The use of speckle tracking echocardiography and cardiac biomarkers for diagnosis of patients with peripartum cardiomyopathy

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Context
Peripartum cardiomyopathy (PPCM) is a well-known though poorly understood disease.

Aim
We aimed to provide new diagnostic tools for patients with PPCM using speckle tracking echocardiography (STE) and cardiac biomarkers.

Patients and methods
This is a case–control study. We recruited 20 patients with newly discovered PPCM and 20 control women. They were subjected to 2D traditional echocardiography, STE, and serum analysis for N-terminal probrain natriuretic peptide (NT-proBNP) and cardiac troponin I (cTn-I).

Results
The mean age of the patients was 29.7 ± 7.63 years. Overall, 75% of them presented in the postpartum period. Patient's left ventricular ejection fraction (LVEF) was impaired compared with controls at presentation (34.2 ± 8.84 vs. 62.65 ± 5.61%, $P < 0.001$). Their serum level of NT-proBNP was 1416.55 ± 590.23 versus 60.55 ± 26.398 pg/ml ($P < 0.001$) and for cTn-I, it was 0.1 ± 0.16 versus 0 ± 0 ng/ml ($P = 0.014$). The STE showed reduction of global longitudinal strain (GLS) (−10.02 ± 6.76 vs. −19.49 ± 2.82%, $P < 0.001$) and global circumferential strain (GCS) (−11.84 ± 3.34 vs. −23.63 ± 2.93%, $P < 0.001$). The GLS of apical four chamber view had 100% sensitivity and 40% specificity, GLS of apical two chamber view had 100% sensitivity and 60% specificity, GLS of apical three chamber view had sensitivity and specificity of 80%, and GCS of left ventricle had 100% sensitivity and 80% specificity for prediction of LVEF.

Conclusion
Global longitudinal and circumferential strains are depressed in patients with PPCM. GLS apical four chamber view, GLS apical two chamber view, and GCS had high sensitivity and 40–80% specificity for LVEF changes, so strain can be used as an objective marker of left ventricular dysfunction in patients with PPCM. NT-proBNP and cTn-I can help in the diagnosis of peripartum patients presented to emergency room with symptoms and signs of heart failure.

Keywords:
biomarkers, heart failure, myocardial strain, peripartum, speckle tracking

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Introduction

Peripartum cardiomyopathy (PPCM), first described in 1849, is a well-known though poorly understood malady [1].

The Working Group on PPCM of the Heart Failure Association of the European Society of Cardiology [1] proposed that the PPCM is a nonfamilial form of left ventricular (LV) systolic dysfunction occurring toward the end of pregnancy up to the few months after delivery, where no other causes of this dysfunction could be detected.

This disease's mortality rates are not yet well characterized, ranging from 4 to 50% [2].

This relatively rare disease has geographically variable incidence ranging from 1: 100 live births in some of the sub-Saharan countries to as rare as 1: 2500–1: 4000 in the USA [1].

Complete recovery of left ventricular ejection fraction (LVEF) is more frequent in PPCM compared with other forms of cardiomyopathy and occurs mostly within the first 6 months of treatment, ranging from 20 to 60% in different studies [3], and other studies have demonstrated recovery beyond 6 months [4].

The definite mechanisms of PPCM are still unknown; however, some general risk factors for cardiovascular disease (such as hypertension, diabetes, and smoking)

and pregnancy-related factors (such as aging, number of childbearing, drugs-facilitating delivery, and malnutrition) have received some attention [5].

Symptoms of PPCM usually overlap with the symptoms of normal pregnancy such as dyspnea and pedal edema.

As it is a disease of exclusion, different modalities are needed for the diagnosis of PPCM and include ECG, cardiac biomarkers, and different cardiac imaging modalities such as chest radiography, two-dimensional (2D) echocardiography, cardiac MRI, and 2D speckle tracking echocardiography (STE).

The more recently developed STE is a gray-scale based and angle-independent technique that permits more comprehensive assessment of myocardial deformation. Global longitudinal strain (GLS), which is the myocardial deformation from the base toward the apex, recently has been validated as a quantitative index for global LV function [6].

With the use of myocardial deformation imaging, ventricular dysfunction may be detected in a preclinical phase [7]. Studies of patients with dilated cardiomyopathy showed that STE can prognosticate those patients with cutoff values of −4.9 and −12% for GLS in the prediction of events [8]. Similarly, studies of patients with malignancy treated with chemotherapeutics showed reduction of the GLS before overt reduction of the LVEF, providing a window of opportunity for preventive measures [9].

N-terminal probrain natriuretic peptide (NT-proBNP) is markedly elevated in most patients with PPCM with little overlap to healthy peripartum women [10]. COPERNICUS NT-proBNP substudy showed that heart failure (HF) patients with NT-proBNP less than 199 pg/ml carried better prognosis than those with levels more than 504 pg/ml [11].

Studies of cTn revealed that beside their role in acute coronary syndromes, troponins have important function in both acute and chronic HF [12]. The ADHERE study showed higher mortality in hospitalized patients with HF and raised cTn levels at the time of admission [13].

Patients and methods

This investigation conforms with the principles outlined in the Declaration of Helsinki (*Br Med J* 1964; ii: 177). The study duration was 18 months, and all (n = 20) women either pregnant in the last trimester of pregnancy or in the few months postpartum who presented with symptoms and signs of HF and their 2D transthoracic echocardiography (TTE) revealed impaired LVEF were recruited. Women who are documented to be cardiomyopathic owing to valvular, ischemic, or hypertensive heart disease and those with pre-existing idiopathic cardiomyopathy were excluded from the study. The diseased patients were compared with equivalent number of age-matched and weight-matched group of women who were either pregnant in the third trimester or few months in the postpartum period.

The diseased group was subjected to thorough history taking, clinical examination, full TTE assessment, and evaluation of serum levels of NT-proBNP and cardiac troponin I (cTn-I) at admission. Control group was assessed once.

TTE and 2D STE evaluation were done according to the latest European Society of Cardiovascular Imaging guidelines [14,15], using Philips EPIQ7 (Philips healthcare company, Washington USA) ultrasound system and the latest Philips speckle tracking (ST) software (Q.Lab 10 [Philips health care company Washington, USA]) for speckle tracking analysis. ECG gated three-beat loops of apical four, three, and two chambers views in addition to short-axis views at the level of mitral valve, papillary muscle, and cardiac apex were recorded to assess the longitudinal and circumferential strains. After acquiring, the loops were uploaded to the ST software, the view was defined, then automatic delineation of the myocardial borders was done. Manual adjustment of the border delineation by the operator was carried out when necessary.

Overall, 5 ml of blood was withdrawn from the patients and control; 2 ml was used for assessment of serum cTn-I using PATHFAST cTnI (reagent for PATHFAST)-REF: PF-1011-K kits (Mitsubishi chemical Europe GmbH, Wllstaetterstr 30,40549Duesseldorf, Germany), and the remaining 3 ml of blood was centrifuged and the resultant serum was stored at −50°C. Using human NT-proBNP ELISA kits (catalog no. SG 10015; SinoGeneclon Biotech Co. Ltd, Hangzhou, China), assessment of the NT-proBNP levels of the stored serum was carried out.

Results

During 18 months, 20 women with PPCM were included in this study. The mean age and BMI were 29.7 ± 7.63 years and 29.5 ± 2.62 Kg/m2, respectively. Overall, 45% of the patients gave birth to a single male fetus, whereas 50% gave birth to a single female fetus. The main presentation was LV function with

New York Heart Association (NYHA) class IV, with 75% of the patients presented in the postpartum period (Table 1).

The mean LVEF was 34.2 ± 8.84% in the patients versus 62.65 ± 5.61% in the controls (P < 0.001). LV diastolic dysfunction was evident in all of the patients and ranged from grade I up to grade III, whereas all of the controls showed normal LV diastolic function (average LV E′ wave velocity of the patients was 7.62 ± 1.94 cm/s vs. 13.31 ± 1.35 cm/s of the controls, P < 0.001) (Table 2).

Cardiac enzymes were significantly raised in patients compared with controls. NT-proBNP was 1416.55 ± 590.23 pg/ml in the patients versus 60.55 ± 26.398 pg/ml in the controls (P < 0.001), and cTn-I was 0.1 ± 0.16 ng/l in the patients versus 0 ± 0 ng/l in the controls (P = 0.014) (Table 2).

On presentation, the patients' STE showed marked reduction of all segmental strains and consequently of the GLS and global circumferential strain (GCS) (−11.84 ± 3.34 vs. −19.49 ± 2.82% and −10.02 ± 6.76 vs. −23.63 ± 2.93%, respectively, with P < 0.001) (Table 3).

A strong positive correlation was found between the LV GLS and LVEF (R = 0.634, P = 0.027) and between the LV GCS and LVEF (R = 0.743, P = 0.006).

Table 1 The demographic data of the patient and the control groups

	Patients (n=20)	Controls (n=20)	P
Age (years)	29.7±7.63	28.6±7.47	0.648
Weight (kg)	86.45±22.13	83±10.39	0.532
Height (cm)	161.45±19.65	165±5.1	0.439
BSA (m^2)	1.89±0.13	1.9±0.14	0.879
BMI (kg/m^2)	29.5±2.62	30.34±2.66	0.319

Values are represented as mean±SD.

Table 2 Serum cardiac biomarkers and two-dimensional echocardiographic parameters of the patient and control groups

	Patients	Controls	P
NT-proBNP (pg/ml)	1416.55±590.23	60.55±26.398	<0.001**
Troponin-I (ng/ml)	0.1±0.16	0±0	0.014*
LVEDD (mm)	59.75±11.49	46.05±5.43	<0.001**
LVESD (mm)	49.05±11.74	29.85±4.03	<0.001**
IVSd (cm)	0.79±0.11	0.86±0.15	0.078
PWd (cm)	0.74±0.17	0.85±0.11	0.017*
EDV (ml)	140.65±48	85.2±19.22	<0.001**
ESV (ml)	88.45±35.72	36.15±13.36	<0.001**
FS (%)	16.8±4.58	33.75±4.85	<0.001**
EF by M-mode (%)	34.2±8.84	62.65±5.61	<0.001**
EF by Simpson (%)	34.5±7.77	61±5.55	<0.001**

Values are represented as mean±SD. EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; FS, fractional shortening; IVSd, interventricular septum dimension in diastole; LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; NT-proBNP, N-terminal probrain natriuretic peptide; PWd, posterior wall dimension in diastole. *Significant. **Highly significant.

Table 3 The two-dimensional speckle tracking echocardiographic strain values of the patients and control groups

	Patients (n=20)	Controls (n=20)	P
GLS A4C (%)	−12.28±3.2	−19.74±3.27	<0.001**
GLS A2C (%)	−10.95±4.2	−19.33±3.34	<0.001**
GLS A3C (%)	−11.68±3.48	−18.68±3.13	<0.001**
GLS (%)	−11.84±3.34	−19.49±2.82	<0.001**
EF by STE (%)	36.22±6.85	56.93±5.62	<0.001**
GCS basal level (%)	−10.66±3.45	−18.62±4.2	<0.001**
GCS mid cavity (%)	−11.66±5.6	−21.87±3.34	<0.001**
GCS apical level (%)	−13.17±5.83	−32.51±5.57	<0.001**
GCS (%)	−10.02±6.76	−23.63±2.93	<0.001**

Values are represented as mean±SD. A2C, apical two chamber view; A3C, apical three chamber view; A4C, apical four chamber view; EF, ejection fraction; GCS, global circumferential strain; GLS, global longitudinal strain; STE, speckle tracking echocardiography. **Highly significant.

Discussion

The main findings of our study can be summarized as follows: (i) the main presentation of PPCM was severe HF with NYHA class III–IV. (ii) Most of our patients presented postpartum. (iii) NT-proBNP and cTn-I were significantly elevated on presentation. (iv) Both LVEF by traditional 2D echocardiography and STE strain parameters were severely depressed in our patients.

Sliwa *et al.* [16] showed in their study similar results, with the mean age of the patients being 30.7 ± 6.4 years; overall, 36.6% of patients with PPCM were in NYHA functional class III and 32.2% in class IV. Two-third of patients presented after delivery (mostly within the first month postpartum) and one-third prepartum.

The mean LVEF of our patients was 34.2 ± 8.84%, and diastolic and systolic dimensions were 59.75 ± 11.49 and 49.05 ± 11.74 mm, respectively. In accordance to our results, Sliwa *et al.* [16] and Li *et al.* [17] showed close echocardiographic findings with mean LV end-diastolic dimension of 60.3 ± 8.0 and 60.7 ± 5.2 mm and LVEF of 32.2 ± 9.9 and 36.1 ± 6.6%, respectively. However, 40% of our patients had normal LV end-diastolic dimension.

Serum NT-proBNP and cTn-I were markedly raised in the patients compared with the controls. In a study of 43 women who were newly diagnosed with PPCM by Forster *et al.* [18], there were elevated serum levels of NT-proBNP specially in those who did not show improvement of the cardiac function on follow up. The baseline median serum levels of NT-proBNP were significantly higher in nonimprovers (NIMP) than in improvers (IMP) (NIMP: 2203.1 fmol/ml vs. IMP: 1632 fmol/ml, P = 0.0013). After 6 months,

NT-proBNP levels were still significantly (P = 0.0018) lower in IMP compared with NIMPs (IMPs: 935 fmol/ml, range: 331–2059 fmol/ml; NIMP: 1713 fmol/ml, range: 883–2895 fmol/ml).

Among 106 recruited patients in the study of Hu *et al*. [19], there were 33 patients with cTnT concentrations more than 0.04 ng/ml and 73 patients with cTnT concentrations less than or equal to 0.04 ng/ml; the normal reference range of the used kits is less than 0.01 ng/ml. After a 6-month follow-up, there was significantly smaller LVEF [35.42% vs. 50.16%, P = 0.0001] and more persistent LV dysfunction [84.8 vs. 31.5%, odds ratio = 12.17 (95% CI: 4.17–35.57), P = 0.001] in patients with cTnT more than 0.04 ng/ml than in patients with cTnT less than or equal to 0.04 ng/ml.

STE is a novel technique for assessing LV function. Moreover, there are different packages for STE from different vendors, so there is considerable intervendor variability of the values of different STE parameters. To our knowledge, very few studies were carried out to assess the LV function of patient with PPCM using the STE.

Briasoulis *et al*. [20] in a study on 47 patients newly diagnosed as having PPCM performed STE but using ST package diff erent from that used in our study. However, Briasoulis *et al*. [20] found reduction of the longitudinal strain profile of the LV. GLS was −8.8 ± 4 for cases versus −15.2 ± 1.9 of the controls (P < 0.001).

Sugahara *et al*. [21] in a study on 100 patients with PPCM to assess the racial difference in the recovery of LV function after PPCM found that the GLS absolute values were reduced too.

There is no available study assessing the circumferential strain in patients with PPCM. We found that the GCS was depressed in the patients compared with the controls (−10.02 ± 6.76 vs. −23.63 ± 2.93%, P < 0.001).

Conclusion

(1) Both longitudinal strain and circumferential strain are depressed in patients with PPCM. GLS of apical four chamber view, GLS of apical two chamber view, and GCS had high sensitivity and 40–80% specificity for LVEF changes
(2) On the basis of these findings, strain can be used as an objective marker of LV dysfunction in patients with PPCM.NT-proBNP and cTn-I can help in the diagnosis of peripartum patients presented to emergency room with symptoms and signs of HF.

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Conflicts of interest

There are no conflicts of interest.

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