Vector synthesis high-resolution electrocardiography, atrial natriuretic peptide and N-terminal prohormone brain natriuretic peptide for estimation of cardiac load in pregnancy

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Abstract

Aim: We analyzed atrial natriuretic peptide (ANP), N-terminal pro-brain natriuretic natriuretic peptide (NT-proBNP) and vector synthesis high-resolution electrocardiography (ECG), to estimate cardiac load with circulatory dynamic change from pregnancy through the post-partum period.

Methods: The subjects were singleton pregnant women (n = 19), who were divided into three stages: stage 1, 34–36 weeks of gestation; stage 2, 2–6 post-partum days; and stage 3, 1–3 months after delivery. Vector synthesis high-resolution ECG, ANP and NT-proBNP were analyzed for all subjects.

Results: A pregnant woman with massive uterin liomyoma expressed largest the corrected recover time (RTc) dispersion in I + II of tow Dimensional (2D) color distribution map ANP and NT-proBNP were significantly higher in stage 2 than in stages 1 and 3.

Conclusions: ANP, NT-proBNP and vector synthesis high-resolution ECG there might be able to evaluate cardiac load of normal pregnancy.

Key words: atrial natriuretic peptide, cardiac load, N-terminal prohormone brain natriuretic peptide, pregnancy, vector synthesis high-resolution electrocardiography RTc dispersion.

Introduction

Circulating plasma and the circulating blood volume begin to increase at 6 weeks and at 10–12 weeks of gestation, respectively. An approximately 33% increase occurs at 21–24 weeks of gestation, compared with blood volume before pregnancy. The blood volume increases to its maximum of 45–50% at approximately 32 weeks of gestation.¹² The volume then becomes constant or slowly increases.³ With these changes in the circulating blood volume, right heart afterload may be triggered by pregnancy-associated physiological events such as maternal fat accumulation, increased extracellular fluid due to elevated blood progesterone, pressure on peripheral blood vessels, and lower blood flow congestion. Peripartum cardiomyopathy and takotsubo cardiomyopathy rarely develop in the perinatal period – they occur primarily in the early post-partum phase – but these conditions result in poor outcomes in some patients.⁴ Causes include reaction to deviant circulatory load in pregnancy, pregnancy-induced hypertension, and pulmonary edema (a side-effect of ritodrine hydrochloride). Its prediction and predictors, however, have not been clarified. Thus, we focused on items related to the evaluation of maternal cardiac volume load in publicly funded prenatal checkups: high-resolution electrocardiograms (ECG), and peptide hormones secreted by the heart. The aim of the present study was therefore to perform detailed evaluation of cardiac load in normal pregnant women without complications such as hypertension and tocolytic therapy with ritodrine hydrochloride, using vector synthesis high-resolution ECG.

In 2007, Nakai et al. developed an original vector synthesis 187-channel high-resolution ECG based on the
vector projection theory by Frank,\(^5\) and reported that cardiomyopathy, cardiac load, and fetal ECG can be non-invasively evaluated using this device.\(^6\)–\(^9\) The traditional ECG is displayed as a weave form converted from electric potential, but vector synthesis high-resolution ECG can present the recover time (RT) disorientation, which may be helpful in predicting which patients with non-sustained ventricular tachycardia (VT) are likely to have inducible VT by programmed stimulation, and more, detect the spatial distribution of high-frequency late positional and vermicular depolarization, and increased RT dispersion suggestive of a right ventricular outflow region.\(^6\) In 2013, Terata et al. succeeded in analyzing the cardiac load of pregnant and post-partum women using vector synthesis high-resolution ECG without echocardiography.\(^10\)

The history of the natriuretic peptide hormone family, known as heart failure markers, began with the discovery of specific granules in guinea pig atrial cells by Krich in 1956. In 1984, Kangawa and Matsuo isolated and identified atrial natriuretic peptide (ANP), which consists of 28 amino acids, from the human atrium.\(^11\) BNP hormone is separate from the N-terminal part of pro hormone termed NT-proBNP.\(^12\) The first measurement of NT-proBNP was reported by Hunt.\(^13\) In this study, we try to analyze noninvasive vector synthesis high resolution ECG, ANP and NT-pro BNP value for evaluate from normal pregnancy to postpartum.

**Methods**

**Patients**

Normal singleton pregnant women \((n = 19)\) attending the outpatient clinic of the gynecology department or who were admitted to the gynecology ward of Iwate Medical University Hospital (Morioka, Japan) and could be followed between November 2014 and July 2015, were enrolled in the present study. All patients provided written consent. Iwate Medical University Ethics Committee approved this study on 1 May 2014 (approval number H26–20). We classified 34–36 weeks of gestation as stage 1; 2–6 days after delivery as stage 2; and 1–3 months after delivery as stage 3.

**Subject characteristics**

The following patient data were recorded: age, history of pregnancy, examination at age of gestation, body mass index (BMI), blood pressure, height (cm)/fundus of the uterus (cm) ratio, gestation at delivery, neonatal birth weight and blood loss during lobar.

**Peptide hormone measurement**

For ANP and NT-proBNP measurement, blood was collected from the vein into tubes containing ethylenediamine tetra-acetic acid. The collected blood into tubes containing ethylenediamine tetra-acetic acid was centrifuged at 4°C at \(×3000\)g for 10 min and the supernatants were stored in polypropylene tubes at \(−30°C\) until assayed. ANP and NT-proBNP were measured on electrochemiluminescence immunoassay.

**Vector synthesis high-resolution ECG**

The set up consists of a laptop, input box containing a high-amplitude/high-resolution amplifier (IB-81, Fukuda Denshi), and original software to analyze digital ECG signals (ECG Manager; ICS Iwate, Morioka, Japan). The minimum resolution was 0.076 \(\mu\)V, and the input signal sampling frequency was 2 kHz. Silver–silver chloride magnet electrodes (Magne Lode TE-18-5, Fukuda Denshi) were used. With regard to vector synthesis high-resolution ECG indices, X-Y-Z lead ECG were averaged and processed through a band-pass filter (finite impulse response [FIR] type, 45–200 Hz), and filtered QRS (fQRS) was measured in vector magnitude waveforms. The inflection points of the P, QRS, and T waves were determined using differentiation.\(^6\)–\(^8\) From lead vectors corresponding to the center electrode and 187 electrodes on the body surface (Fig. 1), a 187-channel ECG was synthesized, current density determined, and a “D distribution map of RT dispersion representing the variation of the repolarization time was prepared (Fig. 2).\(^6\)\(^,\)\(^7\) Spatial distribution of the variation in heart muscle repolarization time can be evaluated using this map. The map divide four sections that I + II according to the right heart.

**Statistical analysis**

Data were analyzed using SPSS version 23.0. (IBM, Japan). Multiple groups were analyzed using variance (ANOVA) and Kruskal–Wallis test, data are represented by mean ± S.E. and regression curves were used to analyze correlations. \(P < 0.05\) was regarded as significant.

**Results**

Subject characteristics are listed in Table 1 maternal age was 34.3 ± 5.0 years old, gravidity was 1.9 ± 1.7, and parity was 1.1 ± 0.9 height (cm)/uterine fundus (cm) ratio was 0.20 ± 0.02 birthweight was 2857.1 ± 543.0 g, and loss of blood at delivery was 887.8 ± 518.2 g.
Blood pressure and BMI are listed in Table 2. Systolic/diastolic blood pressure in stages 1, 2, and 3 was 107.5 ± 2.6/66.1 ± 2.0 mmHg, 112.1 ± 15.7/71.2 ± 9.7 mmHg, and 116.4 ± 3.5/70.1 ± 9.6 mmHg, respectively. Stage 3 measurements were increased compared with stages 1 and 2, but the difference between systolic and diastolic blood pressure was not significant ($P = 0.222$ and $P = 0.300$). BMI was 23.9 ± 2.2, 24.0 ± 2.0, and 22.6 ± 2.6 for stages 1, 2, and 3, not significantly different between the stages ($P = 0.141$; Fig. 3).

Table 3 lists the vector synthesis high-resolution ECG indices, and ANP and NT-proBNP.

Vector synthesis high-resolution ECG
fQRS in stages 1, 2, and 3 was 99.8 ± 1.6 ms, 108.2 ± 1.3 ms, and 109.7 ± 1.9 ms, respectively (Table 3), showing that stage 3 was significant higher compared with stages 1 and 2 ($P < 0.0001$). The standard value is 44 ms, reported by Wison et al.\textsuperscript{17} RTc dispersion in stages 1, 2, and 3 was 48.8 ± 5.7 ms, 45.6 ± 3.3 ms, and 46.2 ± 2.8 ms, respectively ($P = 0.827$). This was not significantly different between each stage (Fig. 4), but all RTc were higher than the standard value. Figure 2 shows the 2D color distribution map of RTc dispersion in a patient with massive uterine leiomyoma (patient 4). This patient did not develop pulmonary hypertension, anterior wall infarction or dilated cardiomyopathy, and she recovered well without cardiac complications after cesarean section.

ANP and NT-proBNP
The standard ANP level is 43.0 pg/mL,\textsuperscript{15} and the standard NT-proBNP level is 125 pg/mL.\textsuperscript{16} ANP in stages 1, 2, and 3 was 23.2 ± 2.4 pg/mL, 58.4 ± 14.0 pg/mL, and 23.8 ± 4.4 pg/mL, respectively. Stage 2 was higher than stages 1 and 3 ($P = 0.001$).
proBNP was 37.6 ± 4.0 pg/mL, 170.2 ± 27.5 pg/mL, and 41.6 ± 10.0 pg/mL in stages 1–3, respectively, and again stage 2 was significantly higher than stages 1 and 3 (P < 0.0001; Fig. 4). There was weak relationship between NT-proBNP and fQRS in stage 1 compare with stage 2 and 3. (r² = 0.22, P = 0.033; Fig. 5).

Discussion

The time-course of vector synthesis high-resolution ECG and changes in the peptide hormone levels were investigated in the normal singleton pregnant and post-partum women. This confirmed that cardiac

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volume load resulting from increased circulating blood volume flow into the right heart system rather than the left heart system in normal pregnant and postpartum women. A characteristic of pregnant women is that the preload increases because of an increase in circulating blood volume. With regard to changes in blood pressure, the arterial smooth muscle relaxes and vascular resistance decreases in late pregnancy. In the lower limbs, resistance increases because the pelvic vein and inferior vena cava are pressed on, suggesting that the pre- and afterloads increase during pregnancy. In addition, the uterine weight increases in a multiple pregnancy and in a massive uterine leiomyoma, which may press on the pelvic vein and thorax and further increase cardiac load. In all patients, variation in repolarization time in quadrants I + II was large throughout the period. This phenomenon suggest right cardiac load relate to increasing circulation of blood volume in pregnancy from 20 to 32 weeks of gestation.

**Figure 3** (a) Body mass index (BMI), (b) systolic blood pressure (SBP) and (c) diastolic blood pressure (DBP) vs stage (P = NS). Data given as SEM.

**Table 3** Change in vector synthesis high-resolution ECG indices, ANP and NT-pro BNP

| Patient ID no. | Stage 1 | Stage 2 | Stage 3 | Stage 1 | Stage 2 | Stage 3 | Stage 1 | Stage 2 | Stage 3 |
|----------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
|                | fQRS (ms) | RTc dispersion (ms) | ANP (pg/mL) | NT-proBNP (pg/mL) |
| 1              | 106      | 109     | 107     | 24      | 17      | 36      | 5       | 35.6    | 5.1     |
| 2              | 97       | 103     | 107     | 51      | 45      | 54      | 17.8    | 66.5    | 15.6    |
| 3              | 97       | 106     | 97      | 72      | 36      | 35      | 20.2    | 23.4    | 21.6    |
| 4              | 97       | 112     | 103     | 86      | 80      | 49      | 28.3    | 12.6    | 82.6    |
| 5              | 91       | 111     | 113     | 12      | 38      | 57      | 14.5    | 14.4    | 17      |
| 6              | 97       | 106     | 110     | 43      | 57      | 57      | 9       | 40.9    | 10.3    |
| 7              | 99       | 106     | 119     | 47      | 52      | 33      | 19.8    | 57.1    | 24.9    |
| 8              | 98       | 109     | 98      | 65      | 35      | 51      | 23.5    | 107     | 24.2    |
| 9              | 107      | 115     | 118     | 48      | 45      | 45      | 20.3    | 38.2    | 14      |
| 10             | 78       | 101     | 111     | 38      | 56      | 27      | 21.1    | 80.4    | 19      |
| 11             | 100      | 106     | 89      | 2       | 22      | 29      | 40.9    | 111     | 61.5    |
| 12             | 111      | 117     | 116     | 26      | 46      | 36      | 38.6    | 59.2    | 34      |
| 13             | 108      | 112     | 115     | 90      | 45      | 51      | 22.6    | 29.3    | 23.7    |
| 14             | 94       | 105     | 105     | 78      | 62      | 62      | 18.2    | 33.6    | 26.1    |
| 15             | 103      | 92      | 121     | 71      | 43      | 63      | 35      | 27.7    | 7.6     |
| 16             | 100      | 105     | 110     | 21      | 57      | 30      | 15.3    | 5       | 7.4     |
| 17             | 99       | 110     | 102     | 46      | 44      | 51      | 36.4    | 18.1    | 5.7     |
| 18             | 109      | 109     | 118     | 46      | 34      | 51      | 29.2    | 51      | 31.5    |
| 19             | 107      | 122     | 122     | 61      | 52      | 62      | 30.2    | 54.9    | 20.5    |

High-resolution ECG: fQRS and RTc dispersion. Peptide hormone: ANP and NT-proBNP.
Atrial natriuretic peptide, BNP, and NT-proBNP are well-known heart failure markers.19,20 When an increase in the preload stimulates the heart muscle to extend, ANP and BNP are secreted primarily by the atrial and ventricular muscles.21 ANP secreted by the atria reflects the circulating blood volume, and BNP secreted by the ventricles primarily serves as an index of left ventricular dysfunction.22

fQRS was significantly high in stage 3 compared with stages 1 and 2; in addition, RTc dispersion in all stages was higher than the standard value. This shows that the effect of cardiac load related to conduction system that continue to postpartum. On the 2D distribution map of RTc dispersion, there was a marked variation in quadrants I + II in all three stages. ANP and NT-proBNP levels were high in stage 2 compared with stage 1 and 3, in those fact say that right cardiac load spread to stimulate to product ANP and NT-proBNP during pregnant, and then it may be reach to peak point at stage 2, also it could be prediction the heart frailer when a pregnant woman had sever pregnancy induced hypertension or high dose of ritodrine sulfate by intravenous infusion with bed-rest fQRS and NT-proBNP reflect increasing blood volume from 20 to 32 weeks of gestation, and also, induced production of NT-proBNP with changed myocardium and conduction system of cardiac load at stage 1. Finally, it could appear index of the vector synthesis high resolution ECG and value of peptide hormone after reflection of the circulating blood volume, we think that It can be said this is a feature of the pregnant woman circulation system.

Particularly, the emphasis to say that regard to the pregnancy-induced hypertension and long-term bed-rest to treat threatened premature labor with therapy of ritodrine hydrochloride is a β2 receptor stimulator has problematic side effects such as tachycardia, increased cardiac output, and peripheral vascular dilatation.23,24 The frequency of pulmonary edema due to the side effect of ritodrine hydrochloride is only approximately 0.3%, but it is common.25 Stage 2 ANP and NT-proBNP may be as possible indicators of cardiac load in the normal pregnancy, however we think that those phenomenon indicate that ANP and NT-proBNP after the increasing blood volume prevent damage of myocardial. In the postpartum, circulating blood flow with pressure into the pulmonary artery, subsequently reperfuses to the left heart system through the right heart system, which may lead to persistently high NT-proBNP value and change.

Figure 4 Comparison of two serum peptide hormone levels and index of vector synthesis high-resolution ECGA by each stages in the study. (a) arterial natriuretic peptiod (ANP), (b) N-terminal of the prohoromon brain natriuretic peptide (NT-proBNP), (c) filtered QRFS (fQRS), (d) corrected recovery time (RTc). The line inside boxes indicate the mean value, and the upper and lower limits of boxes and whiskers indicate the interquartile ranges. *P < 0.005.
of RTc. This phenomenon is consistent with Marey’s law. Based on the stage 3 findings, peptide hormone level normalizes with the recovery of normal circulatory dynamics in the post-partum period, but the right ventricle may still be the center of the ECG phenomena, and improvement in the myocardial load may require time.

Interestingly, NT-proBNP was 40 pg/mL (stage 1), 292 pg/mL (stage 2) and 208 pg/mL (stage 3) in the present patient 4 with massive uterine leiomyoma. All of these levels were higher than in the other patients, despite the fact that ANP was almost normal during the observation period. In addition, the 2D RTc dispersion color distribution map showed that the repolarization time markedly varied in quadrants I + II, indicating that volume overload burden was placed on the right heart system, although the patient recovered without cardiac complications after cesarean section. We therefore consider that NT-proBNP has more impact than ANP as a biomarker of cardiac load. Cardiomyopathy is a group of heart diseases that involve abnormal mechanical function, which often causes ventricular hypertrophy and dilation, or abnormal electrophysiological function, or both, meaning that the right heart failure is occurred by low blood pressure and low cardiac output state which according to rise of venous pressure induced pulmonary congestion, and lead to the left heart failure finally, therefore, These cases need to observe by a cardiologist for evaluation of cardiac function. In routine pregnancy examination, it is difficult to evaluate maternal cardiac load. This study has shown, however, that ANP, NT-proBNP, and iQRS are involved in pregnancy-related changes in circulatory dynamics during pregnancy and the post-partum period in normal pregnant women.

Given that pregnant women with cardiomyopathy are rare, we did not have such patients in hospital in the study period. Therefore, we could not evaluate pathologic cardiac function of such cases. In conclusion, however, this study shows that the use of ANP, NT-proBNP and vector synthesis high-resolution ECG may be effective as a screening test to prevent cardiomyopathy for pregnant and post-partum women. Particularly, the 2D RTc dispersion distribution map can be used to visualize cardiac load regions in normal pregnant and post-partum women. Given that the present sample size was small, further study with a larger sample size and comparisons with conventional electrophysiological studies and echocardiography are required to verify the clinical usefulness of vector synthesis high-resolution ECG for evaluating cardiac load in normal pregnant and post-partum women before development of cardiac complications.

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Disclosure

The authors declare no conflicts of interest.

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