

openheart Association of peripartum troponin I levels with left ventricular relaxation in women with hypertensive disorders of pregnancy

Takeshi Umazume,¹ Satoshi Yamada,² Takahiro Yamada,¹ Satoshi Ishikawa,¹ Itsuko Furuta,¹ Hiroyuki Iwano,² Daisuke Murai,² Taichi Hayashi,² Kazunori Okada,³ Mamoru Morikawa,¹ Hiroyuki Tsutsui,² Hisanori Minakami¹

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/openhrt-2018-000829>).

To cite: Umazume T, Yamada S, Yamada T, *et al.* Association of peripartum troponin I levels with left ventricular relaxation in women with hypertensive disorders of pregnancy. *Open Heart* 2018;**5**:e000829. doi:10.1136/openhrt-2018-000829

Received 30 March 2018
Revised 1 July 2018
Accepted 24 July 2018



© Author(s) (or their employer(s)) 2018. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Department of Obstetrics, Hokkaido University Graduate School of Medicine, Sapporo, Japan

²Department of Cardiovascular Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Japan

³Faculty of Health Sciences, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Correspondence to

Dr Takeshi Umazume;
takeuma@med.hokudai.ac.jp

ABSTRACT

Objective Women with hypertensive disorders of pregnancy (HDP) show elevated risk of heart failure despite decreased circulating plasma volume compared with those with normotensive control pregnancies (NCP). This study was performed to better characterise the heart in women with HDP and determine whether high-sensitivity troponin I (hs-TnI) around childbirth predicts reduced left ventricular (LV) relaxation at 1 month postpartum.

Methods Echocardiography was performed longitudinally during the first, second and third trimesters and immediately postpartum within 1 week and 1 month postpartum in 24 women with HDP, with simultaneous determination of blood variables in comparison with 51 women with NCP.

Results Compared with NCP, HDP showed greater antepartum left atrial (LA) volume, LV mass and inferior vena cava (IVC) diameter, higher peripartum brain natriuretic peptide/N-terminal pro-B-type natriuretic peptide and hs-TnI with the highest value immediately postpartum, and lower early diastolic mitral annular velocity (e') during pregnancy/postpartum. In analyses of data on HDP and NCP, hs-TnI at the third trimester as well as that immediately postpartum was negatively correlated with later e' at 1 month postpartum. The areas under the receiver operating characteristic curves were 0.82 and 0.81 for hs-TnI at the third trimester and immediately postpartum, respectively, in the prediction of reduced LV relaxation at 1 month postpartum.

Conclusion Reduced LV diastolic function and decreased splanchnic blood reservoir may contribute to the increased third trimester IVC diameter and LA volume in women with HDP. The rise in hs-TnI around childbirth was associated with poor LV relaxation ability at 1 month postpartum.

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) are a risk factor for both peripartum cardiomyopathy (PPCM)^{1–3} and cardiomyopathy in later life.⁴ Indeed, the levels of cardiac biomarkers, such as brain natriuretic peptide (BNP) and troponin I, are increased in

Key questions

What is already known about this subject?

► Cardiac changes and the significance of increased high-sensitivity troponin I (hs-TnI) have not been studied extensively in hypertensive disorders of pregnancy (HDP), although HDP is a risk factor for heart failure.

What does this study add?

► Greater antepartum left atrial volume and inferior vena cava diameter, higher peripartum hs-TnI level, and lower early diastolic mitral annular velocity (e') at 1 month postpartum were characteristic features of HDP.
► Peripartum hs-TnI level was negatively correlated with later e' at 1 month postpartum.

How might this impact on clinical practice?

► Peripartum hs-TnI rise is likely to occur in HDP and predicts poor left ventricular relaxation ability at 1 month postpartum.

women with HDP compared with those with normotensive control pregnancy (NCP).^{5–7} These observations suggest that somewhat pathological cardiac remodelling, that is, relative lack of capillary density and replacement with fibrosis,^{8,9} is more likely to occur in HDP than in NCP.

Blood volume increases physiologically by approximately 40% in pregnancy,¹⁰ and this volume expansion is associated with morphofunctional cardiac changes in pregnancy, such as increased left ventricular (LV) mass,^{11–13} increased left atrial (LA) volume,^{11,12} decreased systemic vascular resistance (SVR)¹³ and significantly reduced ratio of early to late diastolic transmitral flow velocity.^{11–13} As the maximal cardiac changes in morphology occur within 1 week after childbirth,¹⁴ pathological remodelling may be likely to occur around childbirth.

Troponin I reflects cardiac remodelling⁸ and predicts the outcome of patients with heart failure.^{8,15} PPCM is characterised by reduced LV ejection fraction (LVEF) and is accompanied by persistent LV diastolic dysfunction. If this is indeed the case, perinatal troponin I would predict a sustained decrease in LV relaxation monitored by early diastolic mitral annular velocity in pregnant women.

The degree of volume expansion is lower in HDP, especially in pregnancies complicated by preeclampsia,¹⁶ while LV preloading monitored by LA volume is increased to a greater extent¹¹ in HDP compared with NCP. Preeclampsia is characterised by sympathetic overactivity¹⁷ and a marked increase in SVR.¹³ Splanchnic organs constitute 10% of the body weight, but contain 25% of the total blood volume, and thus the splanchnic vasculature serves as an important blood reservoir for the circulatory system.^{18,19} Sympathetic activation expels blood from splanchnic capacitance vessels, producing a rapid increase in venous return up to 800 mL.^{18,19} If this is the case in HDP, the inferior vena cava (IVC) diameter and LA volume would be increased in women with HDP, resulting in increased risk of heart failure compared with those with NCP.

This study was performed to better characterise the heart in HDP in relation to various cardiac biomarkers, using longitudinally prospectively collected data on simultaneous echocardiography and blood variables from women with HDP.

METHODS

Participants

This project began in April 2014. All pregnant women who were scheduled to give birth at Hokkaido University Hospital were invited to participate in this study. All participants were recommended to undergo echocardiography at each of the first, second and third trimesters of pregnancy, and immediately postpartum within 1 week after childbirth (designated as 'PP1') and approximately 1 month postpartum (designated as 'PP2') on enrolment, and to provide blood samples at the same time as each echocardiography scan. Of 701 Japanese women with singleton pregnancies who gave birth at the Hokkaido University Hospital during the 2-year study period between April 2014 and March 2016, 151 women undergoing simultaneous echocardiography and blood sampling at least once participated in this project. Of these 151 women, 24 fulfilled both of the following criteria: (1) having these tests during at least three of five stages of pregnancy/postpartum; and (2) complication with HDP, including chronic hypertension, gestational hypertension and preeclampsia, in the current pregnancy. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg on at least two occasions recorded 12 hours apart in pregnancy. Chronic hypertension was defined as hypertension noticed before gestational week 20 with no proteinuria. Gestational hypertension was defined

as onset of hypertension at gestational week ≥ 20 with no proteinuria, and preeclampsia was defined as onset of both hypertension and proteinuria at gestational week ≥ 20 . The present study compared echocardiography findings and blood biomarkers of the 24 HDP with those of 51 NCP reported elsewhere.¹⁴

Echocardiographic evaluation, biochemical procedures and statistical methods

Transthoracic echocardiography, including two-dimensional, colour Doppler and tissue Doppler imaging, was performed by a single trained operator (TU) blinded to the biochemical data using the same equipment (ProSound Alpha 7; Hitachi, Tokyo, Japan) according to the guidelines of the European Association of Cardiovascular Imaging.²⁰

Biochemical procedures

Serum and plasma were collected at the time of each echocardiography scan and stored at -20°C until assays of the following four biomarkers: high-sensitivity troponin I (hs-TnI), N-terminal pro-B-type natriuretic peptide (NT-proBNP), BNP, and estimated glomerular filtration rate (eGFR) obtained using the following equation: $0.739 \times 194 \times \text{serum creatinine}^{-1.094} \times \text{age (years)}^{-0.287}$.²¹ The hs-TnI, BNP and NT-proBNP concentrations were measured using counting immunoassay kits (ARCHITECT High-Sensitivity Troponin-I, ARCHITECT BNP-JP and ARCHITECT CK-MB (Abbott Japan, Chiba, Japan) and Elecsys proBNP II STAT Assay (Roche Diagnostics KK, Tokyo, Japan), respectively).

Statistical methods

Statistical analyses were performed using JMP Pro V.12 (SAS, Cary, North Carolina, USA) and SPSS Statistics V.24.0. Changes in variables within a group were compared using Wilcoxon's rank-sum test and Student's t-test with Bonferroni correction. The associations between echocardiographic parameters and biomarker levels at five time points (first, second and third trimesters, and PP1 and PP2) were tested using the mixed effects model to examine the correlations at each time point. Dependent (echocardiographic parameters) and independent (biomarker levels) variables were standardised to interpret the regression coefficients as the correlation coefficients. The covariance structure at each time point showed compound symmetry. In all analyses, $p < 0.05$ was taken to indicate statistical significance. However, a significant finding regarding a linear correlation between two standardised variables was defined as that meeting both $p < 0.05$ and standardised regression coefficient (β) > 0.25 or < -0.25 . For analyses of the associations between peripartum biomarker levels with later e' at 1 month postpartum (PP2), Pearson's product-moment correlation coefficient was used to measure linear correlations.

Table 1 Demographic characteristics of participants and timing of examination

	NCP	HDP	P values
Women (n)	51	24	
Nulliparous women	30(59%)	18(75%)	0.173
Age(year)	34.3±5.1	35.6±5.6	0.198
Gestational week at delivery	38.9±1.3	35.1±4.9	<0.001
Weekly weight gain, kg*	0.25±0.10	0.31±0.20	0.127
Infant weight, kg	3.1±0.4	2.2±1.1	<0.001
Number of tests† given	255	95	
Number of tests† per woman	5.0±0.0, 5 (5–5)	4.0±0.8, 4 (3–5)	<0.001
Timing of the tests†			
First trimester, weeks	11.6±1.2 (51, 100%)	11.3±0.9 (14, 58%)	
Second trimester, weeks	25.2±1.0 (51, 100%)	25.2±1.2 (16, 67%)	
Third trimester, weeks	36.4±0.6 (51, 100%)	35.6±2.6 (19, 79%)	
PP1 (postpartum days 2–6)	3.3±0.8 (51, 100%)	3.4±1.1 (24, 100%)	
PP2 (postpartum days 23–39)	30.9±3.7 (51, 100%)	30.2±3.3 (22, 92%)	

Data are presented as mean±SD. HDP, hypertensive disorders of pregnancy including 2, 6 and 16 women with chronic hypertension, gestational hypertension and preeclampsia, respectively. The number of women with the tests is indicated in brackets.

*Value of gestational weight gain divided by gestational week at delivery.

†The tests consisted of simultaneous echocardiography and blood sampling.

NCP, normotensive control pregnancy.

RESULTS

Twenty-four women with HDP and 51 women with NCP underwent echocardiography 95 times (average, 4.0 times/person) and 255 times (5.0 times/person), respectively (table 1); 14 (58%) vs 51 (100%), 16 (67%) vs 51 (100%), 19 (79%) vs 51 (100%), 24 (100%) vs 51 (100%), and 22 (92%) vs 51 (100%) of the 24 women with HDP vs 51 women with NCP underwent simultaneous echocardiography and blood sampling at the first, second and third trimesters, and at PP1 and PP2, respectively. All data of women with NCP are reported elsewhere (online supplemental table).¹⁴

Changes in echocardiographic parameters in women with HDP versus women with NCP

Compared with women with NCP, women with HDP showed increased LV mass index due to increased LV wall thickness; decreased averages of early diastolic septal and lateral mitral annular velocity (e'), causing increases in the ratio of early diastolic mitral flow velocity to e' (E/e') and the ratio of systolic pulmonary venous flow velocity to anterograde diastolic pulmonary venous flow velocity (S/D); decreased index of long axis contractility, that is, decreased average of systolic septal and lateral mitral annular velocity (s'), but no significant changes in the index of short axis contractility, that is, shortening fraction; increased IVC diameter and LA volume index concomitant with increased SVR in the third trimester; and persistent postpartum reduced cardiac function, such as e' , s' and S/D (table 2, figure 1).

Changes in blood variables in women with HDP versus women with NCP

Women with HDP were characterised by increased peripartum levels of BNP, NT-proBNP and hs-TnI, and decreased levels of eGFR, compared with women with NCP (figure 2).

Associations of biomarkers with echocardiographic parameters determined simultaneously during pregnancy and postpartum

All four blood variables shown in figure 2 were analysed with regard to correlations of four measurements on echocardiography, that is, LV end-diastolic dimension, LA volume index, LV mass index, LVEF and e' , using all data obtained from 24 women with HDP and 51 women with NCP. NT-proBNP, BNP and hs-TnI were significantly positively correlated with LA volume index and LV mass index, while eGFR showed significant negative correlations with these levels (figure 3). Only eGFR was significantly correlated with e' . BNP was the best predictor of LA volume index, while hs-TnI was the best predictor of LV mass index. None of the blood variables were significantly correlated with LVEF.

Correlations of biomarker levels around childbirth with later e' at 1 month postpartum.

Reduced LV relaxation monitored by e' was characteristic of HDP and persisted until 1 month postpartum (PP2) in women with HDP (figure 1). The hs-TnI levels at the third trimester and immediately postpartum (at PP1) exhibited significant negative correlations with later e' at 1 month postpartum (PP2) (figure 4),

Table 2 Echocardiographic and blood parameters in 24 women with hypertensive disorders of pregnancy.

	First trimester (n=14)	Second trimester (n=16)	Third trimester (n=19)	PP1 (n=24)	PP2 (n=22)
Clinical data					
Gestational week and postpartum day	11.3(0.9)	25.2(1.3)	35.6(2.6)	3.4(1.1)	30(3.3)
Heart rate,beats/min	70(10)	80(10)	75 (9)†	84 (16)*†	76 (11)†
Echocardiographic parameters					
LVDd,mm	45.0(3.8)	46.1(3.7)	47.3(3.9)	47.5(6.0)	46.0(4.0)
Shortening fraction,%	34.0(3.2)	34.6(4.8)	34.6(4.0)	34.3(4.1)	32.1(5.4)
Interventricular septum thickness,mm	7.5(0.9)†	8.4 (1.3)†	9.4 (1.2)*†	9.7 (1.6)*†	9.1 (1.2)*†
LV posterior wall thickness,mm	6.9 (0.9)†	8.0 (1.5)*†	8.4 (1.1)*†	9.0 (1.2)*†	8.1 (1.1)*†
LV mass,g	100.3(25.2)	125.3 (41.2)†	141.6 (21.8)*†	152.8 (29.6)*†	131.7 (31.6)*†
LV mass/BSA, g/m ²	61.7(14.8)	71.8 (20.9)†	82.0 (11.7)*†	89.5 (15.5)*†	79.5 (16.2)*†
Maximum LA volume,mL	35.2(9.4)	46.2 (10.3)*†	53.3 (13.2)*†	54.4 (13.6)*†	42.0 (9.0)†
Maximum LA volume/BSA, mL/m ²	21.6(5.7)	26.5 (4.9)†	30.7 (6.9)*†	31.8 (7.6)*†	25.2 (5.0)†
Inferior vena cava diameter,mm	12.3(5.3)	13.5(3.5)	13.1 (2.9)†	15.3(5.3)	14.0(4.6)
Stroke volume,mL	69.3(7.1)	68.6(7.5)	72.6 (9.3)†	77.4 (12.4)*	63.2(9.9)
Cardiac output,L/min	4.9(1.0)	5.5(0.8)	5.3(1.0)	6.3 (1.1)*†	4.7(0.8)
Systemic vascular resistance, dyn-s/cm ⁵	1459(360)	1252 (187)†	1488 (405)†	1229 (249)†	1644 (281)†
Mitral inflow E/A	1.56(0.31)	1.45(0.27)	1.26(0.35)	1.35(0.58)	1.15 (0.31)*†
Pulmonary vein inflow S/D	1.01(0.32)	1.24(0.27)	1.23(0.23)	1.33 (0.41)*†	1.33 (0.36)*†
TDI mitral annulus					
s' ave ,cm/s	9.6(1.1)	10.2 (1.8)†	9.1 (1.5)†	9.3 (1.8)†	9.0 (1.7)†
e' ave ,cm/s	13.7 (2.7)†	12.7 (2.1)†	10.7 (2.3)*†	11.7 (2.1)†	10.7 (2.1)*†
E/e' ave	6.1 (1.4)†	6.3 (1.7)†	7.4 (2.1)†	7.6 (1.9)†	6.4 (1.8)†
Blood data					
NT-proBNP,pg/mL	42 (33–67)	30 (17–71)	70 (30–199)†	185 (99–487)*†	47 (19–74)
BNP, pg/mL	11.6 (8.4–14.7)	12.7 (6.4–19.6)†	17.9 (12.5–91.2)†	45.6 (19.5–110)*	8.1 (2.9–11.3)
hs-TnI,pg/mL	1.3 (0.3–2.1)	1.4 (0.6–4.7)	3.6 (1.1–6.6)*†	6.9 (3.3–12.7)*†	1.6 (1.1–3.0)†
eGFR, mL/min/1.73m ²	108 (94–133)	107 (94–121)†	91 (79–100)*†	85 (80–97)*†	89 (76–99)*

Clinical and echocardiographic data are presented as means (SD). Blood data are presented as medians (25th–75th).

*P<0.05 versus baseline value of the same group determined in the first trimester.

†P<0.05 versus the value of normotensive control women (online supplementary table).¹⁴ Numbers of women with available data on BNP was limited; 14, 15, 16, 21, and 19 women at the 1st, 2nd, 3rd trimesters of pregnancy and PP1 (postpartum day 2–7), and PP2 (postpartum day 23–39), respectively.

A, late diastolic mitral flow velocity; BNP, brain natriuretic peptide; BSA, body surface area; D, antegrade diastolic pulmonary venous flow velocity; E, early diastolic mitral flow velocity; e' ave, average of early diastolic septal and lateral mitral annular velocity; eGFR, estimated glomerular filtration rate; hs-TnI, high-sensitivity troponin I; LA, left atrium; LV, left ventricle; LVDd, LV end-diastolic dimension; NT-proBNP, N-terminal pro-B-type natriuretic peptide; s' ave, average of systolic septal and lateral mitral annular velocity; S, systolic pulmonary venous flow velocity; TDI, tissue Doppler imaging.

although hs-TnI was not correlated with e' determined simultaneously (figure 3). The eGFR levels at the third trimester and immediately postpartum (at PP1) exhibited significant positive correlations with later e' at 1 month postpartum (at PP2) (figure 4). The correlation coefficient (r value) was greater for hs-TnI than for eGFR. Thus, hs-TnI around childbirth was the best predictor of later e' at 1 month postpartum (at PP2).

The areas under the curves (AUCs) of the receiver operating characteristic curves (ROCs) were 0.82 and 0.81 for hs-TnI determined at the third trimester and immediately postpartum (PP1), respectively, in the prediction of reduced LV relaxation at 1 month postpartum (e'<7.7 cm/s, fifth percentile value of 51 women with NCP at 1 month postpartum) (figure 5). The corresponding AUCs of ROC were 0.63 and 0.74 for eGFR

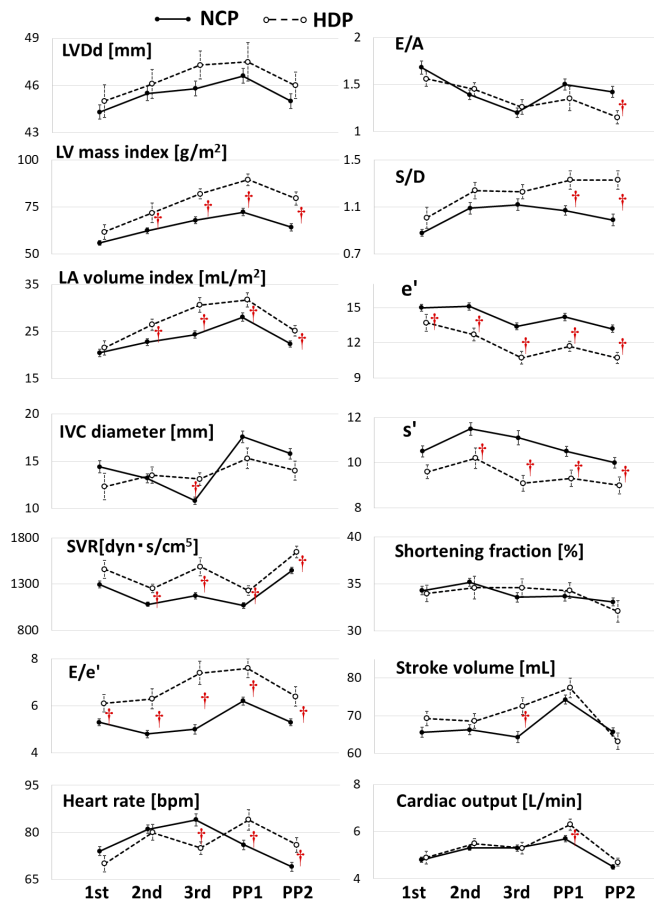


Figure 1 Representative echocardiographic findings: women with HDP versus women with NCP. † $P < 0.05$ between the two groups. Vertical bars indicate \pm SE. bpm, beats per minute; e' , average of early diastolic septal and lateral mitral annular velocity; E/A, ratio of early to late diastolic transmitral flow velocity; E/e' , ratio of early diastolic mitral flow velocity to e' ; HDP, hypertensive disorders of pregnancy; IVC, inferior vena cava; LA, left atrial; LV, left ventricular; LVDd, LV end-diastolic dimension; NCP, normotensive control pregnancy; PP1, immediately postpartum within 1 week after childbirth; PP2, approximately 1 month postpartum; s' , average of systolic septal and lateral mitral annular velocity; S/D, ratio of systolic pulmonary venous flow velocity to anterograde diastolic pulmonary venous flow velocity; SVR, systemic vascular resistance.

determined at the third trimester and immediately postpartum (PP1), respectively (data not shown).

DISCUSSION

This study demonstrated increased IVC diameter and LA volume index with increased SVR and reduced e' during the third trimester and postpartum persistence of reduced cardiac function as determined by e' , s' and S/D in women with HDP compared with women with NCP. In pregnant women, the hs-TnI level around childbirth was significantly negatively correlated with later LV diastolic function as determined by e' at 1 month postpartum.

Splanchnic organs serve as an important blood reservoir for the circulatory system.^{18 19} This blood reservoir

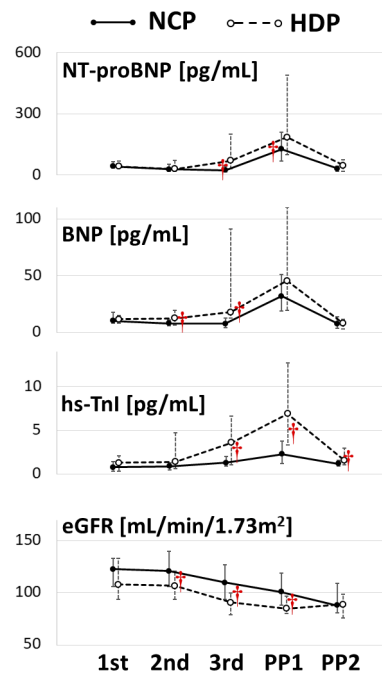


Figure 2 Changes in blood biomarker levels during pregnancy/postpartum. † $P < 0.05$ between the two groups. Vertical bars indicate 25th–75th percentile values. Data on BNP were determined in a limited number of women (see footnote for table 2). BNP, brain natriuretic peptide; HDP, hypertensive disorders of pregnancy; eGFR, estimated glomerular filtration rate; hs-TnI, high-sensitivity troponin I; NCP, normotensive control pregnancy; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PP1, immediately postpartum within 1 week after childbirth; PP2, approximately 1 month postpartum.

decreases with sympathetic activation, resulting in a rapid increase in venous return up to 800 mL. Preeclampsia is characterised by sympathetic overactivity,¹⁷ and ischaemia occurs in the splanchnic organs in severe forms of preeclampsia, such as the hemolysis, elevated liver enzymes and low platelet (HELLP) syndrome.^{22 23} Women with preeclampsia accounted for 67% (16/24) of women with HDP in this study (see footnote for table 1). It was speculated that all three factors, that is, reduced splanchnic blood reservoir leading to increased venous return, increased SVR and reduced LV diastolic function, contributed to increased IVC diameter and LA volume index despite decreased circulating blood volume in women with HDP.

HDP is a prominent risk factor of PPCM.^{1–3} LV diastolic dysfunction usually results from impaired LV relaxation and is consistently seen in patients with cardiomyopathy.²⁴ As dynamic changes in circulating volume are likely to occur peripartum, we used only e' , and not mitral inflow, LA volume or E/e' , as an index of LV diastolic function in this study, and demonstrated persistent postpartum reduced LV relaxation (monitored by e') in women with HDP. It was reasonably speculated that women with persistent postpartum reduced e' were at higher risk of PPCM or future cardiomyopathy compared with those

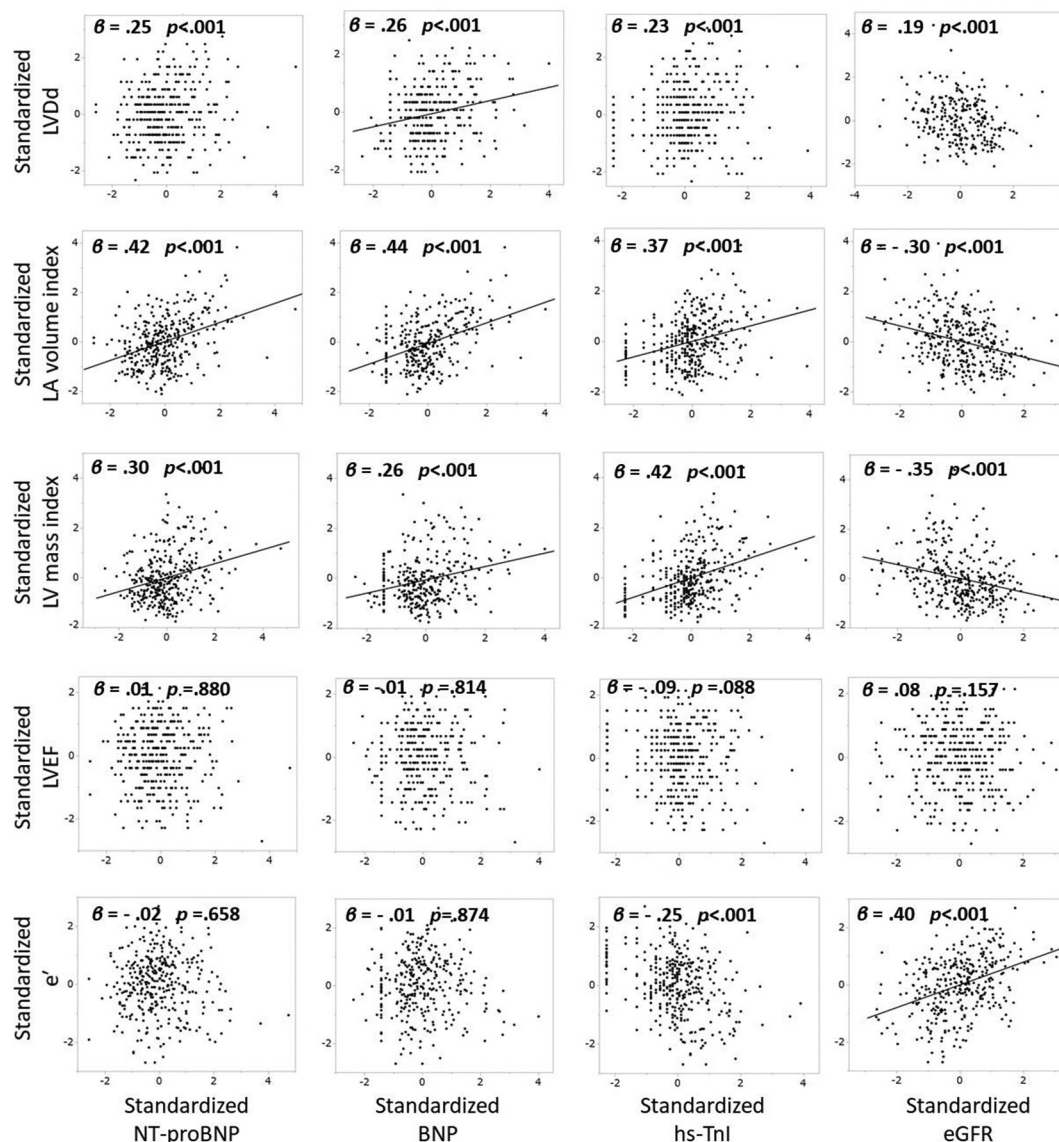


Figure 3 Standardised regression coefficients between blood variable levels and echocardiographic measurements. All data on biomarkers and five echocardiographic parameters determined simultaneously in 24 women with HDP and 51 women with NCP were used for this analysis. β , standardised regression coefficient. The regression line was drawn for $\beta > 0.25$ or $\beta < -0.25$. When hs-TnI level was below the limit of detection (0.1 pg/mL), we assumed that hs-TnI was present at a serum concentration of 0.1 pg/mL. BNP, brain natriuretic peptide; e', average of early diastolic septal and lateral mitral annular velocity; eGFR, estimated glomerular filtration rate; HDP, hypertensive disorders of pregnancy; hs-TnI, high-sensitivity troponin I; LA, left atrial; LV, left ventricular; LVDD, LV end-diastolic dimension; LVEF, LV ejection fraction; NCP, normotensive control pregnancy; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

without such findings. PPCM is rare, occurring in 1 in 300–4000 pregnant women.^{1–3} Determination of blood biomarkers capable of predicting long-lasting reduced e' at childbirth would contribute to identification of women requiring follow-up regarding cardiac status on echocardiography. Therefore, the present study was performed to identify such biomarkers, and we found that peripartum hs-TnI was significantly negatively correlated with e' at 1 month postpartum. Thus, peripartum hs-TnI predicted poor LV relaxation at 1 month postpartum in this study and may be useful in the detection of women requiring follow-up of cardiac status.

Both BNP/NT-proBNP and hs-TnI exhibited peak values immediately postpartum in both women with HDP and with NCP, consistent with the results of previous studies.^{5, 25} BNP is bioactive and cardioprotective, improving LV diastolic function,²⁶ and may be secreted in response to atrioventricular stretching to alleviate cardiac load,^{27, 28} perhaps simply reflecting the changes in heart morphology in pregnancy. The level of hs-TnI also reflects cardiac changes in morphology at the time of blood sampling, similar to BNP/NT-proBNP (figure 3). In addition, as hs-TnI reflects LV fibrosis and cardiac myocyte damage,^{8, 29} it was reasonable that higher hs-TnI

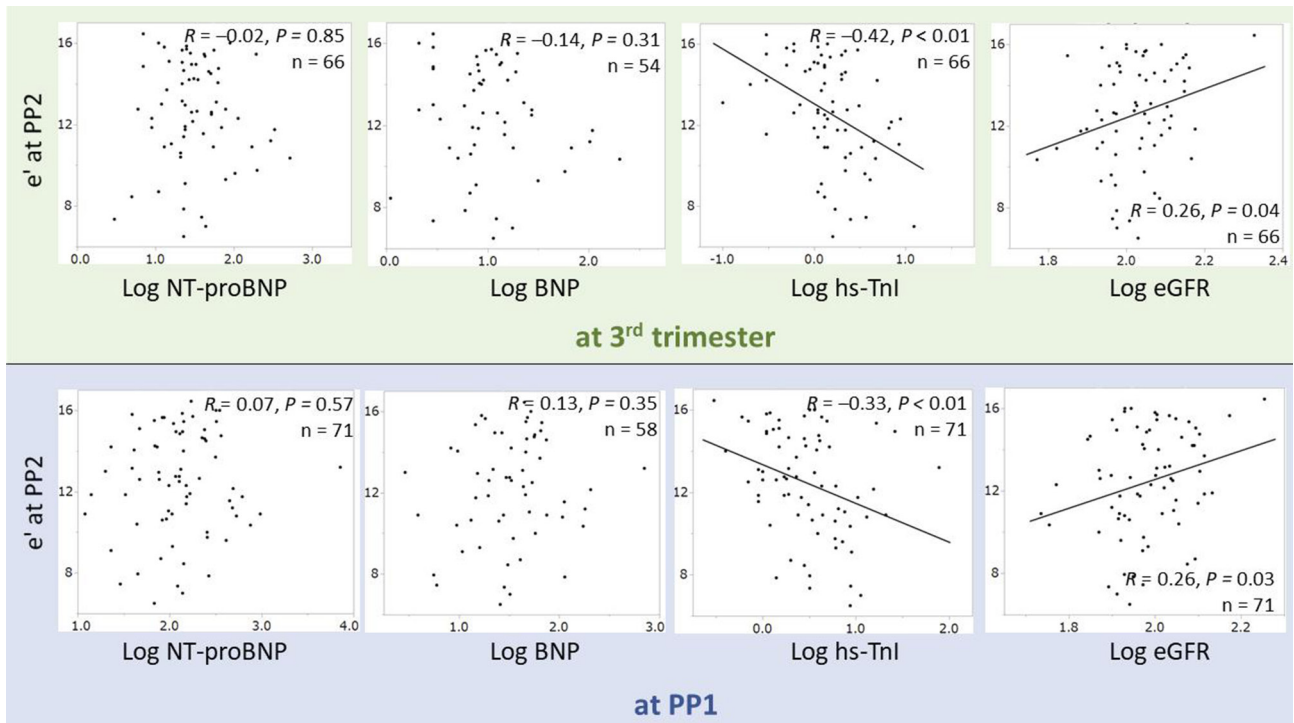


Figure 4 Associations of peripartum biomarker levels with e' at 1 month postpartum (PP2). BNP, brain natriuretic peptide; e' , average of early diastolic septal and lateral mitral annular velocity; eGFR, estimated glomerular filtration rate; hs-TnI, high-sensitivity troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PP1, immediately postpartum within 1 week after childbirth.

around childbirth predicted sustained reduction of e' in this study.

A significantly positive correlation was observed between eGFR and e' in this study, consistent with findings in non-pregnant subjects.³⁰ This suggested that reduced eGFR was likely to accompany increased E/e' , an index of LV end-diastolic pressure, as shown in figures 1 and 2. Pulmonary congestion as a sign of heart failure may be likely to occur under such conditions with increased LV end-diastolic pressure. HDP is a prominent risk factor for

heart failure in pregnancy,² and both pulmonary congestion and impaired renal function indeed occur more often in HDP than NCP.³¹ Thus, reduced eGFR can be considered as a sign of impaired renal function and as a precursor of pulmonary congestion in pregnancy. In addition, persistent postpartum reduced eGFR may be a risk factor of heart failure in future life.

Study limitations

The low prevalence rate of HDP (approximately 5.0%), delayed referral of patients with HDP to our hospital and acute worsening of the patient's condition followed by emergent caesarean section resulted in missing data in some women with HDP in this study. Because LV diastolic dysfunction is usually the result of impaired LV relaxation,²⁴ we did not use the proposed diastolic function criteria of Nagueh *et al*²⁴ for difference in age of subjects and used only e' as an index of LV diastolic function in this study. These factors may have distorted the results.

CONCLUSIONS

Persistent postpartum reduced LV relaxation is a characteristic feature of women with HDP. Reduced splanchnic blood reservoir in addition to reduced LV diastolic function as well as increased SVR may have contributed to the increased third trimester IVC diameter and LA volume, resulting in increased risk of heart failure despite decreased circulating blood volume in women with HDP. A rise in hs-TnI around childbirth was associated with poor LV relaxation ability at 1 month postpartum.

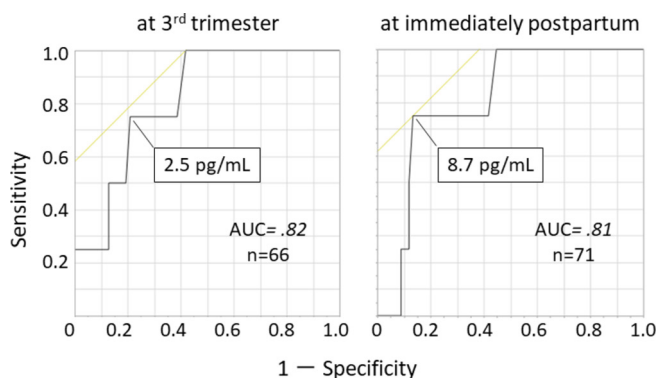


Figure 5 Receiver operating characteristic curves of hs-TnI at third trimester and immediately postpartum in the prediction of reduced e' (< 7.7 cm/s) at 1 month postpartum. The e' of 7.7 cm/s corresponded to the fifth percentile value of 51 women with normotensive control pregnancy at 1 month postpartum. AUC, area under the curve; e' , average of early diastolic septal and lateral mitral annular velocity; hs-TnI, high-sensitivity troponin I.

Contributors TU, SY, TY, SI, IF, HI, DM, TH, KO, MM, HT and HM participated in the design of the study and collected data on each pregnant woman who participated in this study. TU participated in the design of the study, performed statistical analyses and drafted the manuscript. HM conceived of the study, and participated in its design and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript.

Funding This study was funded by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan (grant number: 18K0927908 and 2646246804).

Competing interests None declared.

Patient consent Obtained.

Ethics approval This prospective observational study was performed in accordance with the provision of the Declaration of Helsinki and was conducted after receiving approval from the Institutional Review Board of Hokkaido University Hospital (013–0262, 4 April 2014).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

Open access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0>

REFERENCES

- Bello N, Rendon ISH, Arany Z. The relationship between pre-eclampsia and peripartum cardiomyopathy: a systematic review and meta-analysis. *J Am Coll Cardiol* 2013;62:1715–23.
- Elkayam U. Clinical characteristics of peripartum cardiomyopathy in the United States: diagnosis, prognosis, and management. *J Am Coll Cardiol* 2011;58:659–70.
- Sliwa K, Fett J, Elkayam U. Peripartum cardiomyopathy. *Lancet* 2006;368:687–93.
- Behrens I, Basit S, Lykke JA, et al. Association between hypertensive disorders of pregnancy and later risk of cardiomyopathy. *JAMA* 2016;315:1026–33.
- Umazume T, Yamada T, Ishikawa S, et al. Prospective study on changes in blood variables in pregnant women at higher risk of peripartum cardiomyopathy. *ESC Heart Fail* 2015;2:208–15.
- Resnik JL, Hong C, Resnik R, et al. Evaluation of B-type natriuretic peptide (BNP) levels in normal and preeclamptic women. *Am J Obstet Gynecol* 2005;193:450–4.
- Fleming SM, O’Gorman T, Finn J, et al. Cardiac troponin I in pre-eclampsia and gestational hypertension. *BJOG* 2000;107:1417–20.
- Chin CW, Shah AS, McAllister DA, et al. High-sensitivity troponin I concentrations are a marker of an advanced hypertrophic response and adverse outcomes in patients with aortic stenosis. *Eur Heart J* 2014;35:2312–21.
- Shiojima I, Sato K, Izumiya Y, et al. Disruption of coordinated cardiac hypertrophy and angiogenesis contributes to the transition to heart failure. *J Clin Invest* 2005;115:2108–18.
- Pritchard JA. Changes in blood volume during pregnancy. *Anesthesiology* 1965;26:393–9.
- Cong J, Yang X, Zhang N, et al. Quantitative analysis of left atrial volume and function during normotensive and preeclamptic pregnancy: a real-time three-dimensional echocardiography study. *Int J Cardiovasc Imaging* 2015;31:805–12.
- Estensen ME, Beitnes JO, Grindheim G, et al. Altered maternal left ventricular contractility and function during normal pregnancy. *Ultrasound Obstet Gynecol* 2013;41:659–66.
- Simmons LA, Gillin AG, Jeremy RW. Structural and functional changes in left ventricle during normotensive and preeclamptic pregnancy. *Am J Physiol Heart Circ Physiol* 2002;283:H1627–H1633.
- Umazume T, Yamada T, Yamada S, et al. Morphofunctional cardiac changes in pregnant women: associations with biomarkers. *Open Heart* 2018;5:e000850.
- Miller WL, Hartman KA, Burritt MF, et al. Profiles of serial changes in cardiac troponin T concentrations and outcome in ambulatory patients with chronic heart failure. *J Am Coll Cardiol* 2009;54:1715–21.
- Silver HM, Seebeck M, Carlson R. Comparison of total blood volume in normal, preeclamptic, and nonproteinuric gestational hypertensive pregnancy by simultaneous measurement of red blood cell and plasma volumes. *Am J Obstet Gynecol* 1998;179:87–93.
- Schobel HP, Fischer T, Heuszer K, et al. Preeclampsia -- a state of sympathetic overactivity. *N Engl J Med* 1996;335:1480–5.
- Gelman S, Mushlin PS. Catecholamine-induced changes in the splanchnic circulation affecting systemic hemodynamics. *Anesthesiology* 2004;100:434–9.
- Fallick C, Sobotka PA, Dunlap ME. Sympathetically mediated changes in capacitance: redistribution of the venous reservoir as a cause of decompensation. *Circ Heart Fail* 2011;4:669–75.
- Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;16:233–71.
- Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009;53:982–92.
- Hosokawa A, Umazume T, Yamada T, et al. Maternal bradycardia occurring prior to onset of HELLP syndrome in a woman with pre-eclampsia. *BMJ Case Rep* 2017;2017:bcr-2016-217964.
- Kobayashi T, Tokunaga N, Isoda H, et al. Vasospasms are characteristic in cases with eclampsia/preeclampsia and HELLP syndrome: proposal of an angiospastic syndrome of pregnancy. *Semin Thromb Hemost* 2001;27:131–6.
- Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016;29:277–314.
- Yamada T, Koyama T, Furuta I, et al. Effects of caesarean section on serum levels of NT-proBNP. *Clin Endocrinol* 2013;78:460–5.
- Clarkson PB, Wheelton NM, Macleod C, et al. Brain natriuretic peptide: effect on left ventricular filling patterns in healthy subjects. *Clin Sci* 1995;88:159–64.
- Houben AJ, van der Zander K, de Leeuw PW. Vascular and renal actions of brain natriuretic peptide in man: physiology and pharmacology. *Fundam Clin Pharmacol* 2005;19:411–9.
- McGrath MF, de Bold ML, de Bold AJ. The endocrine function of the heart. *Trends Endocrinol Metab* 2005;16:469–77.
- Keller T, Zeller T, Peetz D, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Engl J Med* 2009;361:868–77.
- Masugata H, Senda S, Goda F, et al. Echocardiographic assessment of the cardio-renal connection: is left ventricular hypertrophy or diastolic function more closely correlated with estimated glomerular filtration rate in patients with cardiovascular risk factors? *Clin Exp Hypertens* 2010;32:113–20.
- Ananth CV, Lavery JA, Friedman AM, et al. Serious maternal complications in relation to severe preeclampsia: a retrospective cohort study of the impact of hospital volume. *BJOG* 2017;124:1246–53.