Imbalanced Angiogenesis in Peripartum Cardiomyopathy
— Diagnostic Value of Placenta Growth Factor —

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Background: Concentrations of the anti-angiogenic factor soluble fms-like tyrosine kinase-1 (sFlt-1) are altered in peripartum cardiomyopathy (PPCM). In this study we investigated changes in the angiogenesis balance in PPCM.

Methods and Results: Plasma concentrations of sFlt-1 and the pro-angiogenic placenta growth factor (PlGF) were determined in patients with PPCM during the post-partum phase (n=83), in healthy women at delivery (n=30), and in patients with acute heart failure (AHF; n=65). Women with cardiac failure prepartum or associated with any form of hypertension, including pre-eclampsia, were excluded. Compared with non-pregnant women, in women with AHF and PPCM, median PlGF concentrations were greater (19 [IQR 16–22] and 98 [IQR 78–126] ng/mL, respectively; P<0.001) and the sFlt-1/PlGF ratio was lower (9.8 [6.6–11.3] and 1.2 [0.9–2.8], respectively; P<0.001). The sFlt-1/PlGF ratio was lower in PPCM than in normal deliveries (1.2 [0.9–2.8] vs. 94.8 [68.8–194.1], respectively; P<0.0001). The area under the curve for PlGF (cut-off value: 50ng/mL) and/or the sFlt-1/PlGF ratio (cut-off value: 4) to distinguish PPCM from either normal delivery or AHF was >0.94. Median plasma concentrations of the anti-angiogenic factor relaxin-2 were lower in PPCM and AHF (0.3 [IQR 0.3–1.7] and 0.3 [IQR 0.3–1] ng/mL, respectively) compared with normal deliveries (1,807 [IQR 1,101–4,050] ng/mL; P<0.001).

Conclusions: Plasma of PPCM patients shows imbalanced angiogenesis. High PlGF and/or low sFlt-1/PlGF may be used to diagnose PPCM.

Key Words: Angiogenesis; Peripartum cardiomyopathy (PPCM); Placental growth factor; Relaxin-2

The incidence and prevalence of pregnancy-related heart disease is increasing worldwide.1 One of the conditions that is increasingly being recognized as an important contributor to early (<2 days postpartum) and late (up to 1 year postpartum) maternal death is peripartum cardiomyopathy (PPCM).2 PPCM most commonly presents with acute heart failure in the weeks following pregnancy, leading to urgent hospitalization.

Editorial p 1578

Despite improvements in diagnosis and management, PPCM continues to have significant morbidity and mortality.3,4 For reasons unknown, the time of onset of symptoms of PPCM varies according to region and ethnic group, with Black Africans presenting almost exclusively postpar-
Imbalanced Angiogenesis in PPCM

Table 1. Clinical Characteristics of PPCM Patients, Controls, and Parturients

<table>
<thead>
<tr>
<th></th>
<th>Healthy non-pregnant (n=29)</th>
<th>Pregnant (n=10)</th>
<th>At delivery (n=30)</th>
<th>PPCM patients (n=83)</th>
<th>AHF non-pregnant subjects (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>28 (24–31)</td>
<td>28 (25–38)</td>
<td>33 (30–37)</td>
<td>28 (24–34)</td>
<td>54 (48–61)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>60 (56–66)</td>
<td>–</td>
<td>–</td>
<td>30 (22–35)</td>
<td>30 (20–40)</td>
</tr>
<tr>
<td>Parity</td>
<td>3 (2–3)</td>
<td>–</td>
<td>–</td>
<td>2 (1–3)</td>
<td>–</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120 (114–125)</td>
<td>–</td>
<td>–</td>
<td>111 (107–122)</td>
<td>128 (105–158)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>70 (70–78)</td>
<td>–</td>
<td>–</td>
<td>70 (69–79)</td>
<td>77 (69–95)</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>78 (70–94)</td>
<td>105 (77–131)</td>
</tr>
</tbody>
</table>

Data are presented as the median (interquartile range). All subjects in all groups except the acute heart failure (AHF) group were women. In the AHF group, 45% of subjects were female. Additional information on AHF non-pregnant subjects is provided in Table S1. DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; PPCM, postpartum cardiomyopathy; SBP, systolic blood pressure.

 Methods

Plasma samples in the postpartum phase were collected prospectively from PPCM patients (n=83) seen at the Chris Hani Baragwanath Hospital, Soweto, the Groote Schuur Hospital, Cape Town (South Africa), or referred to the Assistance Publique-Hôpitaux de Paris, France. Inclusion criteria were as described previously, namely: (1) age ≥16 and ≤40 years; (2) symptoms of congestive heart failure that developed in the last months of pregnancy or during the first 5 months postpartum; (3) no other identifiable cause for heart failure; (4) left ventricle ejection fraction ≤45% by transthoracic echocardiography; and (5) sinus rhythm. Exclusion criteria were: (1) significant organic valvular heart disease; (2) systolic blood pressure >160mmHg or diastolic blood pressure >100mmHg; (3) clinical conditions other than cardiomyopathy that could increase plasma concentrations of inflammatory markers; and (4) severe anemia (hemoglobin <9g/dL). No patients with prepartum PPCM were included in the present study because in South Africa PPCM presenting prepartum is very rare; in addition, patients with postpartum cardiac failure associated with any form of hypertension, including pre-eclampsia, were excluded because we have shown previously that they have different characteristics. Clinical assessment, echocardiography, and blood analysis for PPCM patients were performed at the time of admission and hospitalization. Plasma samples were also collected from healthy non-pregnant women (n=29), healthy pregnant women (n=10; 20–36 weeks gestation), and healthy women after delivery (within 24h of delivery; n=30). Plasma samples from relatively young patients with acute heart failure (AHF; n=65; almost half of whom were women) from the “Biomarcoeurs” cohort were collected at admission. None of the patients was using heparin when blood samples were taken.

The primary objective of the present study was to focus on women after delivery and to assess whether plasma concentrations of factors contributing to the angiogenic balance, especially the sFlt-1/PlGF ratio, can distinguish between women with PPCM and those with a normal delivery, as well as between women with PPCM and those patients with other, non-pregnancy-related, causes of AHF.

The present study was approved by the relevant human research ethics committees of the participating institutes and complies with the Declaration of Helsinki. All study participants, including healthy women, provided written informed consent before entering into the study. The present study is a sub-study of the cohort registered with ClinicalTrials.gov (ID: NCT01374880).

Biomarker Testing

During initial patient examination, and within 4h of the unscheduled admission for acute dyspnea, blood samples were collected in plastic tubes containing EDTA, and aliquots of EDTA-plasma samples were stored in a standardized manner at −80°C until further analysis. Prior to analysis, samples were centrifuged through Nanosep micro-concentrator filters (Pall Filtron, Northborough, MA, USA) to remove proteins. Plasma concentrations of the different plasma biomarkers were quantified using commercially available kits. N-Terminal pro B-type natriuretic peptide (NT-proBNP) and sFlt-1 were quantified on a Roche Cobas E601 analyzer (Roche, Meylan, France), whereas copeptin and mid-regional pro-adrenomedullin (MR-proADM) were quantified on a Kryptor compact analyzer (Thermo-Fisher Scientific, Pittsburgh, PA, USA). An ELISA was used to determine plasma concentrations of soluble ST2 (sST2), as described previously (Presage...
Analyses of Myocardial Biopsies

Analyses were performed on myocardial biopsies taken at the time of heart transplantation from 6 donor hearts not suitable for transplantation (controls), 13 explanted hearts from patients transplanted for end-stage heart failure (AHF) patients, and from PPCM patients (n=2; 17 days and 20 months after onset of the disease). Clinical data have been described previously. Quantitative polymerase chain reaction (qPCR) was used to measure the mRNA expression of BNP, PI GF,
VEGF, relaxin, Flk1, Flt1 and sFlt1. Protein expression of Flk1, Flt1, VEGFα, PlGF and relaxin-2 was evaluated using immunoblotting. Tissue localization of the proteins was determined by immunofluorescence. For further details see Supplementary Methods.

Statistical Analysis
Results are expressed as median values with the interquartile range (IQR) or as counts and percentages. Comparisons of biomarkers among predefined groups of patients in the postpartum phase or not (see above for details) were made using Kruskal-Wallis or Mann-Whitney tests. The discriminative ability of each biomarker was evaluated by the c-statistic, identical to the area under the receiver operating characteristics (ROC) curve. Two outcomes were considered: (1) PPCM vs. delivery; and (2) PPCM vs. AHF non-pregnant. Statistical analyses were performed using R statistical software (http://www.r-project.org/). Two-sided P<0.05 was considered significant.

Results

The clinical characteristics of the different study groups, namely healthy non-pregnant women, healthy peripartum women (i.e., antepartum [median 29 weeks gestation] and at delivery [<24 h]), women with PPCM (median admission time 4.0 [IQR 3.4–4.6] weeks after delivery; all breastfeeding), and subjects with AHF, are given in Table 1 and Table S2.

Plasma Concentrations of Angiogenic Factors During Pregnancy and at Delivery
Plasma concentrations of the pro-angiogenic (PlGF, VEGF) and anti-angiogenic biomarkers (sFlt-1 and relaxin-2), as well as the sFlt-1/PlGF ratio, were all higher in pregnant women than in healthy non-pregnant women (Figure 1; Table 2). At delivery, PlGF and VEGF concentrations decreased, whereas sFlt-1 and relaxin-2 concentrations remained high and the sFlt-1/PlGF ratio was increased compared with values during pregnancy (Figure 1; Table 2).

Plasma Concentrations of Angiogenic and Cardiovascular Factors in Women With PPCM
Compared with non-pregnant AHF subjects, women with PPCM had similar high levels of NT-proBNP (Table 2), but different pro-angiogenic and anti-angiogenic profiles. Indeed, compared with AHF subjects, women with PPCM had much higher PlGF concentrations (median [IQR] 19 [16–22] and 98 [78–126] ng/mL, respectively; P<0.001), similar levels of VEGF and sFlt-1, and a lower sFlt-1/PlGF ratio (9.8 [6.6–11.3] and 1.2 [0.9–2.8], respectively; P<0.001; Figure 1; Table 2). Subjects in the AHF and PPCM groups had very low plasma concentrations of relaxin-2 (Figure 1), but concentrations of sST2 and MR-proADM were lower in the PPCM than AHF group (38.4 [21.9–72.4] vs. 82.2 [55–127.2], respectively, for sST2 [P<0.0001]; 0.7 [0.4–1.1] vs. 1.1 [0.8–1.7], respectively, for MR-proADM [P=0.00012]). Of note, circulating concentrations of the biomarkers evaluated herein did not differ according to age or sex in the AHF non-pregnant group (Table S3). No association was observed between pro- and anti-angiogenic factors and either left ventricular ejection fraction (LVEF) or NT-proBNP in PPCM patients.

Compared with women at delivery, women with PPCM had higher PlGF and VEGF concentrations (median [IQR] 97.5 [77.5–125.5] vs. 29 [19.2–40.8] ng/mL for PlGF [P<0.0001]; 268.5 [123–403.8] vs. 91 [6–141.5] ng/mL for VEGF [P<0.001]) and lower sFlt-1 concentrations (165 [99–265] vs. 3454.5 [1,716–4,566] pg/mL; P<0.0001), leading to a lower sFlt-1/PlGF ratio in the PPCM group (1.2 [0.9–2.8] vs. 95 [69–194]; P<0.0001). Relaxin-2 concentrations were lower in the PPCM group (0.3 [0.3–4.3] ng/mL than at normal delivery (1,807 [1,101–4,050] ng/mL; P<0.001; Figure 1), as were sST2 concentrations (Table 2).

Diagnostic Properties of Biomarkers Studied in PPCM vs. Non-Pregnant AHF
As indicated in Figures 2, 3 and Table S4, sFlt-1/PlGF and PlGF have striking diagnostic value in distinguishing PPCM from healthy women with a normal delivery or non-pregnancy-related AHF. ROC analyses comparing PPCM with non-pregnant AHF showed that the sFlt-1/PlGF ratio can discriminate PPCM from AHF (threshold at a cut-off value of 4). Similarly, PlGF discriminated between PPCM and AHF (threshold at a cut-off value of 32 ng/mL). The specificity and sensitivity of the sFlt-1/PlGF ratio were 0.92 and 0.74, respectively, for distinguishing PPCM from AHF.
ratio in diagnosing PPCM was 1.0 and 0.87–1.0, respectively (Table S4). As seen in Figure 2, sST2 and MR-proADM also exhibited good diagnostic value in diagnosis PPCM, although their sensitivity and specificity were much lower than those of PlGF or the sFlt-1/PlGF ratio. Figure 3 further shows that, when combined, sFlt-1/PlGF and relaxin-2 levels may define 3 clusters of patients: PPCM, AHF and delivery.

Myocardial biopsies from 2 explanted PPCM subjects were compared with myocardial biopsies of explanted subjects with DCM or control hearts. In biopsies from PPCM subjects, increased mRNA and protein expression was found for PlGF, sFlt-1, and relaxin-2 in myocardium and sFlt-1 in the endothelium (Figure 4 and Table S5).

Discussion

Impaired Angiogenesis in the Plasma of PPCM Patients

The present study revealed an angiogenic imbalance in favor of angiogenic factors in PPCM patients. Indeed,
PIGF was markedly higher and the sFlt-1/PIGF ratio markedly lower in PPCM than healthy women at the time of delivery. Furthermore, plasma sFlt-1 was low in the present PPCM cohort compared with women at delivery, and this is in line with plasma Flt-1 concentrations recently measured in peripartum cardiomyopathy patients.7 sFlt-1 is known to antagonize interactions of PIGF and VEGF with their endothelial receptors by binding to them. Accordingly, low plasma concentrations of sFlt-1 measured in the present study could explain the high plasma concentrations of the angiogenic factors PIGF and VEGF in PPCM patients. A low sFlt-1/PIGF ratio in PPCM patients was unlikely to be related to the AHF episodes because non-pregnant AHF subjects had a very high sFlt-1/PIGF ratio, almost 10-fold higher than that in PPCM patients.

An angiogenic imbalance in PPCM has been previously observed in experimental studies: Patten et al12 demonstrated that mice that lack cardiac peroxisome proliferator-activated receptor-γ coactivator-1α (PGC1α), a powerful regulator of angiogenesis, develop profound PPCM. Importantly, pro-angiogenic therapy with recombinant VEGF allowed for amelioration of PPCM. In contrast, Seno et al13 reported that an anti-PIGF neutralizing antibody prevented pressure overload-induced cardiac dysfunction in an sFlt-1-knockout mouse model. These experimental studies indicate that therapies targeting angiogenic imbalance in PPCM may be successful. This requires further exploration.

Relaxin-2 is a naturally occurring peptide initially identified as a reproductive hormone and a key player in maternal hemodynamic and renal adjustments that accommodate pregnancy.10 Intravenous relaxin (a relaxin-2 analog) has recently been shown to improve clinical symptoms and organ function when given at the time of hospital admission to patients with AHF.11 In the present study, plasma concentrations of relaxin-2 (measured in 2 independent laboratories) were very low in patients admitted with AHF, regardless of whether they were non-pregnant AHF or PPCM patients. This contrasts with findings of a previous study, which reported increased plasma relaxin-2 concentrations in stable chronic heart failure, especially in patients with New York Heart Association Class IV heart failure.15 Although relaxin-2 has been shown to stimulate VEGF expression,13 mechanisms regulating relaxin-2 expression (except placental overexpression during pregnancy) and release in the plasma are unknown. Interestingly, plasma concentrations of relaxin-2 have been shown to be very high during normal human pregnancy (ranging between 500 and 1,500 pg/mL), with peak values in the first trimester that decline in the second and third trimesters.16 This observation is consistent with the markedly increased production of relaxin from gestational tissue. Outside of pregnancy, as demonstrated in the present study, plasma relaxin concentrations decline sharply and are primarily derived from non-gestational tissue, such as the myocardium.

Myocardial biopsies of PPCM patients performed in the present study show a global increase in the mRNA and protein expression of all pro- and anti-angiogenic factors measured in PPCM compared with control and DCM patients. However, pronounced differences in sFlt-1 and relaxin-2 (RLN2) mRNA expression in cardiac tissues of PPCM and of AHF patients contrasts with the lack of difference in circulating sFlt-1 and relaxin-2 concentrations between these 2 groups. This may suggest that the contribution of cardiac sFlt-1 or relaxin-2 to plasma levels is minor. In contrast, myocardial expression and circulating concentrations of PIGF were consistently increased in PPCM compared with AHF and control subjects, suggesting that, in PPCM, the heart may be an important source of circulating PIGF. This needs to be confirmed in further studies.

Little information is available on the myocardium in human PPCM. Previous histological studies demonstrated structural remodeling of myocardial capillaries in PPCM patients suggestive of endothelial damage and disturbed microcirculation.17 The findings of the present study further confirm the importance of angiogenic imbalance in PPCM.

In summary, the present study showed that PPCM was associated with altered angiogenesis in both the plasma and hearts of PPCM patients.

Clinical Relevance

There is an increased awareness of PPCM promoted by a dedicated working group at the Heart Failure Association of the European Society of Cardiology (www.escardio.org) and the International Registry on Peripartum Cardiomyopathy, which is part of the EURObservational Research Programme, with more than 450 PPCM patients from 40 countries recruited thus far (http://www.eorpc.org). In addition, the number of original and review publications on PPCM on PubMed has increased substantially over the past 20 years. However, PPCM remains a diagnosis of exclusion: all patients should undergo investigations to identify any alternative etiology for heart failure. In this context, there is a need for diagnostic biomarkers. The present study showed that PPCM patients presenting post-partum, the most frequent form of PPCM, have a unique biomarker feature: PIGF and/or the sFlt-1/PIGF ratio, readily available biomarkers in obstetric hospitals, may, in the days or weeks following delivery, discriminate PPCM from other causes of acute dyspnea, whether they are related to acute decompensated heart failure or not. Other cardiovascular biomarkers, namely copeptin, MR-proADM, and sST2, performed less well in the diagnosis of PPCM.

Study Limitations

In the present study, PPCM patients were included from a limited number of countries and future studies should have a wider geographic representation. Expanding the study to a larger population of different ethnic backgrounds, including patients presenting prepartum and with contributing comorbidities, such as pre-eclampsia, is now achievable in the context of the EURObservational Research Programme. In countries with a high rate of pregnant women with a history of heart disease, acute dyspnea during the peripartum phase may be related to decompensation of cardiac disease or to PPCM. It would have been of interest to assess angiogenesis in women after delivery who had been admitted for acute dyspnea not related to PPCM; however, such patients and such presentation are rare and so difficult to include in a study. It has to be noted that that the patients with PPCM in the present study were diagnosed during the postpartum and not the antepartum period. In order to determine whether the biomarkers identified as possible diagnostic tools for PPCM in the present study are more widely applicable to the general population, future
studies should include all patients admitted for acute dyspnea during the peripartum phase and assess plasma PI GF and/or the sFlt-1/PIGF ratio in these patients. The number of myocardial biopsies for PPCM in the present study was extremely low. However, for many biomarkers tested, mRNA and protein expression differed considerably in PPCM compared with DCM and controls subjects. Despite this, larger studies are needed in the future to confirm the findings presented herein.

One important limitation of the present study is related to the highly specific physiological changes that take place during the peripartum phase, which involves upregulation and fast clearance of pregnancy-related hormones, growth factors, and cytokines. In particular, concentrations of PI GF, sFlt-1 and relaxin-2 are markedly elevated towards the end of pregnancy and in the first days after delivery, but return to normal thereafter. In the present study, we did not obtain plasma samples from “normal” pregnant women 4 weeks after delivery. Therefore, the differences observed in the aforementioned serum markers may be due, at least in part, to differences in the timing of blood sampling between the immediate postpartum controls and the PPCM patients, in which sampling was performed at the time of diagnosis. Therefore, the generally lower relaxin-2 concentrations in the serum of PPCM patients could also be explained by the later timing of blood sampling in relation to delivery and may simply reflect normal clearance of the hormone postpartum. However, persistence of high PI GF concentrations and very low values for the sFlt-1/PIGF ratio in PPCM patients is unusual in the postpartum phase and may be markers of PPCM. In order to better assess the postpartum time course of these biomarkers, future studies should compare women in the days, weeks, and months following delivery and, ideally, include breastfeeding and non-breastfeeding women. The effects of lactation on physiological regression of postpartum left ventricular hypertrophy, the role of prolactin products, and reverse remodeling under healthy conditions and in diseased hearts deserve further research, because these factors may have implications for a number of cardiovascular diseases in women who are pregnant.

Another important limitation of the present study is the lack of echocardiographic characteristics other than LVEF. It would be interesting to describe echocardiographic profiles of cardiac dysfunction in PPCM patients and to investigate correlations with pro- and anti-angiogenic factors.

Conclusions

The present study showed impaired angiogenesis in the plasma and myocardial tissues of PPCM patients. Compared with other biomarkers that have been shown to be altered in PPCM, such as microRNAs, both PI GF and/or the sFlt-1/PIGF ratio are readily available biomarkers in obstetrics that can be used to ascertain a diagnosis of PPCM in acute dyspneic patients. The results of the present study highlight the close interaction between the cardiovascular system and the placenta, providing further evidence for the already described cardioplaental syndrome.

Acknowledgments

The authors acknowledge Lauren Nicholson for help with sample collection from healthy control patients and Sylvia Dennis for assistance with manuscript preparation. The authors further acknowledge Grazia Bagagli (Roche Diagnostics) for providing the sFlt-1 kits and Régine Merval for technical support. The authors thank the tissue bank of Bichat Hospital (Paris, France) for providing cardiac tissues.

Sources of Funding

The authors acknowledge the overall support of the Medical Research Council South Africa, National Research Foundation South Africa, the University of Cape Town (to K.S.), the Heart Failure Association of the European Society of Cardiology (to K.S., A.M.), an INSERM/ AP-HP Interface grant (to J.-L.S.), the Ligue Française contre la Cardiomyopathie (to M.-F.S.), a training grant from the French Government and the Embassy of France in Lithuania (to J.M.), and a HOMAGE (Heart OMics in AGEn) grant (#305507) funded by the European Union.

Conflict of Interest

A.M. reports being on advisory boards for Bayer, Cardiorentis, and The Medicines Company and receiving lecture fees from Alere, Edwards, Orion, Novartis, Vifor, and Thermo-Fisher. A.C.S. has been a consultant for Novartis. A patent application is pending on biomarkers in cardiovascular disease during the peripartum period. The patent belongs to the Assistance Publique-Hôpitaux de Paris (France), to which A.M. and J.-M.L. belong, and the University of Cape Town (South Africa), to which K.S. belongs. The inventors (J.-M.L., K.S., A.M.) may benefit from the patent application. The remaining authors have no conflicts of interest to declare.

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Imbalanced Angiogenesis in PPCM


Supplementary Files

Supplementary File 1
Supplementary Methods

Figure S1. Comparison of relaxin-2 measures between INSERM U942 Laboratory (Paris, France) and the Academic Unit of Reproductive and Developmental Medicine, The University of Sheffield Medical School (Sheffield, UK).

Table S1. Characteristic of the ELISA quantification used throughout the study

Table S2. Additional characteristics of non-pregnant AHF patients (n=65)

Table S3. Comparisons of biomarkers among non-pregnant AHF patients according to sex and age

Table S4. Specificity and sensitivity of biological markers to discriminate PPCM from non-pregnant AHF subjects

Table S5. Clinical characteristics of the 2 PPCM patients who underwent myocardial biopsies

Please find supplementary file(s); http://dx.doi.org/10.1253/circj.CJ-16-1193