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

Shino Tanaka,[1] Rie Oyama,[1] Akimune Fukushima,[2] Akihiko Kikuchi[1] and Toru Sugiyama[1]

[1] Department of Obstetrics and Gynecology, Iwate Medical University

[2] Department of Clinical Genetics, Iwate Medical University

Iwate Medical University, Department of Obstetrics and Gynecology

19-1 Uchimaru, Morioka, Iwate, 0208505,Japan

Tel:81-19-651-5111, Fax: 81-19-622-1900, E-mail: s.tanaka0401.hsm@gmail.com

Corresponding author: Shino Tanaka.

Iwate Medical University, Department of Obstetrics and Gynecology

19-1 Uchimaru, Morioka, Iwate, 0208505, Japan

Tel: 81-19-651-5111, Fax: 81-19-622-1900, E-mail: s.tanaka0401.hsm@gmail.com

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Short running title: Vector high-resolution ECG and Pregnancy

Abstract

Aim: We analyzed the atrial natriuretic peptide (ANP), the N-terminal pro B-type natriuretic peptide (NT-pro BNP) and the vector synthesis high-resolution electrocardiography, to estimate cardiac load with the circulatory dynamic change through the postpartum from pregnancy. Methods: The subjects were singleton pregnant women (n=19), who were divided three stages 1; 34–36 weeks of gestation, stage 2; 2–6 days postpartum, and stage3; 1–3 months after delivery. We preformed the vector synthesis high-resolution electrocardiography and measured ANP and NTproBNP . Results: The two-dimensional distribution map of the RTc dispersion markedly were comprised in I + II on all cases. The ANP and NT-proBNP levels in stages 2 were significant higher than stage 1 and 3. Conclusions: This study maybe predictable to prevention of cardiomyopathy for pregnant and postpartum women using the vector synthesis high-resolution electrocardiography and ANP, NT-proBNP.

Introduction

Circulating plasma and the circulating blood volume begin to increase at 6 weeks and 10–12 weeks of gestation, respectively. An approximately 33% increase occurs at 21–24 weeks of gestation, compared to the blood volume before pregnancy. The blood volume increases to its maximum of 45%–50% at approximately at 32 weeks of gestation[1-2]. 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 an elevated blood progesterone level, pressure on peripheral blood vessels, and lower-blood flow congestion. Peripartum cardiomyopathy and Takotsubo cardiomyopathy-rarely develop in the perinatal period, primarily in early postpartum, but these conditions result in poor outcomes in some patients [4]. The cause includes reactions to deviant circulatory loads in pregnant, and pregnancy-induced hypertension, and pulmonary edema which is a side effect of ritodrine hydrochloride. However, its prediction and predictors have not been clarified. Thus, we focused on items related to the evaluation of the maternal cardiac volume load in publicly funded “prenatal checkups,” high-resolution electrocardiograms, and peptide hormones secreted by the heart. The aim of the present study is to perform detailed evaluation of cardiac lode in a normal pregnant woman without complications such as hypertension and premature delivery undergoing tocolytic therapy with ritodrine hydrochloride, using the vector synthesis high-resolution electrocardiography.

In 2007, Nakai [6-9] et al. developed an original vector synthesis 187-channel high-resolution electrocardiography hat was based on the vector projection theory by Frank [5], and reported that cardiomyopathy, cardiac loads, and fetal electrocardiograms can be noninvasively evaluated using this device [6-9]. The traditional ECG is displayed as a weave form that is converted by electrical potential, however the vector synthesis high resolution electrocardiography can present that QT (RT) disorientation 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 (HFLP)

and vermicular depolarization, and increased RT dispersion that suggests a right ventricular outflow region[6]. In 2013, Terata et al. succeeded in analyzing the cardiac load of pregnant and postpartum women using the vector synthesis high-resolution electrocardiography without echocardiography[10].

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 [11] isolated and identified atrial natriuretic peptide (ANP), which comprise 28 amino acids, from the human atrium. In 1988, the N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) was isolated from the porcine brain [12]. It was subsequently clarified that it was primarily secreted by the heart [13]. In July 2007, it became possible to measure NT-proBNP. In this study, to estimate cardiac loads from pregnancy to postpartum was analyzed using noninvasive vector synthesis high-resolution electrocardiography, ANP and NT-proBNP level.

Methods

Patients: The normal singleton pregnant women (n=19) were enrolled who attended 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. All patients provided written consent. Iwate Medical University Ethics Committee approved this study on May 1, 2014 (approval number H26-20). We classified 34–36 weeks of gestation as stage 1, 2–6 days postpartum as stage 2, and 1–3 months after delivery as stage 3.

(1) Character of cases: 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 at delivery.

(2) Peptide hormone measurement: The ANP and NT-proBNP level, blood was collected from the vein into ethylenediaminetetraacetic acid-contacting tubes. The collected blood was centrifuged at 4°C at 3000 rpm for 10 minutes and the supernatants were stored in

polypropylene tubes at -30°C until assayed. ANP and NT-proBNP were measured with electrochemiluminescence immunoassy (ECLIA).

(3) The vector synthesis high-resolution electrocardiography: comprises a laptop, input box containing a high-amplitude/high-resolution amplifier (IB-81, Fukuda Denshi), and original software to analyze network with digital ECG signals (ECG Manager; ICS Iwate, Morioka, Japan). The minimum resolution was 0.076 μV, and the input signal sampling frequency was 2 kHz. Silver-silver chloride magnet electrodes (Magne Lode TE-18-5, Fukuda Denshi) were used. For indices of the vector synthesis high-resolution electrocardiography, X-Y-Z lead ECG were averaged and processed through a band-pass filter (finite impulse response [FIR] type, 45-200 Hz), and fQRS was measured in vector magnitude waveforms. The inflection points of the P, QRS, and T waves were judged using the differentiation [7-8,16]. From lead vectors corresponding to the center electrode and 187 electrodes on the body surface (Figure 1), an 187-channel ECG was synthesized, the current density was determined, and a two-dimensional (2D) -distribution map of RTc dispersion representing the variation of the repolarization time was prepared[6-7] (Figure 2). Focusing on the fact that the spatial distribution of the variation in the heart muscle repolarization time can be evaluated using the map. The map was divided into quadrants I–IV, and changes were investigated with I + II as the right heart component, III + IV as the left heart component, and the central region as the transitional zone. The performed position for all of cases, which was supine position during detected fQRS and 2D-distribution map of RTc dispersion.

Statistical analysis

The results was analyzed by SPSS version 23.0. (IBM, Japan). Multiple groups were analyzed using variance (ANOVA) and Kruskal–Wallis Test and a regression curves were used to analyze correlations. A value of $P < 0.05$ was regarded as significant.

Results

Table 1 presents the maternal age was 34.3 ± 5.0 years old, and gravid was 1.9 ± 1.7, para was 1.1± 0.9. The height (cm)/uterine fundus (cm) ratio was 0.20 ± 0.02. The neonatal birth weight was 2857.1 ± 543.0g, and loss of blood at delivery was 887.8± 518.2g.

Table 2 shows blood pressure and BMI of all cases. 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. The result of stage 3 showed increases compere with stage 1 and 2, however it were no significant between systolic and diastolic blood pressure ($P = 0.222$ and $P = 0.300$). The body mass index (BMI) was 23.9 ± 2.2, 24.0 ± 2.0, and 22.6 ± 2.6 for stages 1, 2, and 3, which showed was not significant between each stages ($P = 0.141$) (Figure3).

Table 3 shows the vector synthesis high-resolution electrocardiography indexes, and values of ANP and NT-proBNP.

The vector synthesis high-resolution electrocardiography.

fQRS in stages 1, 2, and 3 was 99.8± 1.6 msec, 108.2 ± 1.3 msec, and 109.7 ± 1.9msec (Table 3), which showed that stage 3 significant high value compared with stages 1 and 2 ($P < 0.0001$). The standard value is 44ms, which was reported by Nakai et.al[14]. The RTc dispersions in stages 1, 2, and 3 were 48.8 ± 5.7msec, 45.6 ± 3.3msec, and 46.2± 2.8msec ($P = 0.827$). The value was not significant difference between each stage (Figure 4), however all value of RTc were higher than standard value. Figure 2 shows 2D-color distribution maps of the RTc dispersion in a patient with massive uterine leiomyoma (case 4). This patient did not develop pulmonary hypertension, anterior wall infarction and dilated cardiomyopathy, and she recovered without cardiac complications after cesarean section.

ANP and NT-proBNP.

The standard ANP level is 43.0 pg/mL, and the standard level of NT-proBNP is 125 pg/mL. The ANP levels in stages 1, 2, and 3 were 23.2 ± 2.4 pg/mL, 58.4± 14.0 pg/mL, and 23.8 ± 4.4 pg/mL. Stage 2 was higher than stage 1 and 3 (p=0.001). The NT-proBNP levels in stages 1, 2, and 3 were 37.6± 4.0pg/mL, 170.2 ± 27.5 pg/mL, and 41.6 ± 10.0pg/mL that stage 2 was

significant higher than the standard in stage 1 and 3, (P<0.0001) (Figure 4). There was only relationship between NT-proBNP and fQRS in stage 1(r^2= 0.22, p=0.033) (Figure 5).

Discussion

The time-course the vector synthesis high-resolution electrocardiography and changes in the peptide hormone levels were investigated in the normal singleton pregnant and postpartum women. This finding clarified that the cardiac volume load resulting from an increased circulating blood volume was burdened on 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 the circulating blood volume. With regard to changes in blood pressure, arterial smooth muscle relaxes and vascular resistance decreases in late pregnancy. The reduction in arterial vascular resistance is more marked in diastolic pressure than in systolic pressure[14]. In the lower limbs, resistance increases because the pelvic vein and inferior vena cava are pressed,[15]which suggests 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 the pelvic vein and thorax and further increase cardiac loads. In all patients, the variation in the repolarization time in quadrants I + II was large throughout the period. We think that this finding may have resulted from right cardiac volume load induced by an increased circulating blood volume in pregnancy at 32 weeks of gestation.

ANP, brain natriuretic peptide (BNP), and NT-proBNP are well-known heart failure markers[17-18]. When an increase in the preload stimulates the heart muscle to extend, ANP and BNP are secreted primarily by the atrial and ventricular muscles[19]. 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[20].

The fQRS significant high value in stage 3 compared with stages 1 and 2, in addition the RTc dispersion of all stages were higher than the standard value. Those results showed that effect of cardiac load relate with pregnancy contented to postpartum. In various stages showed a marked

variation in quadrants I + II of the 2-dimensional distribution map of RTc dispersion. The ANP and NT-proBNP levels were high in stage 2 compare with stage 1 and 3, in this fact, we suggested that increased blood volume impacted cardiac load until postpartum, also it could be prediction the heart frailer when a pregnant woman had sever pregnancy induced hypertension or high dose of retodorine sulfate by intravenous infusion with bed- rest after delivery. fQRS and NT-proBNP values were correlated in stage 1. This result showed fQRS and NT-proBNP reflected for increasing the blood volume before 34 weeks of gestation, also that induced production of NT-proBNP with changed myocardium and conduction system of heart at stage 1. Based on the vector synthesis high-resolution electrocardiography and peptide hormone findings, the blood volume load primarily in the right ventricle resulting from an increase in the circulating blood volume stimulates the heart muscle to extend and conduction system in heart at pregnancy, and then ANP in the atrium is secreted in response to the stimulation. 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 the tocholysis agent which is ritodrine hydrochloride. Ritodrine hydrochloride is a β2 receptor stimulator and it also acts on the β1 receptors and causes problematic adverse effects such as tachycardia, increased cardiac output, and peripheral vascular dilatation[21-22]. The frequency of pulmonary edema due to the adverse effect of ritodrine hydrochloride is only approximately 0.3%, but it is common[23]. In stage 2, the ANP and the NT-proBNP suggested that became index of cardiac load. 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 the persistently high level of NT-proBNP. This phenomenon is consistent with Marey's law. Based on the findings in stage 3, the peptide hormone level normalizes with the recovery of normal circulatory dynamics in the postpartum, but the right ventricle may still be the center of the ECG phenomena, and improvement in the myocardial load may require time.

Interestingly, the NT-proBNP levels were 40 pg/mL (stage 1), 292 pg/mL (stage 2) and 208 pg/mL (stage 3) in our case 4 with massive uterine leiomyoma. All of these results were higher

than those in the other patients, despite her ANP level was almost normal during the observation period. In addition, the 2D-color distribution map of the RTc dispersion gave us important information that the repolarization time markedly varied in quadrants I + II which indicated that volume overload burdened the right heart system, although she 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[24], it means the following, 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 suggest the necessity of continuous observation by a cardiologist and evaluation of maternal cardiac load in a woman's subsequent pregnancies. In routine "pregnancy examination", it is difficult to evaluate maternal cardiac load. However, this study clarified that ANP, NT-proBNP, and fQRS are involved in pregnancy-related changes in circulatory dynamics during pregnancy and the postpartum period in normal pregnant women.

Since pregnant women with cardiomyopathy are rare, we did not have such patients in our 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 the vector synthesis high-resolution electrocardiography may be effective as a screening test to prevent cardiomyopathy for pregnant and postpartum women. Particularly, the 2D-distribution map of RTc dispersion could display cardiac load regions in normal pregnant and postpartum women as color visualization images. Since our 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 the vector synthesis high-resolution electrocardiography for evaluating cardiac load in normal pregnant and postpartum women before they develop cardiac complications.

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Disclosures

None of the authors has any conflict of interest to declare.

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Figure legends

Table 1. Character of case.

Table 2. Result of BMI, Systolic/Diastolic blood pressure and Heart rate

Table 3. Result of the vector synthesis high-resolution, ANP and NT-pro BNP.

Figure 1. Vector-projected property for 187 fixed-positions on a torso surface model:
Eleven parallel, equally spaced transverse levels with 2-inch spacing between the levels. Level 5 coincides with the second intercostal space and level 6 coincides with the center of the heart. Seventeen letter designations (A-I) indicate the intersection with each transverse level of radial lines separated by equal angles of 11.25 degrees emanating from the longitudinal anatomic axis of the torso. A/D indicates analogue-digital translate circuit; PC, personal computer; V2, precordial lead of V2; R, right upper arm; L, left upper arm; F, left lower body; and RF, right lower body.

Figure 2. The 2D-color distribution maps of the RTc dispersion in a patient with massive uterine leiomyoma (case 4). The repolarization time markedly varies in quadrants I + II which indicates that volume overload burdens the right heart system.

Figure 3. The body mass index (BMI), Systolic and diastolic blood pressure in each stage. (A)BMI, (B) Systolic blood pressure and (C) Diastolic blood pressure, which were not significant value between in each stage. p=not significant [NS]. Values are given as SEM.

Figure 4. Atrial natriuretic peptide (ANP), N-terminal of the prohormone brain natriuretic peptide (NT-proBNP), fQRS and RTc dispersion of each stages. (A) ANP: 58.4± 14.0 pg/mL in

stage 2 is high value compared with stage 3 ($p<0.05$). (B)NT-pro BNP: 170.2 ± 27.5 pg/mL in in stage 2 is high value compared with stage 3 ($p<0.05$). (C) fQRS: 109.7 ± 1.9msec in stage 3 is high level compared with stage 1 ($p=0.01$). (D) RTc dispersion: All results were not significant between each stage.

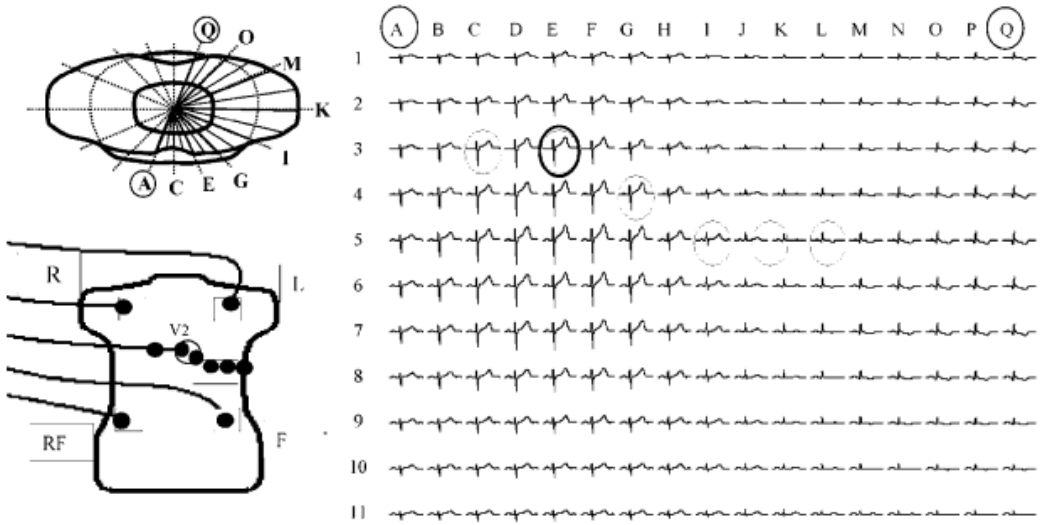
p=not significant [NS]. Values are given as SEM.

Figure 5. Regression analysis of this study. (A) Relationship between ANP and fQRS in stage 1 ($r^2= 0.057$, $p=0.326$). (B) Relationship between BNP and fQRS in stage 1 ($r^2= 0.222$, $p=0.042$). (C) Relationship between NT-proBNP and RTc dispersion in stage 1 ($r^2= 0.018$, $p=0.587$). There was only relationship between NT-proBNP and fQRS in stage 1.

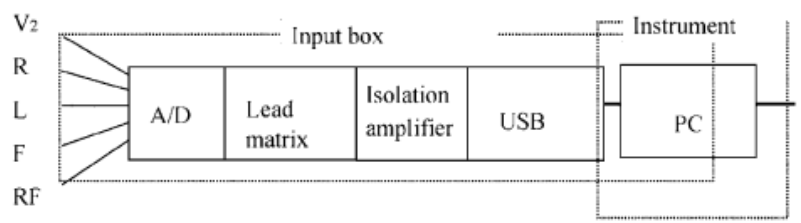
Case	Age (year)	Gravid	Para	Height/fundus ratio	Gestational age at delivery	Blood loss at delivery (g)
1	39	4	1	0.19	34w5d	931
2	24	0	0	0.19	37w5d	666
3	34	3	2	0.19	37w6d	628
4	32	2	1	0.22	37w1d	1111
5	37	1	1	0.19	38w1d	790
6	35	4	1	0.19	37w5d	1079
7	39	2	1	0.21	38w4d	1563
8	23	1	1	0.19	38w1d	1095
9	36	6	1	0.19	39w1d	189
10	37	1	1	0.18	38w0d	313
11	36	0	0	0.22	36w2d	595
12	42	1	1	0.20	41w0d	858
13	38	1	1	0.25	37w3d	2133
14	34	1	1	0.22	38w1d	660
15	29	3	2	0.20	39w6d	662
16	33	1	1	0.17	39w2d	369
17	33	5	4	0.18	40w0d	570
18	36	1	0	0.21	39w2d	692
19	32	2	1	0.18	38w0d	1114

	BMI (kg/m²)			Blood pressure (mmHg)						Heart rate(/min.)		
				Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic			
stage	1	2	3	1		2		3		1	2	3
case												
1	20.4	20.8	20.4	106	74	122	76	105	72	80	62	76
2	24.5	23.4	20.8	110	49	119	74	103	50	73	69	65
3	22.8	22.4	20.8	104	58	89	56	104	58	84	65	65
4	25.3	26.1	22.8	109	71	110	80	107	74	122	92	70
5	23.5	23.9	21.5	116	74	111	74	115	82	100	87	82
6	25.3	25.3	24.0	105	55	106	60	96	56	92	81	68
7	25.9	25.5	25.5	96	56	94	52	106	74	83	76	60
8	21.1	20.3	18.4	94	62	91	66	90	58	96	78	63
9	21.5	20.4	18.6	105	72	121	67	113	69	74	61	67
10	20.6	21.9	21.9	100	72	107	70	116	78	70	74	65
11	26.7	25.9	23.9	93	61	118	84	120	75	91	80	63
12	27.7	26.6	25.3	112	69	122	74	152	82	92	80	69
13	26.8	25.1	22.9	104	58	108	60	130	72	100	77	59
14	21.7	22.2	20.7	93	59	102	64	105	68	100	74	74
15	22.6	23.2	20.1	92	60	100	60	110	60	85	63	70
16	25.2	24.5	23.0	139	82	164	93	152	90	80	65	68
17	26.4	26.0	24.7	116	68	118	71	118	60	74	69	71
18	27.4	26.4	24.9	116	65	119	77	134	83	72	82	65
19	25.3	24.7	22.7	118	62	117	72	127	79	83	69	68

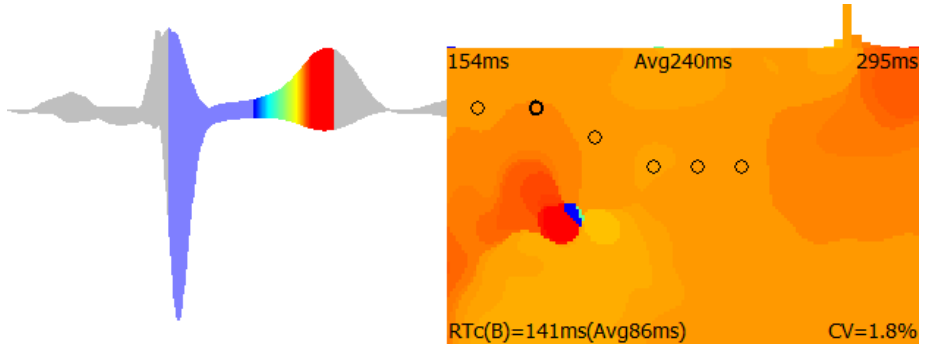
	High-resolution electgraphy						Peptide hormone					
	fQRS (msec)			RTc dispersion (msec)			ANP (pg/mL)			NTproBNP (pg/mL)		
stage	1	2	3	1	2	3	1	2	3	1	2	3
case												
1	106	109	107	24	17	36	5	35.6	5.1	50	183	17
2	97	103	107	51	45	54	17.8	66.5	15.6	36	157	16
3	97	106	97	72	36	35	20.2	23.4	21.6	24	225	33
4	97	112	103	86	80	49	28.3	12.6	82.6	40	292	208
5	91	111	113	12	38	57	14.5	14.4	17	19	270	71
6	97	106	110	43	57	57	9	40.9	10.3	32	106	14
7	99	106	119	47	52	33	19.8	57.1	24.9	13	157	26
8	98	109	98	65	35	51	23.5	107	24.2	50	250	25
9	107	115	118	48	45	45	20.3	38.2	14	54	88	34
10	78	101	111	38	56	27	21.1	80.4	19	13	51	28
11	100	106	89	2	22	29	40.9	111	61.5	46	367	44
12	111	117	116	26	46	36	38.6	59.2	34	43	31	29
13	108	112	115	90	45	51	22.6	29.3	23.7	31	55	31
14	94	105	105	78	62	62	18.2	33.6	26.1	39	454	31
15	103	92	121	71	43	63	35	277	7.6	38	238	24
16	100	105	110	21	57	30	15.3	5	7.4	16	50	33
17	99	110	102	46	44	51	36.4	18.1	5.7	61	55	10
18	109	109	118	46	34	51	29.2	51	31.5	27	52	72
19	107	122	122	61	52	62	30.2	54.9	20.5	82	153	44



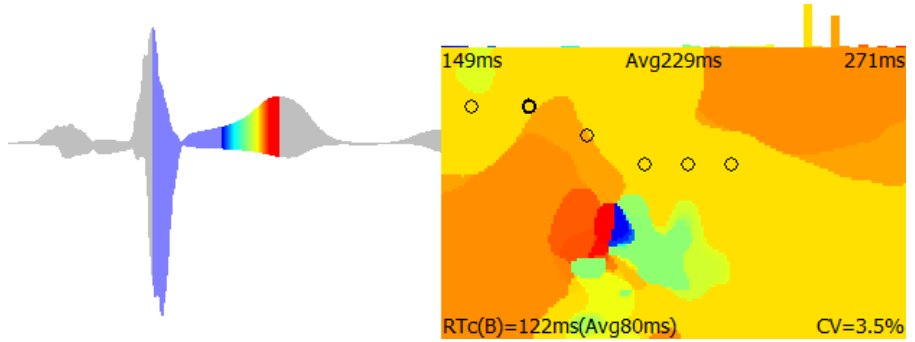
Input signal



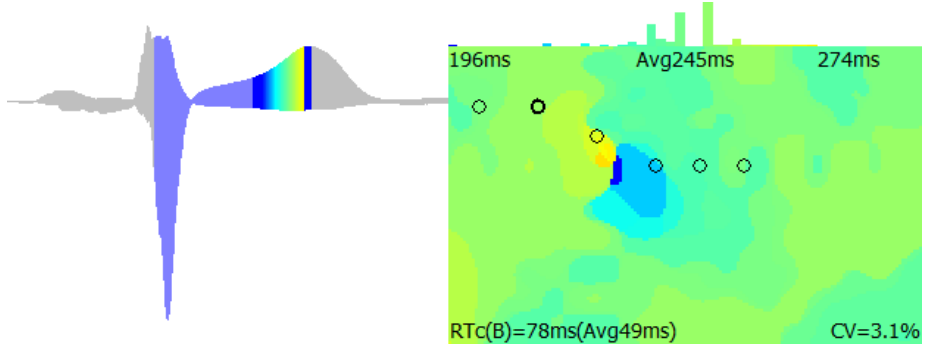
stage 1

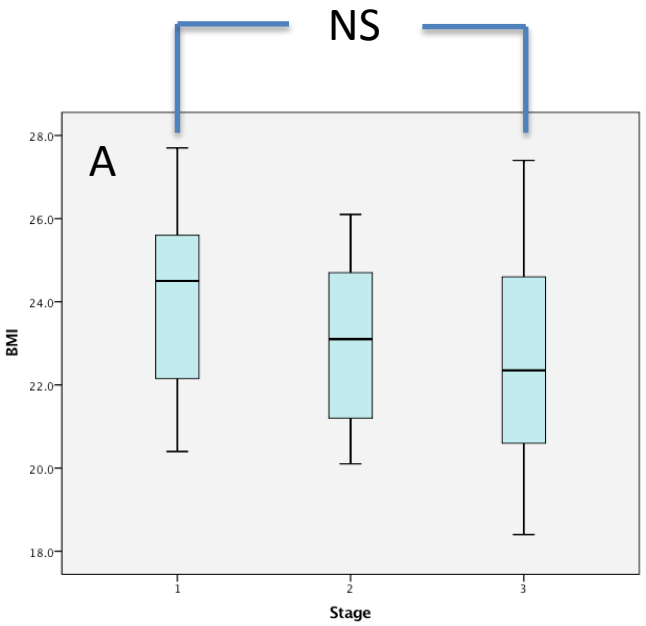


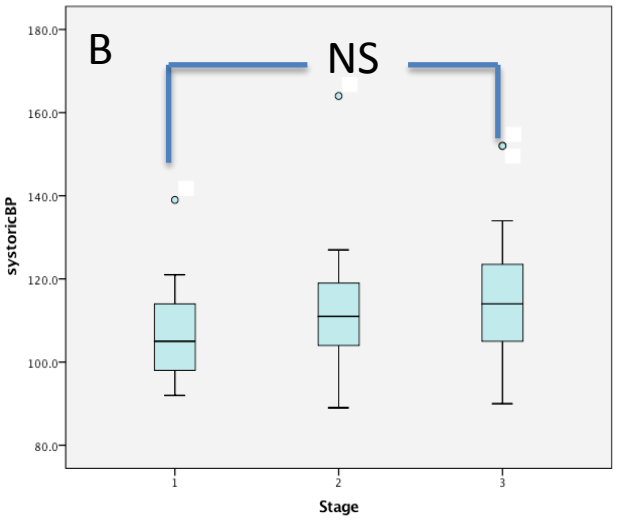
stage 2

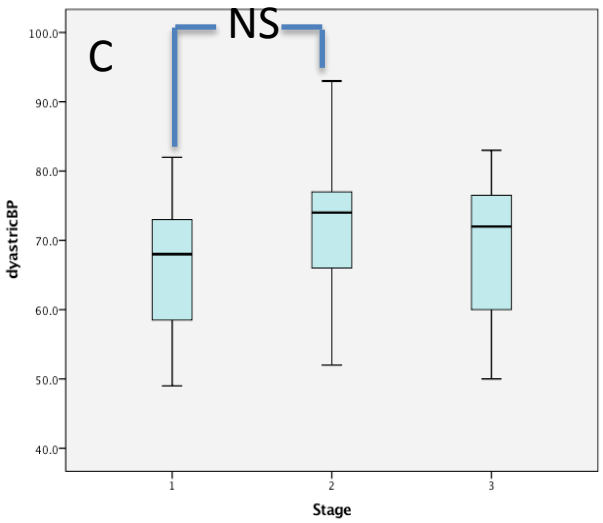


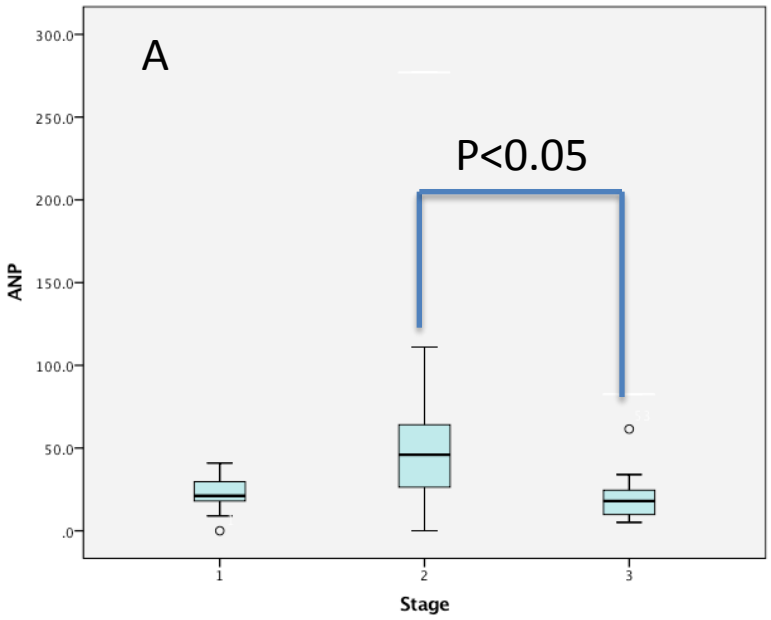
stage 3

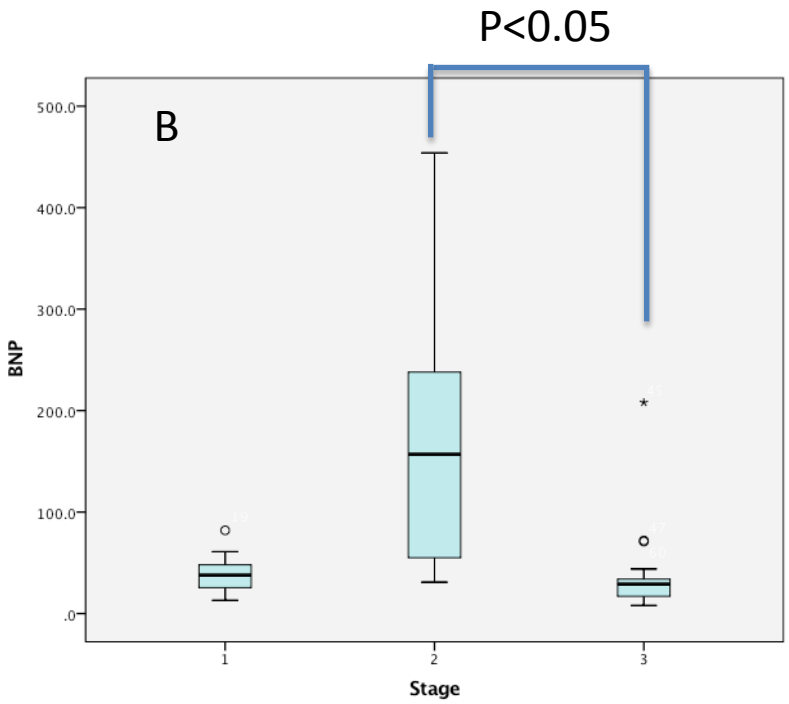


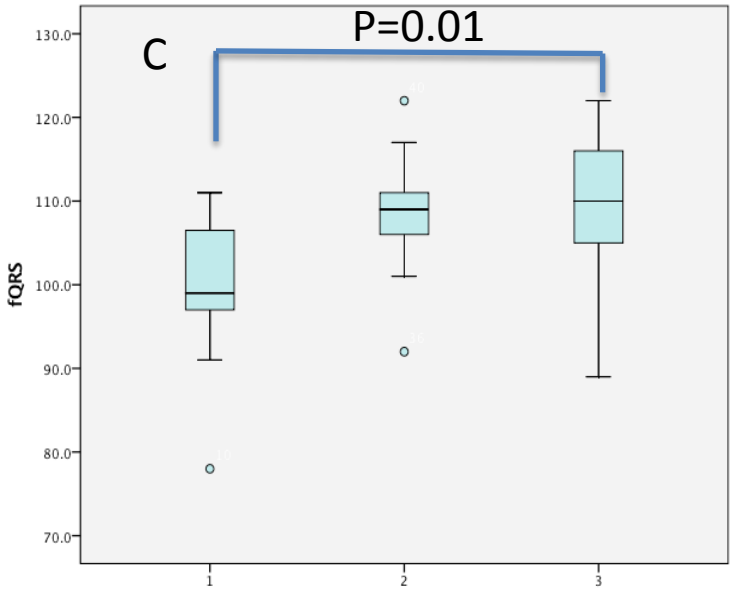

NS
A
BMI
28.0
26.0
24.0
22.0
20.0
18.0
1
2
3
Stage

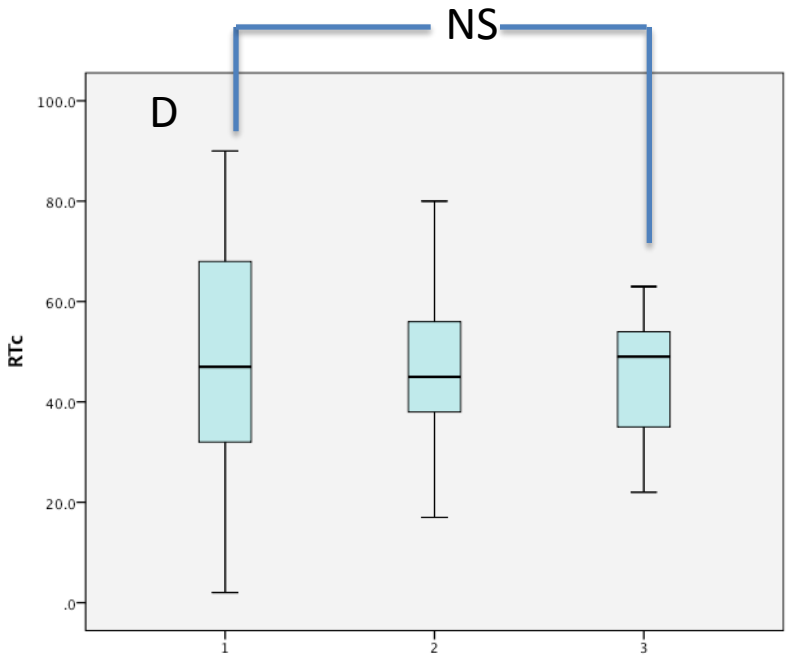

B
NS
systoricBP
180.0
160.0
140.0
120.0
100.0
80.0
1
2
3
Stage

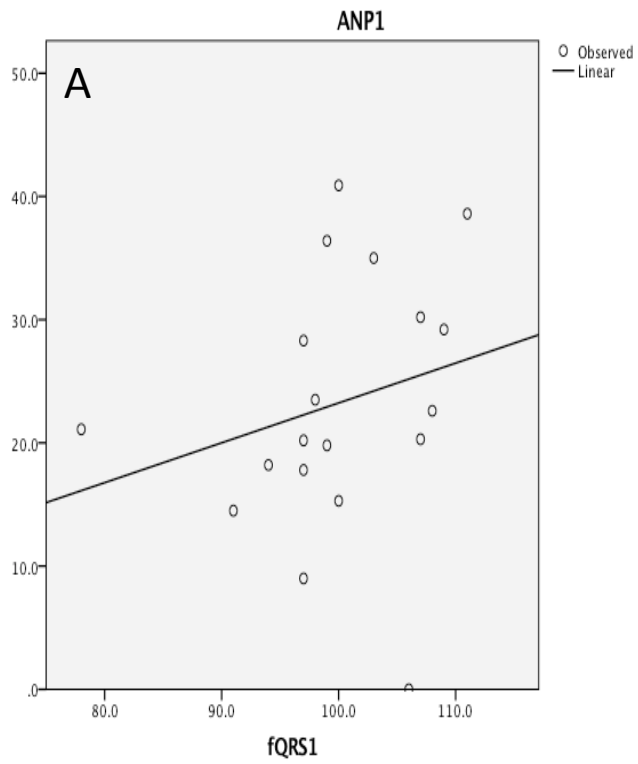

C
NS
dyastricBP
100.0
90.0
80.0
70.0
60.0
50.0
40.0
1
2
3
Stage


A
P<0.05
ANP
300.0
250.0
200.0
150.0
100.0
50.0
.0
1
2
3
Stage

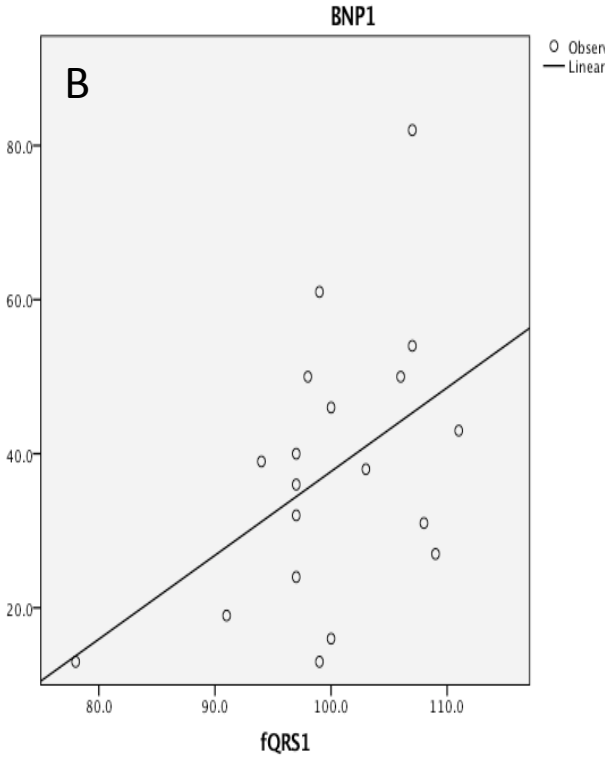

P<0.05
B
BNP
500.0
400.0
300.0
200.0
100.0
.0
1
2
3
Stage


P=0.01
C
fQRS
130.0
120.0
110.0
100.0
90.0
80.0
70.0
1
2
3

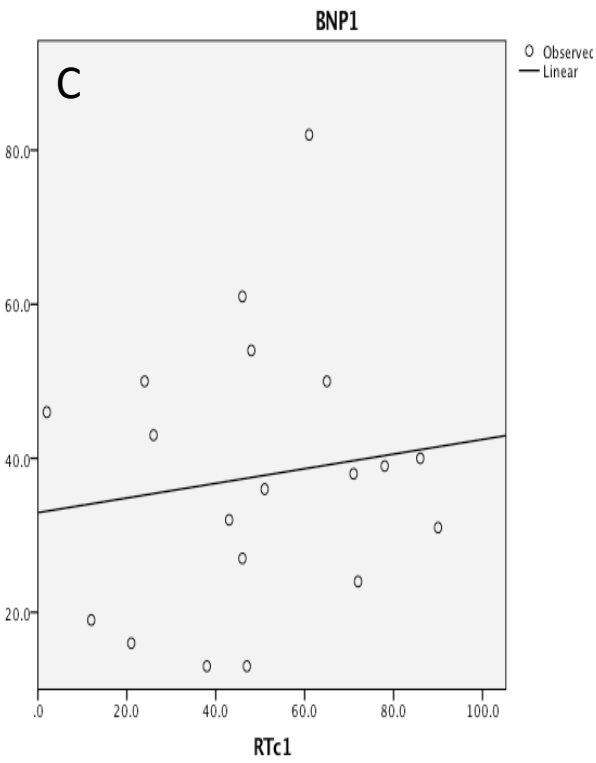

NS
D
RTc
100.0
80.0
60.0
40.0
20.0
.0
1
2
3



r^2=0.056, P=0.3



r^2=0.22, P=0.033



r^2=0.018, P=0.587