivery or within the first months after delivery [1-3]. According to the National Heart, Lung and Blood Institute diagnosis of PPCM is based on exclusion criteria such as absence of any clearly identifiable cause for HF [1, 2]. The current epidemiologic profile of PPCM is largely unknown. The incidence of PPCM appears to be variable depending on the geographic region where the studies were performed with ranges from 1 in 2500-4000 in the USA to 1 in 1000 in South Africa and 1 in 300 in Haiti [3-6]. Data on incidence rates in Europe are still unsure and require epidemiological studies. In the past years the disease has received increasing awareness leading to the formation on the Peripartum Cardiomyopathy Working Group of the Heart Failure Association of the European Cardiac Society (ESC) and to a recent publication of a position statement [1] as well as adding a special section on that condition in the ESC guidelines in pregnancy [7].

Despite optimal management PPCM remains a complex syndrome where rapid progression to end-stage heart failure (HF) is frequently reported [8]. The pathophysiological mechanisms are still not clarified and suggested underlying pathomechanisms include low selenium levels, various viral infections, stress-activated cytokines, inflammation and autoimmune reaction and a pathologic response to hemodynamic stress [3, 9]. Recent discoveries raise the possibility of a common pathway, on which different etiologies that induce PPCM could merge [10]. This proposed pathway points to a coincidental situation where unbalanced oxidative stress and high levels of the nursing hormone Prolactin (PRL) are present [10, 11]. Hereby, the oxidative stress triggers the activation of the protease Cathepsin D that cleaves PRL into an angiostatic and pro-apoptotic 16-kDa PRL that seems to initiate and drive the disease. The 16-kDa PRL mainly impacts on the endothelium [12-15] with potential subsequent negative effects on cardiomyocyte function [10].

This review summarizes the current state of knowledge on symptoms and diagnosis of PPCM and provides novel insights into the pathophysiology behind PPCM with a specific focus on 16-kDa PRL, treatment with the PRL blocker bromocriptine and the potential consequences for the clinical management of PPCM patients.

Definition of PPCM

Recently a position paper by the Working Group on Peripartum Cardiomyopathy from the Heart Failure Association of the ESC proposed a revised definition of peripartum cardiomopathy as „an idiopathic cardiomyopathy presenting with heart failure secondary to LV systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found [1]. It is a diagnosis of exclusion. The LV may not be dilated but the ejection fraction (EF) is nearly always reduced below 45%“ [1]. Although phenotypically PPCM resembles the cardiac characteristics of dilated cardiomyopathy (DCM), it is considered an independent disease distinct from other cardiomyopathies [2].

Diagnosis of PPCM

Physicians are often faced with the situation on how to distinguish between peripartum discomfort in healthy women such as fatigue, mild shortness of breath or mild edema from the pathological symptoms of PPCM. It is important to recognize that PPCM can present very dramatic with acute heart failure needing intensive care admission or subtle over several weeks. However, in general PPCM becomes manifest in the last weeks of pregnancy and within the first months post delivery in previously healthy women mainly through typical symptoms of HF such as dyspnoea, exercise intolerance, cough and orthopnoea [1, 3, 16]. Unspecific symptoms of cardiac congestion as abdominal discomfort, pleuritic chest pain and palpitations can occur additionally. Therefore, establishing the diagnosis of PPCM relies on a high index of suspicion as early signs and symptoms of HF and peripartum associated physiological discomfort are often not easy to be distinguished and can lead to delayed

diagnosis [1, 3, 17]. Goland reported via a retrospective review and analysis of 182 patients with PPCM that the diagnosis was delayed by more than 1 week in 48% of patients with a major adverse event that included death, heart transplantation and defibrillator implantation [18]. Important are a thorough medical history of the exact onset of symptom in relation to pregnancy and subsequent diagnostic confirmation of LV systolic dysfunction by echocardiography and/or MRI. Furthermore, a thorough evaluation is necessary in order to eliminate other potential cardiac and non-cardiac explanations for the patient's clinical presentation.

A detailed description of the differential diagnosis and useful diagnostic tools has recently been published [1]. Here we briefly summarize diagnostic criteria:

Electrocardiogram: A recent publication highlighted that there are no ECG findings that are specific for PPCM [19]. The most common presentation is either sinus rhythm or sinus tachycardia with nonspecific ST-segment and T-wave abnormalities. New onset atrial or ventricular arrhythmias may occur, rarely resulting in significant hemodynamic compromise. QRS voltage is usually low or normal, but sometimes may meet criteria for LV hypertrophy.

Laboratory: Serum markers of inflammation including C-reactive protein (CRP) and high sensitivity CRP (hs-CRP) are usually normal to mildly elevated in normal pregnant patients, but may be significantly elevated in PPCM patients [20]. Oxidized LDL (oxLDL), a marker for oxidative stress, increases incrementally during normal pregnant women while INF-γ, a marker of inflammation, decreases. Both oxLDL and INF-γ are significantly elevated in women with PPCM compared to healthy women in the postpartum period [20]. PPCM patients who present with elevated levels of Fas/Apo-1, a marker of cardiomyocyte apoptosis, are at increased risk for death [9]. Brain natriuretic peptide (BNP) levels are may be slightly higher in pregnant women compared to nonpregnant women as early as the first trimester but do not significantly fluctuate during pregnancy. Most patients with PPCM display marked increase in BNP or N-terminal pro-BNP (NT-proBNP) serum levels compared to healthy pregnancy matched women [20].

Chest x-ray: The Chest x-ray usually shows cardiomegaly due to predominantly LV enlargement, pericardial effusion, or both. Additional findings usually include interstitial infiltrates, pulmonary venous congestion, and pleural effusion.

Echocardiogram: Imaging of the heart is essential to establish the diagnosis of PPCM and can provide important prognostic information if PPCM is suspected. Echocardiography is widely available and has been the primary cardiac imaging modality used to evaluate cardiac dimensions and function in these patients. By definition, the LVEF is usually <45%, LV dilatation is common but not always present, LV diastolic assessment by mitral valve inflow doppler usually reveals a restrictive filling pattern, indicating elevated LV filling pressure [1]. The right ventricular (RV) chamber size and systolic function are usually normal, but RV dilatation with reduced contractile function sometimes occurs and may portend a worse prognosis. Atrioventricular valve regurgitation is often present and may be severe. Ventricular thrombi may be present, particularly in patients with an LVEF <35% [9]. Pericardial effusion is rare.

Cardiac magnetic resonance imaging (MRI): No systematic study of the cardiac MRI findings in PPCM patients has been published yet. However, cardiac MRI has become a useful tool in general evaluating patients with any form of suspected cardiomyopathy. Compared to echocardiography, cardiac MRI can more accurately assess chamber volumes and systolic function and has a higher sensitivity for detection of LV thrombus [21]. Cardiac MRI can also evaluate markers of tissue injury including intracellular and interstitial injury, hyperemia, capillary leakage, necrosis and fibrosis [22]. There is no radiation exposure, so serial testing may safely be performed in most PPCM patients. Administration of gadolinium during pregnancy is not recommended, but is acceptable in lactating women. Case reports detailing the cardiac MRI findings in PPCM patients in either the acute and/or chronic stage of the disease have described varying results [23-25].

Endomyocardial biopsy: Endomyocardial biopsy is sometimes performed in peripartum women where myocarditis is suspected to be the cause for HF. As no histologic classification

for the diagnosis of PPCM has been established, the role of EMB in these patients remains unclear.

Familial predisposition and genetic forms of PPCM

Pregnancy displays a physiological stress test for the human heart and it is therefore not surprising that it can unmask genetic forms of cardiomyopathy. Based on the higher incidence in certain geographic regions genetic background, mainly African ancestry, may play a role, but has not been proven yet [3]. A few cases of PPCM patients with either mothers or sisters who have also been diagnosed with PPCM have been reported [26-30]. In this regard, recent studies strongly suggest that a subset of PPCM is an initial manifestation of familial DCM [30, 31]. Reported mutations associated with PPCM as a form of familial DCM include MYH7, SCN5A, PSEN2, MYH6, TNNT2, cardiac troponin C (TNNC1), and MYBPC3 [30, 31]. Recent studies support this feature also for noncompaction cardiomyopathy [32-34].

Although genetic analysis of PPCM patients is currently under investigation, it seems that for most cases no positive familial history has been reported (expert opinion of Prof. Karen Sliwa and Prof. Denise Hilfiker-Kleiner). Therefore, careful familial anamneses is important in patients with peripartum heart failure but routine genetic testing may only be suggested in the case of positive familial history of cardiomyopathy.

The need for specific biomarkers to distinguish PPCM from other forms of cardiomyopathy

Diagnosis of PPCM should be considered whenever a woman presents with systolic HF symptoms during the peripartum period. However, it is important for risk stratification and management of patients to rule out as good as possible other etiologies for HF such as underlying DCM or genetic cardiomyopathy, especially since PPCM has a high chance for recovery while other types of cardiomyopathy (DCM, genetic forms of cardiomyopathies, noncompaction) may be irreversible. In order to illustrate this problem we describe here the

criteria for noncompaction cardiomyopathy and compare it with the clinical picture of a PPCM patient recently treated at the Medical School in Hannover.

Noncompaction cardiomyopathy (LVNC): The diagnosis of LVNC is usually established by echocardiography, and/or MRI and electrocardiography-gated multi-detector computed tomography to image cardiac structures, with regard to detect noncompacted myocardium. There is considerable overlap with dilated cardiomyopathy, apical hypertrophy, and hypertrophic cardiomyopathy [35]. Per definition patients with LVNC show a combination of criteria which include two-layered hypokinetic noncompacted segments with wall thickening with 2:1 ratio of noncompacted to compacted layers. In most cases perfused recesses or hypokinetic segments and hypertrabeculation and/or presence of a meshwork can be visualized by color-flow echocardiography [36]. Chin et al. [37] defined a quotient of compact myocardium to the thickness of the whole myocardium of less than 0.5 as a criterion for LVNC. Stöllberger et al. [38] describe more than 3 trabecels from the apex to the papillary muscles with perfusion in recess as another criteria for LVNC. Frischknecht et al. [36] state that although some noncompaction criteria are occasionally found in other heart disease types, the combination of all criteria is very specific for noncompaction cardiomyopathy. Importantly, noncompaction cardiomyopathy is predominantly an irreversible genetic disease [39]. Accordingly, the diagnosis of LVNC requires genetic counseling, DNA diagnostics, and cardiological family screening [40].

Our case, a PPCM patient with several criteria of LVNC: A woman, age 41 delivered by a caesarean section twins having had an in-vitro-fertilization before. She was healthy up to this moment except mild diabetes in pregnancy and she had no positive family history of heart disease. Some hours after delivery she showed signs of an acute cardiac decompensation (NYHA IV). Echocardiography and MRI showed a poor left ventricular function (LVEF 26%) with an akinesia of the apical anterior and lateral wall and strongly enhanced trabecularlisation with a myocardium showing two layers (Figure 1). The quotient of compact myocardium to the thickness of the whole myocardium was 0.32. Baseline echocardiography analysis showed that she fulfilled several criteria for LVNC. Subsequently, the patient was

treated with standard therapy for HF (daily adimistration of Bisoporlol, Enalapril, Spironolacton, Torasemid, and Phenprocoumon) together with bromocriptine (5mg/day). Thereafter the patient continuously improved and after six months echocardiography displayed full functional recovery (LVEF 62%). After 12 months in MRI and echocardiography display a normal myocardial structure without a significant double layer (Figure 1). Albeit the pathology of this patient is not clear, the outcome suggests that she may not have had a LVNC initially but that rather a PPCM that showed several criteria of LVNC. Further clinical data sets will have to be collected to get a precise picture of this disease form in peripartum women.

A promising potential diagnostic tool to distinguish PPCM from other cardiomyopathies has recently been described by Walenta et al. [41] who discovered that microparticle profiles differ substantially between patients with PPCM and patients with DCM. Additional markers are warranted and may help in the future to distinguish PPCM from other types of HF allowing an optimal management and risk stratification for these young patients.

Who is at risk for developing PPCM

Risk factors, such as age (teenager or older women), tocolytic therapy, or twin pregnancy may identify subgroups of women with substantially higher incidence rates [3, 17]. Additional risk factors seem to be associated with life style and may include obesity and smoking. Recent data on the pathophysiology of preeclampsia and PPCM indicate that there may be a common pathway leading to the development of severe endothelial dysfunction in both diseases, which may specifically involve the angiostatic 16-kDa PRL [42]. Moreover, recent data indicate that about one fifth of patients with preeclampsia at term display significant diastolic dysfunction and/or some degree of myocardial damage [43]. Since diastolic dysfunction is of prognostic value in the prediction of long-term cardiovascular morbidity this finding significant implications for the acute medical management of preeclampsia [43] and may be a hint that preeclampsia could directly predispose patient to PPCM.

Prolactin and its degradation products in health and disease

The nursing hormone PRL is among the prominent hormones in the peripartum phase and large quantities of PRL are released from the pituitary gland into the circulation during lactation [44]. PRL can exert opposing effects on angiogenesis depending on proteolytic processing of the potentially pro-angiogenic full-length 23-kDa PRL into an anti-angiogenic 16-kDa PRL [44]. 16-kDa PRL, also called vasoinhibin, was initially identified as a potent anti-angiogenic factor [45]. This PRL variant is generated from full-length PRL by cathepsin-D mediated cleavage [46]. To date, the mechanisms by which 16-kDa PRL inhibits angiogenesis have only been partially elucidated. In bovine endothelial cells, the anti-angiogenic activity of 16-kDa PRL appears to be mediated by a saturable high-affinity binding site distinct from the PRL receptor [47]. 16-kDa PRL was found to induce endothelial cell cycle arrest in G0-G1 and G2-M [13], in parallel with inhibition of MAPK activation induced by basic bFGF and VEGF [48]. In addition, 16-kDa PRL has been shown to induce endothelial cell apoptosis by activating Caspase-3 and NF-κB [15]. Moreover, 16-kDa PRL inhibits endothelial cell migration by downregulating the Ras-Tiam1-Rac1-Pak1 signaling pathway [49]. 16-kDa PRL can also, by inhibiting the activation of endothelial nitric oxide synthesis (eNOS), block vasodilatation [12, 50]. More recently, a transcriptomic microarray analysis performed on 16-kDa PRL-treated endothelial cells, highlight links between 16-kDa PRL and the immune system, demonstrating that 16-kDa PRL induces leukocyte adhesion to endothelial cells by activating NF-κB [51]. In Figure 2 we summarize the biological mechanisms by which 16-kDa PRL impact on endothelial cells exerting its anti-angiogenic activity.

Beneficial effects of 16-kDa PRL: An important clinically relevant function of 16-kDa PRL is to attenuate tumor angiogenesis thereby preventing tumor growth and metastasis establishment [52, 53]. In various animal models 16-kDa PRL treatment caused small and narrow vessels, which displayed reduced coverage by pericytes in tumors [53]. Thus, 16-kDa PRL treatment prevents the development of a normally functioning tumor vasculature by

impairing vessel maturation. Moreover, 16-kDa PRL disrupts also lymphangiogenesis, the formation of lymphatic vessels in tumor-bearing mouse models [52].

Detrimental effects of 16-kDa PRL: In contrast to its potential beneficial effect in tumor treatment, 16-kDa PRL has been identified as a pathophysiologic factor in ocular angiogenesis [54] and may play a role in the progression of vasoproliferative retinopathies such as those associated with prematurity [55] or diabetes [56]. Moreover, recent data suggest that 16-kDa PRL is a major factor inducing and driving PPCM [10] and potentially also preeclampsia, a disease that occurs during pregnancy with a high risk of maternal and neonatal morbidity and lethality [12]. In PPCM we reported that excessive generation of 16-kDa PRL in the heart impairs the cardiac capillary network and reduces cardiomyocyte metabolism [10].

Thus, due to its negative effects on angiogenesis, 16-kDa PRL may be used a potent anti-cancer drug but at the same time may act as a pathophysiologic agent on the heart and the eye.

Could 16-kDa PRL-mediated endothelial impairment be the common pathway that induces PPCM

As pointed out in the previous paragraph, recent experimental and clinical studies suggest a causal role for the angiostatic and pro-apoptotic 16-kDa PRL for the initiation and progression of PPCM since the suppression of PRL release by the dopamine D2 receptor agonist, bromocriptine, could prevent the onset of disease in an animal model of PPCM (PPCM due to a cardiomyocyte-restricted knockout of STAT3: STAT3-KO) [10]. This notion is further supported by initial clinical data sets from case reports and small studies showing that the addition of bromocriptine to standard HF therapy was associated with improved LV function and a composite clinical outcome in women with acute severe PPCM [10, 11, 28, 57, 58].

In fact, the prerequisite for the generation of 16-kDa PRL, namely unbalanced oxidative stress that triggers Cathepsin D activity, is induced by many if not all risk factors for PPCM.

In addition, other sources of proteolytic enzymes such as matrix metalloproteinases (MMPs) may also contribute to the generation of 16-kDa PRL in PPCM [59]. In this regard, it has been shown that MMP-1, MMP-2, MMP-3, MMP-8, MMP-9 and MMP-13 are able to cleave human PRL into biologically functional 16 kDa PRL [60]. A potential important role of MMPs for the generation of 16-kDa PRL in PPCM is supported by studies showing that MMP2 serum levels are significantly higher in PPCM patients compared to pregnancy matched controls [20]. Furthermore, MMP-3 levels were substantially higher in hearts from mice with PPCM (STAT3-KO) where it is interesting to note the lowering oxidative stress by the Manganese Superoxide Dismutase (MnSOD) mimeticum MnTABP provided only a partial rescue while blocking prolactin with bromocriptine completely prevented onset of PPCM [10]. Because of these promising experimental and preliminary clinical data sets, a larger multicenter randomized clinical trial with 60 PPCM patients is performed in Germany to further analyze the efficacy of PRL blockade by bromocriptine in PPCM patients.

Bromocriptine an old drug with new formulation and new indication

Bromocriptine acts as an ergot alkaloid dopamine D2 receptor agonist by stimulating postsynaptic dopamine D2 receptors in the central nervous system and was initially approved in the therapy of Parkinson disease, hyperprolactinemia, galactorrhoea and acromegaly [61]. Furthermore, it is able to interfere with various serotonin receptors and corresponding neurons in peripheral organ systems including the cardiovascular system. Clinical indications where bromocriptine is used are summarized:

Suppression of lactation: Bromocriptine has been shown to be safe and highly effective to suppress lactation immediately postpartum and after lactation has been established [62]. It is therefore a widely used drug to suppress lactation in many Western Europe countries. Some case reports associate bromocriptine in postpartum women with an increased risk for thrombotic events such as myocardial infarction [63, 64], a feature that caused its retraction as a drug to stop lactation in the USA. Indeed, PRL may act as a modulator of coagulation activity since it is a substrate for thrombin, which at a physiological pH cleaves a C-terminal

16-kDa PRL fragment that is not angiostatic and displays very low mitogenic activity [65]. However, there is a naturally increased risk for thrombosis and myocardial infarction as well as for spontaneous coronary artery dissection in peri- and postpartum women independent of blocking PRL with bromocriptine [66-69]. Moreover, in the case of PPCM, HF further increases the risk for ventricular thrombosis, a feature we frequently observe before bromocriptine has been applied [28]. We therefore recommend that PPCM patients with severe HF obtain therapeutic or prophylactic anticoagulation therapy especially if they obtain bromocriptine.

Treatment of hyperprolactinemia: Bromocriptine is widely used to treat hyperprolactinemia caused by tumors affecting the hypothalamus, the pituitary gland, or the thyroid gland, which may cause galactorrhea and infertility in women [70]. Recent studies show that high PRL levels in patients with prolactinoma are associated with increased platelet counts, fibrinogen, tissue plasminogen activator inhibitor-1 (PAI-1) and decreased plasma tissue factor pathway inhibitor (TFPI) suggesting a potential hypercoagulable and hypofibrinolytic state, which might augment the risk for atherosclerotic and atherothrombotic complications [71] suggesting that bromocriptine by suppressing PRL in these patients may reduce the risk for thrombotic complications.

Treatment of Parkinson's disease: In Parkinson's disease, bromocriptine reduces the risk of developing motor complications that were partly mediated by the degeneration of dopamine-secreting cells in the substantia nigra pars compacta [72, 73]. Here, dopamine receptor agonists are used in adjunctive therapy to L-dopa to enhance motor fluctuations and as initial monotherapy in treatment of early Parkinson's disease [72].

Treatment of diabetes mellitus type II: Since 2009, bromocriptine is distributed as a quick-release (QR) formulation (Cycloset™) for the therapy of adult patients with diabetes mellitus type 2 [74]. In these patients, bromocriptine treatment diminishes fasting glucose, improves glucose tolerance, decreases plasma insulin levels and is associated with a reduction in cardiovascular morbidity [74, 75].

Conclusion

In recent years the awareness for PPCM has increased for the benefit of these patients. Larger clinical data are collected and analyzed allowing more insights in the pathophysiology of the disease providing important information for diagnosis and management of these patients. In this regard, a large international registry on PPCM has been initiated by ESC via the ESC EURO*OBS* program (www.escardio.org), which will hopefully help to further broaden our understanding of PPCM with regard to its ethiology and geographical differences in its clinical picture and most importantly provide important information to optimize treatment strategies.

Currently, it appears that the 16-kDa PRL pathophysiology is one mechanism that seems to be common in PPCM patients of different etiology and geographical regions. Moreover, first evidences suggest that it is quite specific to patients with PPCM and may be used to develop specific biomarkers for diagnostic but also prognostic purpose in women with peripartum HF.

With regard to treatment options, cumulating experimental and clinical evidence support the usefulness of bromocriptine to treat PPCM albeit final proof has still to be obtained in larger clinical trials.

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Figure legends

Figure 1: Several criteria of noncompaction cardiomyopathy (LVNC) present in PPCM patient at baseline completely resolving in follow up : A) Baseline echocardiography displays a poor LV function (EF 26%) and the typical two layers of myocardium (noncompact myocardium, yellow bar / compact myocardium, blue bar) with more than 3 trabeculae (arrows) together with a large pericardial effusion (PE). B) Baseline MRI (left panel: long axis; right panel: short axis) confirms structure of LV myocardium consistent with a LVNC (noncompact myocardium, yellow bar / compact myocardium, blue bar > 2,3). C) Echocardiography performed 12 months later shows normalized LV function (EF 62%) and normalized myocardial structure. D) MRI (left panel: long axis; right panel: short axis) confirming normalization with noncompact myocardium / compact myocardium < 2,3).

Figure 2: Summary of the anti-angiogenic actions of 16-kDa PRL: 16-kDa PRL inhibits of endothelial cell (EC) proliferation by preventing MAPK activation. Inhibition of EC migration by 16-kDa PRL requires the Ras-Tiam-Rac-Pak pathways while induction of apoptosis occurs via a NF-kB-dependent caspase activation. Blockage of eNOS by 16-kDa PRL inhibits vasodilatation. 16-kDa PRL, through the induction of ICAM-1, VCAM-1 and e-selectin

(SELE) expression, enhances leukocytes-endothelial cell interactions. Tumors treated with 16-kDa PRL show less mature vessels with reduced pericytes coverage by interfering with the Delta/Notch signaling.

Figure 1

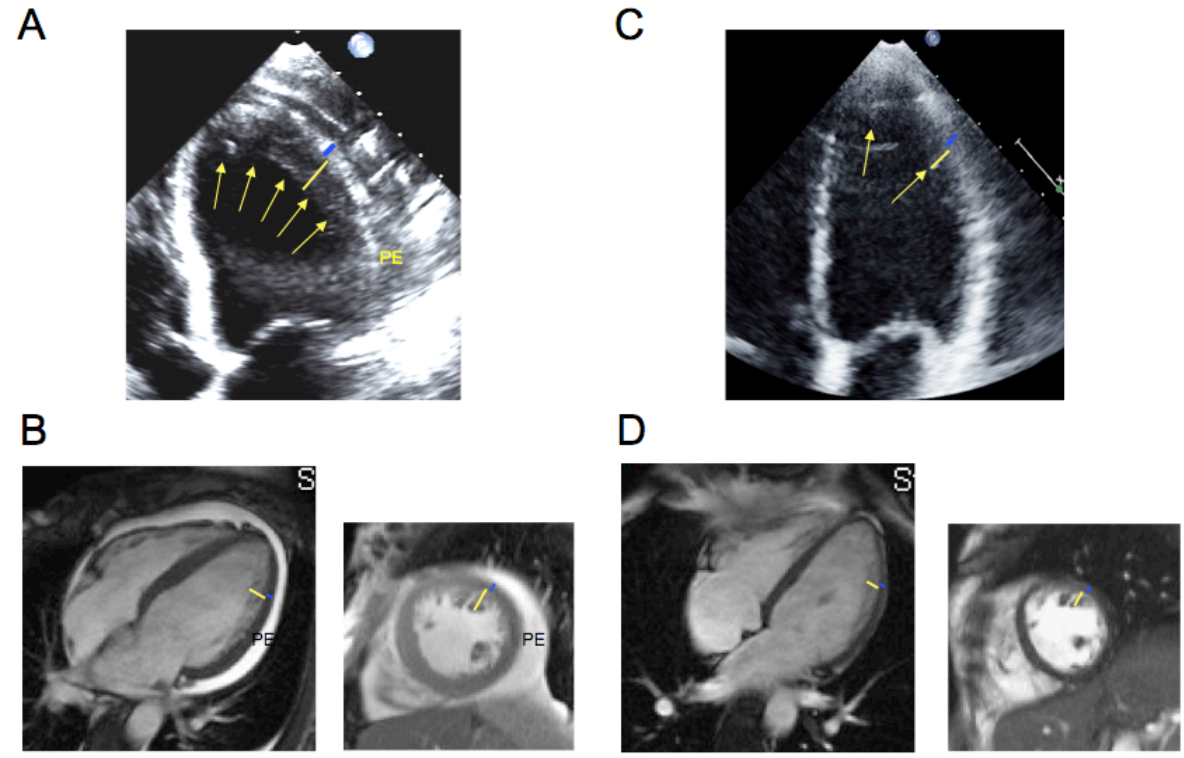

Figure 2


Apoptosis
Impaired Vessel maturation
Caspase 3/8/9 NF-κB
Proliferation Inhibition
Delta/ Notch
MAPK
16K PRL
ICAM VCAM SELE
Ras-Tiam-Rac1
Leukocyte adhesion
eNOS
Migration Inhibition
Vaso-dilatation inhibition