Detection of Peripartum Myocardial Burden by Vector-Projected 187 Channel Electrocardiography and Serum NT-proBNP

Miyuki Terata,1 MD, Kenji Nakai,2 MD, Akimune Fukushima,3 MD, Manabu Itoh,2 Akihiko Kikuchi,1 MD, and Toru Sugiyama,1 MD

SUMMARY

There is no reliable method of screening for pregnant women at high risk of developing severe myocardial disorders. In this study, we used vector-projected 187 channel electrocardiography (DREAM-ECG) and serum biochemical markers to evaluate peripartum myocardial burden in pregnant women. Forty-one pregnant women were examined at 36-37 weeks gestation (GW36), 7 days postpartum (PPD7), and 1 month postpartum (PPM1). Ten non-pregnant control women were assessed at a single time point. Heart rate, sympathetic index, and repolarization index (RTc dispersion) were quantified using the DREAM-ECG system, and serum levels of NT-proBNP, cardiac troponin T, estrogen, and progesterone were determined. Heart rate and the sympathetic index decreased from GW36 to PPM1 (P = 0.0031). The repolarization index decreased over time and was greater than in non-pregnant controls (31 ± 13 ms). Estrogen and progesterone at PPD7 and PPM1 were significantly lower than those at GW36 (P < 0.0001, P < 0.001). NT-proBNP at PPD7 was greater than at GW36 (median 29 pg/mL at GW36, 86 pg/mL at PPD7), and decreased at PPM1 in comparison to PPD7 (median 18.5 pg/mL). Troponin T was in the normal range during the whole period (< 0.003 ng/mL). In conclusion, these results indicate that the peripartum myocardial burden in pregnant women does not return to normal non-pregnant levels by PPM1. We propose that both repolarization indexes such as RTc dispersion by DREAM-ECG and serum biochemical markers may identify pregnant women at high risk of developing severe myocardial damage in the peripartum period. (Int Heart J 2013; 54: 140-145)

Key words: Pregnancy, Activation recovery time, Myocardial impairment, Vector projection

Throughout the pregnancy and postpartum periods the function of the cardiovascular system changes drastically.1 Cardiac output increases from 5 weeks gestation and changes in hemodynamics become apparent from 8 weeks gestation.2 Heart rate at rest increases approximately to 10 beats/minute during pregnancy, and plasma volume and pre-load increase from 10 to 20 weeks gestation.3 It has been reported that cardiac output during pregnancy increases by 20%.4 Such cardiac burdens are considered to be prominent from the second half of pregnancy to the early postpartum period.5

Although peripartum cardiomyopathy (PPCM) is one of the most severe conditions seen in obstetric practice, reliable screening methods for pregnant women at high risk of developing severe myocardial disorders have not been established.6 In current routine clinical obstetrics, myocardial damage is not assessed in pregnant women. Nakai, et al reported that markers of abnormal repolarization, such as T wave alternans and RTc dispersion, could be successfully assessed as risk stratification for myocardial injury using a vector-projected 187-channel high-resolution electrocardiograph system (DREAM-ECG).7,8 In this study, we evaluated peripartum myocardial burden in pregnant women using the DREAM-ECG system and serum biochemical markers.

METHODS

Subjects: We examined 41 pregnant women aged 22 to 40 years, with a singleton pregnancy who delivered an infant at the Iwate Medical University Hospital between March 2011 and August 2012. These registered pregnant women had no history of thyroid diseases, diabetes mellitus, or dyslipidemia. Control subjects for the electrocardiographic analysis consisted of 10 non-pregnant healthy women, aged 24 to 34 years, with no history of cardiac diseases. The mean age of the control subjects was not significantly different from that of the pregnant women. All participants provided written informed consent. This study was approved by the Ethical Review Board of the Iwate Medical University School of Medicine (H22-147).

Experimental design: The pregnant women were examined longitudinally at 36-37 weeks gestation (GW36), 7 days postpartum (PPD7), and 1 month postpartum (PPM1). The control women were examined on one occasion, at the time of enroll-
The DREAM-ECG system consisted of an input box with high resolution and high amplification (IB-81, Fukuda Denshi Co., Ltd., Tokyo) and custom software (ECG manager, ICS Co., Ltd., Morioka, Japan). The minimum resolution was 0.076 μV. The ECG signal was obtained using the Mason-Likar lead system and silver-silver chloride electrodes with magnets (Magunerode®, TE-18 series, Fukuda Denshi Co., Ltd., Tokyo), and was sampled for 10 minutes at 2 kHz. On GW36, PPD7, and PPM1, blood was collected from the pregnant women and their weight and blood pressure were recorded.

**Outcome variables:** Heart rate was determined using the following equation from the R-R interval (HR = 60,000/R-R interval). The sympathetic index was determined as an indicator of sympathetic nerve activity. Spectral analysis of R-R variability was performed, and the sympathetic index was calculated as the ratio of the maximum peak of the high-frequency region (around 0.3 Hz) to the maximum peak of the low-frequency region (around 0.1 Hz) shown in Figure 1. 7-10

187-channel ECG was based on vector-projected theory and was obtained from 187 body surface electrode positions. Two-dimensional repolarization function maps (RTc dispersion maps) were determined from the current density map (Figure 1), and the repolarization index (recovery time (RTc) dispersion and Tpeak-end (T_p-e) dispersion) were determined. 7,8 In brief, values of dispersion were calculated by the difference of the maximum and minimum of corrected RTc intervals and Tp-e intervals after Bazzet correction shown in Figure 1.

Serum NT-proBNP, cardiac troponin T, estrogen, and progesterone were determined. NT-proBNP is a marker of heart failure and has a half-life of 60-120 minutes. 11 Cardiac troponin T is a structural protein of the heart and is a marker of cardiomyopathy, and has a half-life of 120 minutes (Special Reference Laboratory Co., Ltd., Tokyo). Estrogen and progesterone are female hormones secreted from the ovary and the placenta during pregnancy. They play physiological roles in maintaining pregnancy.

**Statistical analysis:** Statistical analysis was performed with Prism 4 software (GraphPad, USA). Comparison between groups was performed using a one-way analysis of variance (ANOVA). P values < 0.05 were considered to be statistically significant.

**Results**

The body mass indices and blood pressures of the pregnant women at GW36, PPD7, and PPM1 are shown in Table I. Two patients developed pregnancy-induced hypertension. The DREAM-ECG and serum biochemical variables of pregnant women at GW36, PPD7, and PPM1 are shown in Table II. There was a temporal change in DREAM-ECG variables. Heart rate decreased with time (81 ± 10 bpm at GW36, 73 ±
22 bpm at PPD7, and 68 ± 8 bpm at PPM1; \( P = 0.0031 \), as did the sympathetic index (1.01 ± 0.19 at GW36, 0.89 ± 0.14 at PPD7, and 0.94 ± 0.14 at PPM1; \( P = 0.0031 \)). RTc dispersion decreased with time (47 ± 19 ms at GW36, 46 ± 14 ms at PPD7, and 44 ± 13 ms at PPM1), and was greater than that in controls (32 ± 14 ms) (Figure 2).

Estrogen and progesterone at PPD7 and PPM1 were significantly lower than those at GW36 (Estrogen: 28,463 ± 9,942 pg/mL at GW36, 52 ± 42 pg/mL at PPD7, and 47 ± 64 pg/mL at PPM1; \( P < 0.0001 \), Progesterone: 208 ± 55 ng/mL at GW36, 1.3 ± 1.3 ng/mL at PPD7, and 0.6 ± 1.8 ng/mL at PPM1; \( P < 0.001 \)). The serum levels of NT-proBNP increased at PPD7 (median 29, range 5-179 pg/mL at GW36, median 86, range 10-496 pg/mL at PPD7, and decreased at PPM1 (median 18.5, range 5-167 pg/mL at PPM1) shown in Figure 3. There was no significant correlation between RTc dispersion and NTproBNP at PPD7. A representative case with pregnancy-related hypertension exhibited increased RTc dispersion and NTproBNP at PPD7 and PPM1 shown in Figure 4. The troponin T level was within the normal range (< 0.003 ng/mL) at GW36, PPD7, and PPM1.
In our study population, there were no cases of PPCM that developed into heart failure.

**DISCUSSION**

The present study showed that RTc dispersion in pregnant women tended to exceed the reference value in non-pregnant control women. Serum levels of NT-proBNP were initially elevated in early postpartum, but subsequently returned to the normal range. These findings suggest that the cardiovascular burden in pregnant women does not recover to a normal non-pregnant level by one month postpartum. Based on these results, we propose that DREAM-ECG and serum biochemical markers may help identify pregnant women at a high risk of developing severe myocardial damage such as PPCM in the peripartum period.

PPCM that manifests as developing heart failure is rarely seen in the peripartum period. However, the cause of myocardial damage is unknown. There were no cases of PPCM in our study population. According to previous reports, the incidence of PPCM in Japan is lower than in the USA (1/20,000 births versus 1/4,075 births). Several reasons, including ethnicity and lifestyle, might underlie this discrepancy, and there is also a possibility that some patients are undiagnosed. Demakis proposed the following diagnostic criteria for PPCM: 1) Development of heart failure in the final 5 postpartum months; and 2) Absence of a determinable etiology for cardiac failure, and presence of diagnostic echocardiographic criteria including left ventricular fractional shortening < 30%, left ventricular ejection fraction < 45%, and end-diastolic dimension > 27 cm/m². The vast majority of PPCM patients are diagnosed during the first month of postpartum.

Risk factors for PPCM include advanced maternal age, multiparity, multiple gestation, pregnancy-induced hypertension syndrome, and the use of tocolytic agents. Cardiac function is decreased in 40% of cases, and heart transplantation is required in 10% of the most severe cases. No effective method for the prediction of PPCM onset has been found. We propose that a new evaluation method that includes both DREAM-ECG variables and biochemical markers may be effective for early screening of PPCM. DREAM-ECG requires a small input box and a personal computer, and can be performed at bedside. A feature of this system is signal-averaging and synthetic 187-channel ECG generation from standard 12-lead ECG data. Theoretically, the activation recovery time of the action potential duration is reflected in the RTc interval, and RTc dispersion may relate to myocardial load or injury.

Previously, Suzuki, *et al* indicated that the interlead difference between corrected recovery time intervals (equal to RTc dispersion) was significantly higher (98 ± 24 msec) in heart failure patients receiving cardiac resynchronization therapy with a defibrillator (CRT-D). In this study, 76% of the heart failure patients had dilated cardiomyopathy, and the preimplantation left ventricular ejection fraction was 25 ± 11%.

In the present study, we have found that RTc dispersion is a simple index for assessing myocardial burden. In addition, analysis of sympathetic nerve activity and depolarization and repolarization abnormalities is possible from the same recording, and the DREAM-ECG system can be used to record fetal ECG. In the future, we would like to see DREAM-ECG used for maternal and perinatal screening of ECG abnormalities such as prolongation QT syndrome of the fetus and myocardial damage in pregnant women.

The usefulness of NT-proBNP, like BNP, as a marker for heart failure is well known. High levels of NT-proBNP in the blood are characterized by a large molecular weight, and NT-proBNP has a long half-life compared to BNP. Measurement of NT-proBNP is possible in serum, as it has a more stable value than BNP. We found that the median value of NT-proBNP was higher at PPD7 than at GW36 or PPM1. Yamada, *et al* reported that the median NT-proBNP level in normal pregnancy...
was 37 pg/mL, 94 pg/dL at postpartum day 3, and 43 pg/mL at postpartum day 7. They stated that increased venous return caused by release of the pressure of the inferior vena cava by the uterus occurs immediately after birth. In the present study, there was no significant correlation between RTc dispersion and NT-proBNP at FPFD7. We believe that RTc dispersion may reflect abnormal electrical repolarization based on the myocardial burden.

Of the two cases with an increased NT-proBNP in the late puerperium, one was complicated by pregnancy-related hypertension. Kale, et al. reported that NT-proBNP was significantly higher in pregnant women with pregnancy-induced hypertension with left ventricular diastolic dysfunction than in normotensive pregnant women. Rafik, et al. evaluated echocardiograms and NT-proBNP levels and reported that left ventricular diastolic function in pregnant women with pregnancy-induced hypertension was significantly lower than in normal pregnant women. An increase in troponin T concentration in the blood is a biomarker of damaged cardiac muscle cell membrane. In the present study, troponin T was in the normal range at all time points in all cases, indicating no heart muscle cell membrane damage.

Progesterone and estrogen levels at both early and late postpartum time points were significantly lower than GW36. This is because the placenta that secretes these hormones is delivered after childbirth, and their blood half-lives are short. The results of the Framingham study strongly suggested that estrogen deficiency after menopause is a risk factor for cardiovascular disease. In addition, Schierbeck, et al. reported that hormone replacement therapy after menopause decreased the rate of heart failure. In the postpartum period, estrogen levels decrease rapidly, and this may create adverse conditions for the cardiovascular system. In the future, it will be interesting to verify the hypothesis that this postpartum period with decreased progesterone and estrogen levels may be related to the incidence of PPCM. A quantitative test for myocardial injury during the course of pregnancy and over the postpartum period is not routine in clinical obstetrics. We believe that the DREAM-ECG system provides a new method for evaluating myocardial damage in a manner that is simple and noninvasive to both the mother and the child.

Limitations: In this study we did not observe any cases of PPCM due to the small number of cases. Echocardiography and nuclear medicine techniques are commonly used for the evaluation of cardiac function. However, nuclear medicine techniques have undesirable effects on the fetus, and recording an echocardiogram in all cases was impossible due to time constraints concerning the length of the hospital stay. We substituted serum levels of NT-proBNP as a marker for evaluating cardiac function. When recording DREAM-ECG data, inadequate signals caused by body movement and electrostatic noise are rare. For the measurements obtained by DREAM-ECG, we eliminated such cases with noisy signals. We did not use a wave noise removal filter for the electrostatic interaction because this may have affected the measurement of RTc dispersion.

Conclusions: In conventional obstetrics, cardiovascular burden in pregnant women is believed to be increased immediately after the second half of pregnancy. The results of the present study suggest that cardiovascular burden does not fully return to the normal level even one month after puerperium. Both repolarization indexes such as RTc dispersion by DREAM-ECG and serum biochemical markers may be useful for the quantification of myocardial burden in pregnant women, and may help to identify pregnant women at high-risk of perinatal myocardial damage.

References

17. Kamiya CA, Kitakaze M, Ishibashi-Ueda H, et al. Different characteristics of peripartum cardiomyopathy between patients complicated with and without hypertensive disorders. -Results from


