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Changes in Heart Rate Variability and QT Variability during the First Trimester of Pregnancy

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Short Title: Early Cardiovascular Changes during Pregnancy

Abstract

The risk of new-onset arrhythmia during pregnancy is high, presumably relating to changes in both haemodynamic and cardiac autonomic function. The ability to non-invasively assess an individual's risk of developing arrhythmia during pregnancy would therefore be clinically significant. We aimed to quantify electrocardiographic temporal characteristics during the first trimester of pregnancy and to compare these with non-pregnant controls.

Ninety-nine pregnant women and sixty-three non-pregnant women underwent non-invasive cardiovascular and haemodynamic assessment during a protocol consisting of various physiological states (postural manoeuvres, light exercise and metronomic breathing). Variables measured included stroke volume, cardiac output, heart rate, heart rate variability, QT and QT variability and QTVI (a measure of the variability of QT relative to that of RR).

Heart rate ($p < 0.0005$, $p < 0.0005$, $p < 0.0005$) and cardiac output ($p = 0.043$, $p < 0.0005$, $p < 0.0005$) were greater in pregnant women in all physiological states (respectively for the supine position, light exercise and metronomic breathing state), whilst stroke volume was lower in pregnancy only during the supine position ($p < 0.0005$). QT_e (Q wave onset to T wave end) and QT_a (T wave apex) were significantly shortened ($p < 0.05$) and QT_eVI and QT_aVI were increased in pregnancy in all physiological states ($p < 0.0005$). QT variability ($p < 0.002$) was greater in pregnant women during the supine position, whilst heart rate variability was reduced in pregnancy in all states ($p < 0.0005$).

Early pregnancy is associated with substantial changes in heart rate variability, reflecting a reduction in parasympathetic tone and an increase in sympathetic activity. QTVI shifted to a less favourable value, reflecting a greater than normal amount of QT variability. QTVI appears to be a useful method for quantifying changes in QT variability relative to RR (or heart rate) variability, being sensitive not only to physiological state but also to gestational age. We support the use of non-invasive markers of cardiac electrical variability to evaluate the risk of arrhythmic events in pregnancy, and we recommend the use of multiple physiological states during the assessment protocol.

1. Introduction

Women tend to have higher intrinsic heart rates (Jose & Collison, 1970) and more prolonged QT intervals (Molnar et al., 1996) compared with men. Some cardiac arrhythmias are also more prevalent in women, such as the increased incidence of supraventricular tachycardias (SVT) (Porter et al., 2004). The risk of new onset SVT is further elevated during normal pregnancy (Kron & Conti, 2007) with 24 per 100,000 pregnancies experiencing SVT (Li et al., 2008), as is the incidence of symptomatic ectopic activity, with up to 50% of pregnant women experiencing non-sustained ventricular arrhythmias at some point during their pregnancy (Kron & Conti, 2007). The incidence of pregnancy-induced arrhythmia appears to be uniform throughout pregnancy with perhaps an increased frequency during late pregnancy (Shotan et al., 1997; Nakagawa et al., 2004), although information on this is limited. This elevated incidence is presumably related to changes in both cardiac autonomic function (for supraventricular events) and in ion channel conduction (for ventricular events) within the myocardium. Pregnancy is also associated with substantial haemodynamic changes, which can cause myocardial stretching and may thus promote arrhythmogenic events (Kanoupakis & Vardas, 2005; Adamson & Nelson-Piercy, 2007). The ability to non-invasively assess (and act upon) an individual's risk of developing arrhythmia during pregnancy would therefore be clinically significant.

Changes in autonomic activity during pregnancy are poorly documented (Kuo et al., 2000). The general consensus is that heart rate variability (HRV, a surrogate marker of cardiac autonomic control that describes beat-to-beat variation in cardiac (RR) interval) decreases with advancing gestation (Speranza et al., 1998; Kuo et al., 2000; Chamchad et al., 2007). However, these findings are mainly based on measurements taken during late pregnancy and then compared with non-pregnant controls. The extent of changes in cardiac autonomic function during earlier stages of pregnancy is not known, but marked increases in sympathetic activity have been observed in other body systems within the first few weeks of conception (Jarvis et al., 2012). Clearly a comprehensive description of normal cardiac autonomic changes from the earliest stages of pregnancy would be necessary in the context of developing a biomarker of antenatal arrhythmogenic risk (Nakagawa et al., 2004).

The QT interval is a measure of ventricular depolarisation and repolarisation within the cardiac cycle, which is strongly influenced by heart rate as well other chronotropic factors. The QT interval has not been extensively studied during pregnancy. QT interval shortens during the second-half of pregnancy and remains reduced for up to three days post-partum, reflecting its heart rate-dependence (Baumert et al., 2010). The QT variability index (QTVI; Berger et al., (1997)) extends the concept of HRV to a comparison of the relative magnitudes of temporal variability within the electrocardiographic RR and QT intervals. QTVI is a good indicator of elevated risk for ventricular arrhythmic events – for example, QTVI is associated with an independent risk for ventricular tachycardia or ventricular fibrillation events (Haigney et al., 2004). QTVI has not been assessed during pregnancy, although Baumert et al. (2010) observed that QT variability is higher by late pregnancy (post 28 weeks gestation) in comparison with non-pregnant women.

The aim of this study was to quantify changes in RR and QT variabilities (including QTVI) during relatively early stages of pregnancy (the end of the first trimester) in the context of assessing their use as possible biomarkers for antenatal maternal arrhythmia risk.

2. Method

2.1 Participants

2.1.1 Non-pregnant: Eligible participants were women aged between 18 and 40 years, were not pregnant at the time of measurement, and had no history of cardiovascular or chronic respiratory disease, sleep apnoea or central or peripheral nervous system disorders. Written informed consent was taken at the initial meeting and participants were provided with a participant information sheet. Ethical approval was obtained from the College of Engineering's Applied Sport and Technology Exercise and Medicine (A-STEM) Ethics Committee and all procedures were conducted in accordance with the Declaration of Helsinki.

2.1.2 Pregnant: Eligible participants were apparently healthy pregnant women aged 18 years or over, with no existing complications of pregnancy at their 12-week dating scan. Participants were recruited via a number of methods (via direct contact at the antenatal

clinic, strategically placed posters, advertisements in local newspapers and via email). Exclusion criteria were: a history of cardiovascular or chronic respiratory problems, sleep apnoea, or a central/peripheral nervous system disorder. Recruited participants were provided with details about the study, including practical requirements and potential risks, and were given one week to consider whether they wished to take part. Individuals who wanted to participate gave their written consent. Participants were informed that they were free to leave the study at any time and this would not affect their standard antenatal care. Ethical approval was obtained from the local (South West Wales) Research Ethics Committee and all procedures were conducted in accordance with the Declaration of Helsinki.

2.2 Physiological measurements

HRV can be quantified reproducibly during rest and exercise (McNarry & Lewis, 2012) and our previous observations indicate that this is also generally true for beat-to-beat haemodynamic variables (D'Silva et al., 2014). Consequently single physiological assessments were considered appropriate at each defined stage of the assessment schedule. Physiological monitoring was carried out on four occasions for pregnant participants: at 12-16, 24 -26 and 34-36 weeks gestational age, corresponding to the end of the three trimesters (T1, T2, T3) and also at 12-weeks post-partum (PP). Non-pregnant participants underwent physiological assessment on one occasion only. All participants were asked to perform a series of postural manoeuvres and various interventions designed to provoke changes in the cardiovascular and autonomic nervous systems. Participants were asked to refrain from drinking tea, coffee, alcohol or a heavy meal within 2 hours prior to assessment and to not exercise within 24 hours prior to assessment.

2.2.1 Experimental protocol: Participants were first asked to lie in a 45° reclined-supine position for six minutes, after which they were asked to stand for the same duration. Participants then performed a light stepping exercise for six minutes, using the Nintendo Wii games console and 'balance board' platform (to provide a visual stimulus for exercise). This was followed by a six minute seated recovery period. Participants then undertook a three minute cognitive test in the seated position (to provoke a sympathetic autonomic response), during which they were asked to repeatedly subtract the number seventeen from a four

digit number. The arithmetic test was carried out in the participant's head (they did not need to give a verbal answer). Participants then breathed in time to a metronome for three minutes at a rate of 20 breaths per minute (designed to initiate a parasympathetic response) and then to return to their normal (spontaneous) breathing pattern for three minutes. The total duration of the measurement protocol was thirty-three minutes.

2.2.2 Physiological variables quantified: Participants underwent continuous Holter ECG monitoring (Pathfinder/Lifecard Digital system; Spacelabs Medical Ltd., UK), providing ECG data with a 1024 Hz sampling frequency. The ECG recordings were assessed for quality by human observation using the Pathfinder system, primarily to verify the absence of excessive noise or artefact. Beat-to-beat cardiac interval (RR) was measured automatically by the Pathfinder system (using a proprietary algorithm) and visually assessed to identify and delete any obvious artefacts (which occurred infrequently, with less than 0.1% of beats edited in this way). Heart rate variability (HRV) was quantified in terms of RMSSD (square root of the mean squared differences in successive RR intervals), SDRR (standard deviation of the RR intervals), LF (low frequency power), HF (high frequency power), VLF (very low frequency power), LFn (normalised low-frequency component), HFn (normalised high-frequency component) and Total Power.

QT_e (Q wave onset to T wave end), QT_a (Q wave onset to T wave apex) and RR intervals were measured for each sinus beat and exported for further analysis using the Reynolds Research Tools software (Del Mar Reynolds Medical Ltd., UK). QT_eVI and QT_aVI were calculated according to the equation described by Berger et al (1997):

$$QTVI = \text{Log}_{10}[(QTV/QTm^2)/(RRv/RRm^2)]$$

where QT_v and RR_v are the variabilities of QT and RR, respectively, and QT_m and RR_m are the mean values of these parameters for each defined period.

RMSSDQT (square root of the mean squared differences in successive QT intervals) and SDQT (standard deviation of the QT intervals) were also calculated. The Task Force Haemodynamic monitor (CNSystems Medizintechnik GMBH, Austria) recorded beat-to-beat cardiovascular performance via impedance cardiography (transthoracic bioelectrical impedance analysis) and beat-to-beat systolic and diastolic blood pressures (SBP, DBP) via

vascular unloading photoplethysmography. The following variables were also determined; heart rate (HR), stroke volume (SV), cardiac output (CO), total peripheral resistance (TPR), compliance, stiffness, left ventricular ejection time (LVET) & end diastolic index (EDI).

2.3 Statistical Analysis

Normality of the data was assessed using the Kolmogorov-Smirnov test. Independent samples t-tests were used to assess between group differences at each stage of the protocol. Data are presented for the non-pregnant participants (NP) and for the first antenatal measurement (T1). Results for the gestational changes will be presented elsewhere. Statistical significance was accepted as $p < 0.05$. All data are presented as Mean \pm SEM (standard error of the mean).

3. Results

3.1 Participant characteristics

Ninety-nine pregnant women completed the first antenatal measurement (T1) at a mean gestational age of 15.1 ± 1.7 weeks and sixty-three non-pregnant participants were assessed. Participant characteristics are displayed in Table 1. 49.5% of pregnant women were nulliparous and 50.5% primiparous or multiparous.

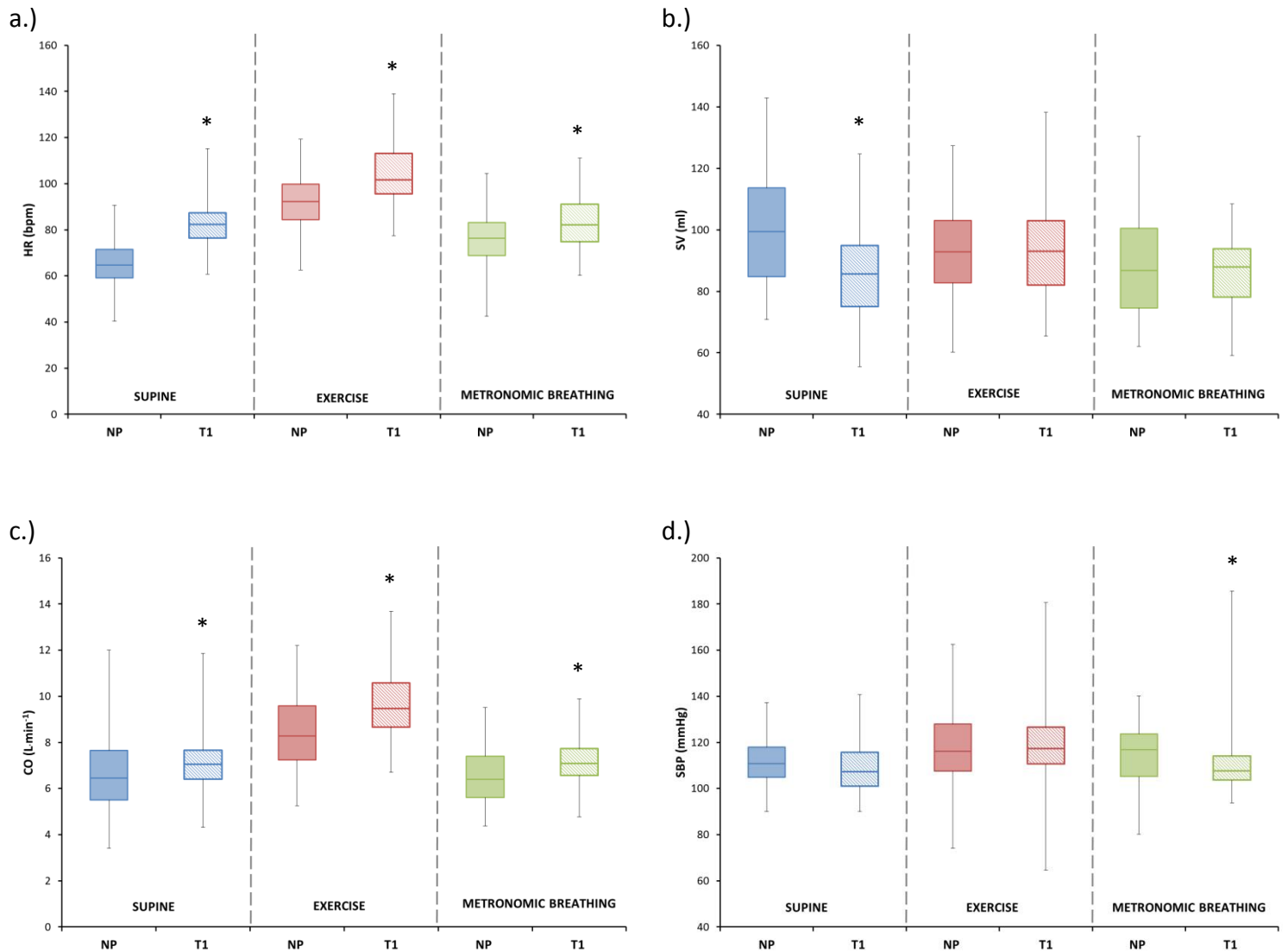
Table 1. Participant characteristics (mean \pm SD)

	Non-pregnant (n=63)	T1 (n=99)
Age (years)	23.5 \pm 5.6	29.1 \pm 4.9
Height (cm)	167.1 \pm 6.7	164.0 \pm 5.3
Weight (kg)	63.9 \pm 9.8	68.8 \pm 14.1
BMI (kg·m ⁻²)	22.9 \pm 2.9	25.6 \pm 5.2

3.2 Haemodynamics

Figure 1 compares the HR, SV, CO and SBP for pregnant and non-pregnant groups during the supine, exercise and metronomic breathing states. In summary: (1) HR ($p < 0.0005$, $p < 0.0005$, $p < 0.0005$ respectively for physiological state) and CO ($p = 0.043$, $p < 0.0005$, $p < 0.0005$) were

significantly greater in pregnant women than in non-pregnant controls in all three states; (2) SV was lower during pregnancy but only in the supine position ($p < 0.0005$); (3) TPR was lower during pregnancy in all states ($p = 0.004$, $p < 0.0005$, $p < 0.0005$); (4) Blood pressure (MBP, SBP, DBP) ($p = 0.010$, $p = 0.008$, $p = 0.011$) and EDI ($p < 0.001$) were significantly reduced in pregnancy only during metronomic breathing; (5) Compliance ($p = 0.001$), EDI ($p < 0.0005$) and LVET ($p < 0.0005$) were all reduced in pregnancy but only in the supine position (Table 2).



* Statistically different from non-pregnant values.

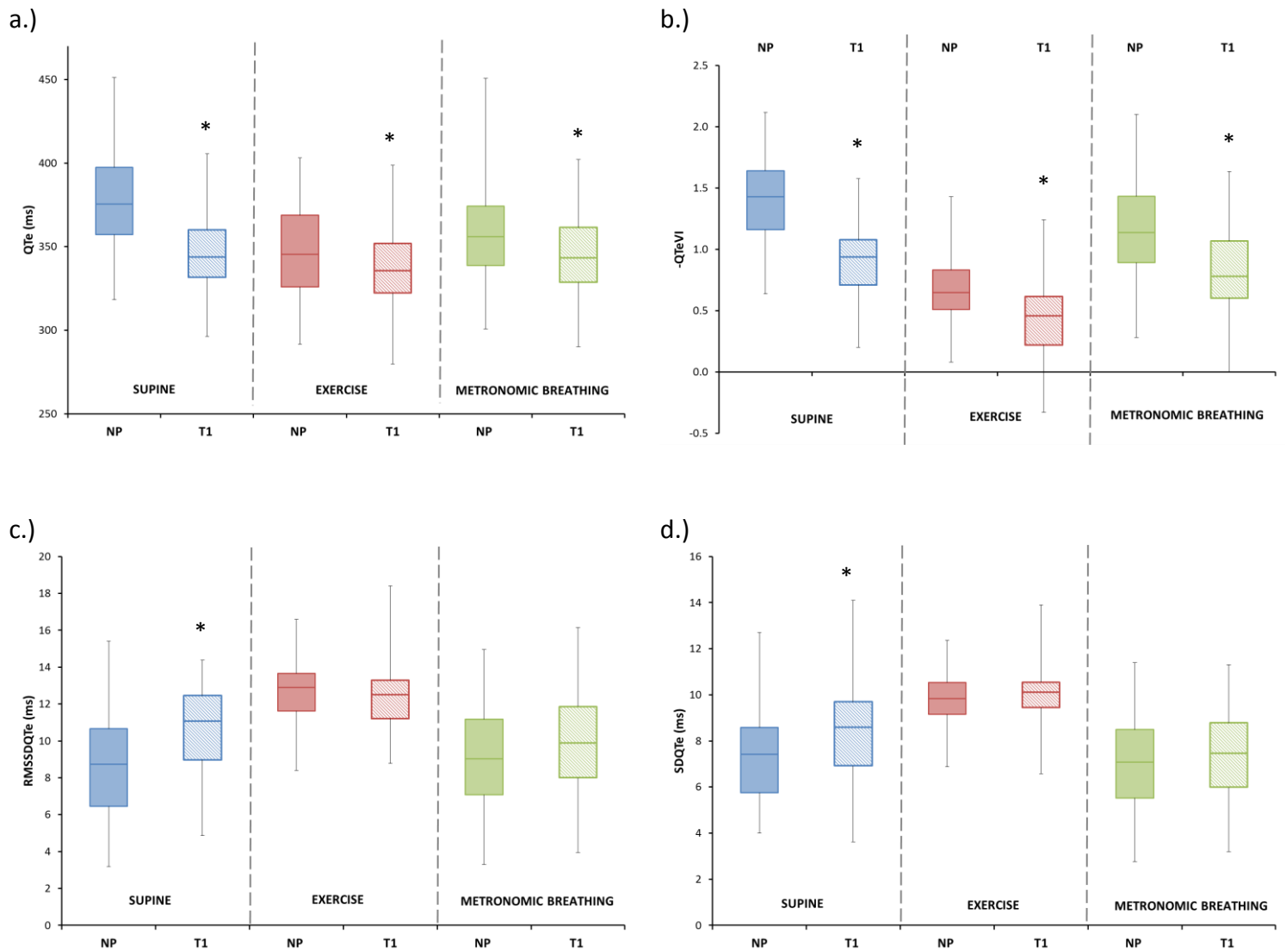
Figure 1. Haemodynamic variables during the supine, exercise and metronomic breathing states for pregnant and non-pregnant groups. Box plots display the median and upper/lower quartiles of the data, whilst the whiskers show the maximum and minimum values. Solid boxes represent non-pregnant participants and shaded bars represent pregnant participants.

3.3 QT Variability

Figure 2 compares QT_e, RMSSDQT_e, SDQT_e and QT_eVI for pregnant and non-pregnant groups during the supine, exercise and metronomic breathing states. All QT_a variables can be found in Table 3. In summary: (1) QT_e and QT_a were significantly shortened in pregnant women than in non-pregnant controls in the supine position ($p < 0.0005$, $p < 0.0005$), during exercise ($p = 0.013$, $p = 0.012$) and during metronomic breathing ($p = 0.001$, $p = 0.001$); (2) QT_eVI and QT_aVI were significantly increased (became less negative) with pregnancy in all physiological states ($p < 0.0005$); (3) RMSSDQT_e and SDQT_e were significantly greater in pregnant women than in non-pregnant controls but only in the supine position ($p < 0.0005$, $p = 0.002$); (4) RMSSDQT_a was greater in the supine posture ($p = 0.009$) and reduced during exercise ($p < 0.0005$) (Table 3).

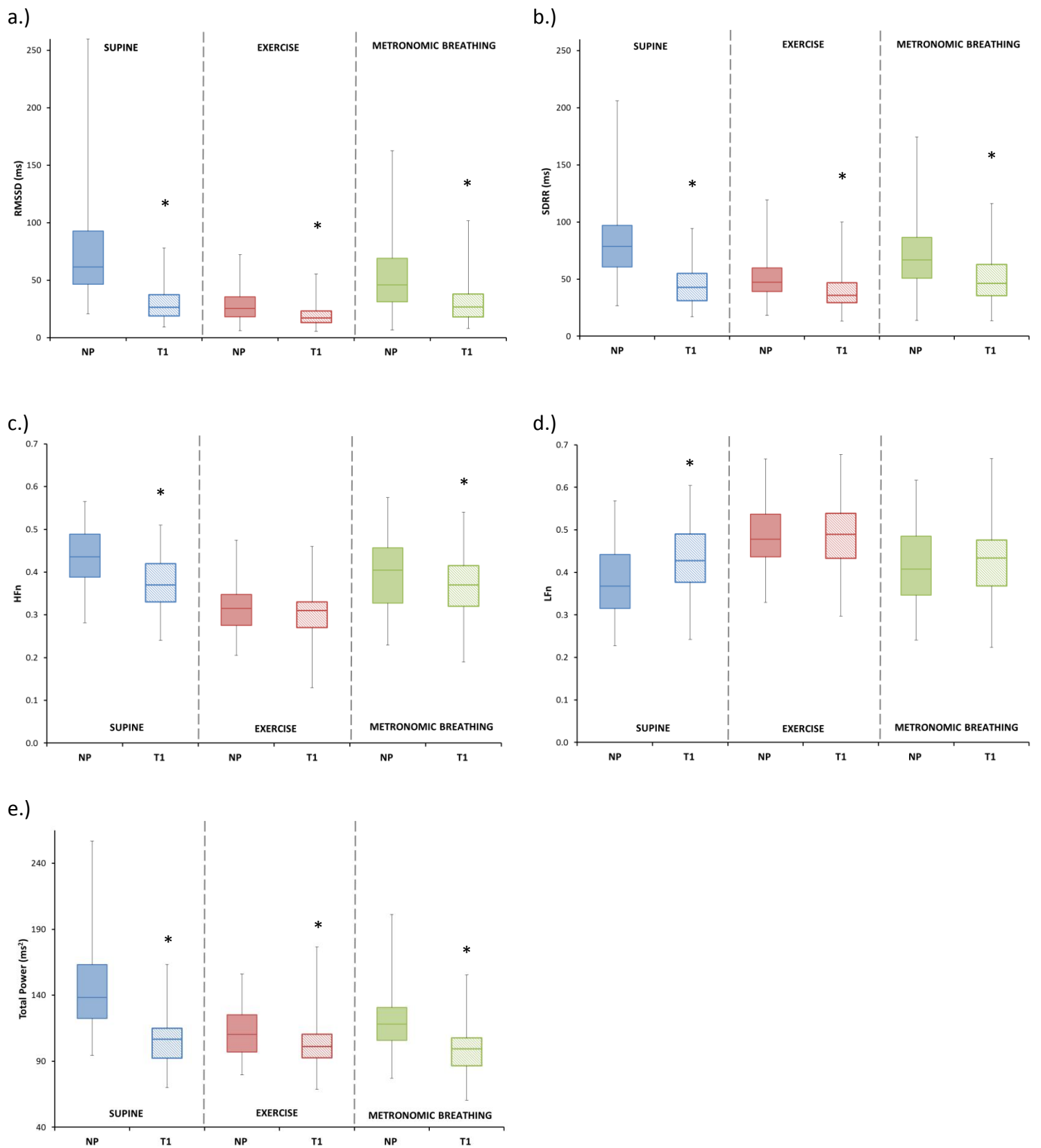
3.4 Heart Rate Variability

Figure 3 compares the RMSSD, SDRR, HF_n, LF_n and Total Power for pregnant and non-pregnant groups during the supine, exercise and metronomic breathing states. In summary: (1) RR ($p < 0.0005$), RMSSD ($p < 0.0005$), SDRR ($p < 0.0005$), Total Power ($p < 0.0005$, $p = 0.014$, $p < 0.0005$), HF ($p < 0.0005$, $p = 0.002$, $p < 0.0005$), and LF ($p < 0.0005$) (Table 4) were lower in pregnant women than in non-pregnant controls in all three states; (2) LF_n was higher during pregnancy but only in the supine position ($p < 0.0005$); (3) HF_n and VLF were lower during pregnancy in the supine position ($p < 0.0005$, $p < 0.0005$ respectively) and during metronomic breathing ($p = 0.015$, $p < 0.0005$ respectively) (Table 4).



* Statistically different from non-pregnant values.

Figure 2. QT variables during supine, exercise and metronomic breathing states for pregnant and non-pregnant groups. Box plots display the median and upper/lower quartiles of the data, whilst the whiskers show the maximum and minimum values. Solid boxes represent non-pregnant participants and shaded bars represent pregnant participants.



* Statistically different from non-pregnant values.

Figure 3. Heart Rate Variability variables during the supine, exercise and metronomic breathing states for pregnant and non-pregnant groups. Box plots display the median and upper/lower quartiles of the data, whilst the whiskers show the maximum and minimum values. Solid boxes represent non-pregnant participants and shaded bars represent pregnant participants.

Table 2. Haemodynamic variables during the supine, exercise and metronomic breathing states for pregnant and non-pregnant groups (mean \pm SEM).

	Supine			Exercise			Metronomic Breathing		
	NP	T1	p	NP	T1	p	NP	T1	p
HR (bpm)	65.5 \pm 1.3	83.0 \pm 1.0	*	91.6 \pm 1.4	103.8 \pm 1.3	*	75.1 \pm 1.5	84.1 \pm 1.1	*
SV (ml)	101.4 \pm 2.4	86.2 \pm 1.5	*	93.4 \pm 2.0	93.2 \pm 1.3	0.924	88.7 \pm 2.0	85.9 \pm 1.1	0.228
CO (L·min ⁻¹)	6.6 \pm 0.2	7.1 \pm 0.1	0.043	8.5 \pm 0.2	9.6 \pm 0.1	*	6.6 \pm 0.1	7.2 \pm 0.1	*
TPR (dyn.sec.cm ⁻⁵)	1025 \pm 32	915 \pm 18	0.004	839 \pm 21	721 \pm 13	*	1047 \pm 23	906 \pm 15	*
Compliance (ml·mmHg ⁻¹)	2.6 \pm 0.1	2.3 \pm 0.05	0.001	2.2 \pm 0.1	2.0 \pm 0.05	0.107	2.1 \pm 0.1	2.2 \pm 0.04	0.608
Stiffness (mmHg·ml ⁻¹)	0.4 \pm 0.01	0.5 \pm 0.01	0.001	0.5 \pm 0.02	0.5 \pm 0.01	0.105	0.5 \pm 0.01	0.5 \pm 0.01	0.608
SBP (mmHg)	111.5 \pm 1.3	108.5 \pm 1.0	0.065	117.5 \pm 2.2	118.9 \pm 1.6	0.524	115.2 \pm 1.4	110.4 \pm 1.2	0.008
DBP (mmHg)	71.0 \pm 1.0	69.8 \pm 0.8	0.345	71.7 \pm 1.4	70.4 \pm 1.1	0.454	72.8 \pm 1.0	69.6 \pm 0.9	0.011
MBP (mmHg)	83.0 \pm 1.1	81.5 \pm 0.9	0.299	87.1 \pm 1.6	86.6 \pm 1.2	0.807	86.2 \pm 1.1	82.5 \pm 1.0	0.010
LVET (ms)	319.4 \pm 2.1	290.2 \pm 1.8	*	271.0 \pm 2.0	255.3 \pm 1.6	*	287.6 \pm 2.9	282.9 \pm 2.0	0.169
EDI (ml·m ⁻²)	93.9 \pm 1.9	79.8 \pm 1.3	*	92.9 \pm 1.4	91.2 \pm 1.1	0.350	88.5 \pm 1.5	82.3 \pm 1.1	0.001

* p < 5x10⁻⁴

Table 3. QT variables during the supine, exercise and metronomic breathing states pregnant and non-pregnant groups (mean \pm SEM).

	Supine			Exercise			Metronomic Breathing		
	NP	T1	p	NP	T1	p	NP	T1	p
QTe (ms)	376.4 \pm 3.8	346.3 \pm 2.3	*	347.2 \pm 3.3	337.3 \pm 2.2	0.013	358.9 \pm 3.9	344.4 \pm 2.3	0.001
QTeVI	-1.4 \pm 0.04	-0.9 \pm 0.03	*	-0.7 \pm 0.04	-0.4 \pm 0.03	*	-1.1 \pm 0.05	-0.8 \pm 0.04	*
RMSSDQTe (ms)	8.9 \pm 0.4	10.6 \pm 0.2	*	12.6 \pm 0.2	12.3 \pm 0.2	0.322	9.2 \pm 0.4	9.9 \pm 0.3	0.120
SDQTe (ms)	7.4 \pm 0.3	8.4 \pm 0.2	0.002	9.8 \pm 0.2	10.1 \pm 0.1	0.053	7.2 \pm 0.3	7.5 \pm 0.2	0.361
QTa (ms)	312.4 \pm 3.5	284.5 \pm 2.1	*	286.7 \pm 2.7	278.3 \pm 1.9	0.012	295.8 \pm 3.5	282.7 \pm 2.1	0.001
QTaVI	-1.3 \pm 0.04	-0.9 \pm 0.03	*	-0.7 \pm 0.04	-0.4 \pm 0.03	*	-1.0 \pm 0.04	-0.7 \pm 0.03	*
RMSSDQTa (ms)	8.6 \pm 0.2	9.3 \pm 0.2	0.009	10.6 \pm 0.2	9.8 \pm 0.1	*	9.5 \pm 0.2	9.3 \pm 0.2	0.475
SDQTa (ms)	6.8 \pm 0.2	7.2 \pm 0.2	0.065	8.3 \pm 0.1	8.4 \pm 0.1	0.481	7.1 \pm 0.2	7.0 \pm 0.2	0.564

* p < 5x10⁻⁴

Table 4. Heart rate variability indices during the supine, exercise and metronomic breathing states pregnant and non-pregnant groups (mean \pm SEM).

	Supine			Exercise			Metronomic Breathing		
	NP	T1	p	NP	T1	p	NP	T1	p
RMSSD (ms)	77.0 \pm 6.3	29.9 \pm 1.5	*	28.3 \pm 1.6	19.3 \pm 0.9	*	53.4 \pm 3.7	29.5 \pm 1.5	*
SDRR (ms)	83.9 \pm 4.4	44.3 \pm 1.6	*	51.9 \pm 2.5	39.5 \pm 1.6	*	73.0 \pm 4.2	50.2 \pm 2.1	*
RR (ms)	951.6 \pm 20.6	733.0 \pm 8.7	*	710.5 \pm 11.3	622.2 \pm 7.4	*	833.8 \pm 19.3	683.4 \pm 9.5	*
HFn	0.44 \pm 0.01	0.37 \pm 0.01	*	0.32 \pm 0.01	0.31 \pm 0.01	0.317	0.40 \pm 0.01	0.37 \pm 0.01	0.015
LFn	0.38 \pm 0.01	0.43 \pm 0.01	*	0.49 \pm 0.01	0.49 \pm 0.01	0.817	0.42 \pm 0.01	0.43 \pm 0.01	0.582
Total Power (ms ²)	146.0 \pm 4.4	106.4 \pm 1.9	*	111.3 \pm 2.3	104.2 \pm 1.9	0.014	121.9 \pm 3.2	99.3 \pm 1.7	*
HF (ms ²)	14.9 \pm 1.1	6.9 \pm 0.4	*	5.7 \pm 0.3	4.5 \pm 0.2	0.002	10.5 \pm 0.7	7.0 \pm 0.4	*
LF (ms ²)	12.5 \pm 0.8	7.8 \pm 0.3	*	8.9 \pm 0.5	7.0 \pm 0.3	*	11.0 \pm 0.8	7.9 \pm 0.4	*
VLF (ms ²)	112.4 \pm 2.7	88.1 \pm 1.6	*	93.4 \pm 1.9	89.3 \pm 1.6	0.073	95.7 \pm 2.1	80.7 \pm 1.1	*

* $p < 5 \times 10^{-4}$

4. Discussion

We measured cardiac performance indices continuously during a protocol consisting of various standardised physiological states, thus providing a comprehensive characterisation of cardiovascular and haemodynamic responses to ‘early’ pregnancy. The main findings were that, compared with non-pregnant values, early pregnancy is associated with (1) increased heart rate and cardiac output in all physiological states, (2) decreased stroke volume but only in the supine position, (3) shortening of QT_e and QT_a intervals in all physiological states, (4) increases in QT_eVI and QT_aVI in all physiological states, (5) increases in RMSSDQT_e and SDQT_e only in the supine position, and (6) reductions in RMSSD, SDRR, and HFn in all states.

Previous studies have strongly debated the time course of haemodynamic changes during early pregnancy (Capeless & Clapp, 1989; Duvetkot et al., 1993). We therefore also measured haemodynamic changes, allowing us to characterise the influence of our protocol on conventional measures of cardiovascular performance. We observed (1) an increase in heart rate and a decrease in stroke volume in the supine position (suggesting that at this stage of pregnancy heart rate is the predominant mechanism for increasing cardiac output), (2) a reduction in total peripheral resistance (TPR) during pregnancy in all states, (3) a reduction in end diastolic volume index (EDI) during the supine posture and in response to

metronomic breathing, (4) a reduction in left ventricular ejection time (LVET) in the supine posture and exercise state, and (5) a reduction in blood pressure in pregnancy but only during metronomic breathing. Consistent with our findings, Duvekot et al. (1993) found an increase in cardiac output, caused by a rise in heart rate, by the tenth week of gestation. Similarly, Capeless & Clapp (1989) found a rise in cardiac output by 8 weeks gestation in comparison to pre-conception values; however this rise was predominantly as a result of increased stroke volume as opposed to heart rate. In contrast to our results Mahendru et al. (2014) found no increase in cardiac output, despite an increase in heart rate at 6 weeks gestation. The early time point at which this measurement was taken may be the reason for this difference. Our observation of a reduction in TPR is also consistent with other authors (Duvekot et al., 1993; San-Frutos et al., 2011). The reduction in blood pressure observed during metronomic breathing may be associated with a reduction in parasympathetic activity with pregnancy.

Baumert et al. (2010) have previously found that QT interval is shortened by the second half of pregnancy (post 28 weeks) in comparison to non-pregnant controls but they found no changes at earlier gestational ages. These authors also observed that rate-corrected QT (QTc) was not changed by pregnancy and so concluded that the duration of ventricular repolarisation is entirely rate-dependent. Gondoni et al. (2011) found a strong relationship between ejection fraction and QTc and since it is well documented that ejection fraction is unaltered with pregnancy (Capeless & Clapp, 1989), this may explain the unaltered QTc with gestation. We have extended these observations by showing that uncorrected QT_e and QT_a are significantly reduced even by the end of the first trimester and notably in all physiological states. This suggests that pregnant women are able to maintain cardiac repolarisation at a safe level, during rest and light exercise, without exposing them to high risk arrhythmia. We did not separately assess rate-corrected QT as our objective here was to examine QT variability and (using QT_{VI}) the relative magnitudes of QT and RR variabilities.

The HRV indices RMSSD, SDRR and HF_n were all reduced during pregnancy, whilst LF_n increased. Notably HF_n was reduced in both the supine and metronomic breathing states, both of which are associated with dominant parasympathetic control. Thus these changes in HRV appear to reflect a substantial reduction in parasympathetic tone and an increase in sympathetic activity by the end of the first trimester of pregnancy. Sympathetic activity has

previously been noted to increase by late pregnancy (measured using HRV) (Speranza et al., 1998; Kuo et al., 2000; Voss et al., 2000), with sympathetic hyperactivity at this stage indicating an increased risk of hypertension and pre-eclampsia (Greenwood et al., 2003) but its relative influence during early pregnancy has not been convincingly determined. Jarvis et al. (2012) observed marked increases in systemic sympathetic neural activity within the first weeks of conception (via muscle sympathetic neural activation). Conversely, Kuo et al. (1997) reported a higher vagal and a lower sympathetic modulation in three different recumbent positions (in particular the supine position) during pregnancy. An increase in baseline (supine) sympathetic activity during the early stages of pregnancy might have advantageous effects as it enhances the ability of pregnant women to adapt to haemodynamic changes and thus reduces the risk of orthostatic hypotension upon standing. Interestingly, LFn (a surrogate measure of sympathetic activity) was the same for both pregnant and non-pregnant women during light exercise, despite a further increase in cardiac output in the pregnant participants. This suggests that light exercise poses no increased risk to women during the early stages of pregnancy. Further longitudinal characterisations of HRV are therefore required to clarify the dynamics of cardiac autonomic control during pregnancy.

Whether these observed alterations in autonomic control of heart rate (supraventricular influences) also influence ventricular myocardial repolarisation (i.e. QT interval duration and variability) is yet to be clearly determined. Myocardial repolarisation might be influenced by pathological, physiological or other structural changes in the heart, or by autonomic neural activity changes (Piccirillo et al., 2007). Using an analogous approach to the time-domain assessment of HRV we assessed QT variability in terms of two statistical measures: RMSSDQT_e and SDQT_e. We found that in the supine position QT variability was increased by the end of the first trimester in comparison to non-pregnant controls, whilst no changes were seen during exercise or metronomic breathing states. It might be speculated that the autonomic nervous system could influence ventricular repolarisation independently of the sino-atrial node, considering the observed reduction in parasympathetic activity during the first trimester, as studies have shown parasympathetic withdrawal to have an important influence on the shortening of the QT interval at higher heart rates during exercise (Magnano et al., 2002) and therefore the same mechanism might be relevant to the

physiological changes during pregnancy. However ventricular repolarisation is thought to be predominantly controlled by the beta-adrenergic system and any vagal effects are indirect and secondary to changes in heart rate (Can et al., 2002). Advancing gestation is also associated with hypervolaemia, leading to structural changes in the left ventricle. These changes may alter specific regions and layers of the ventricular tissue thus altering ion channel activity.

The QT variability index (QTVI), first proposed by Berger et al. (1997), describes the relative magnitude of temporal variability in myocardial depolarisation and repolarisation phases. It has been suggested that QTVI can be used to quantify the relative autonomic influences on the atrial and ventricular myocardium during rest and exercise, and that it might reflect the balance between heart rate-dependent and heart rate-independent influences on the QT interval (Lewis & Short, 2008). Previously an increase in QTVI has been associated with a greater susceptibility to ventricular arrhythmias and sudden death (Berger et al., 1997; Atiga et al., 2000). However, ours is the first study to investigate the influence of pregnancy on QTVI. We found that QTVI was elevated as a result of early physiological changes associated with pregnancy in all physiological states. QTVI was highest during exercise in both the pregnant and non-pregnant women, further increased in the pregnant women. This increase in QTVI suggests that QT variability is more predominant over changes in RR variability at this time, indicative of a parasympathetic shift in the sympatho-vagal balance with pregnancy. As pregnancy is associated with an increase in arrhythmogenic events (Siu et al., 2001; Nakagawa et al., 2004; Li et al., 2008) the use of QTVI as a potential biomarker for screening patients at such an early stage might be of great clinical importance. QTVI is known to be further increased with exercise (Lewis et al., 2006; Lewis & Short, 2008). At moderate intensities of exercise Lewis et al. (2006) reported a progressive increase in QTVI with work rate. Healthy non-pregnant individuals typically have a QTVI value of around -1 or lower at rest: Dobson et al. (2013) reported a mean QTVI of -1.34 in 173 healthy volunteers (unpublished data). Consistent with Dobson et al. (2013) we noted non-pregnant values of -1.4 and -1.3 (for QT_eVI and QT_aVI respectively) but higher values of around -0.9 in pregnant women. Despite increased values with pregnancy, at no point did QTVI become positive or exceed a value of 0.1, a value proposed as a discriminator for higher risk of arrhythmogenic events (Atiga et al., 1998). This indicates that QT variability is not markedly influenced by

pregnancy during the first trimester, suggesting that it is unlikely to be the cause of the increased risk of arrhythmia in pregnancy. It remains to be seen whether QTVI increases further during later gestation, and more work is needed to evaluate whether QT variability might be the cause of increased arrhythmia susceptibility during that stage of pregnancy. Our study has shown that QTVI is a sensitive marker of not only physiological state but also of gestational age and therefore its use to determine arrhythmogenic events in normal and abnormal pregnancy should be considered. Using QTVI as a marker of arrhythmogenic activity during pregnancy might enable non-invasive assessment of the need for anti-arrhythmic treatment as well as quantifying the influence of lifestyle factors such as exercise on cardiac electrical function.

Limitations

We used late first trimester/early second trimester values as a baseline measure to characterise the extent of cardiovascular changes within 'early' pregnancy. Ideally we would have recruited women prior to conception because it is known that physiological changes are evident as early as the sixth week of gestation, and this would have enabled a true assessment of 'early' pregnancy changes. However, owing to time constraints and a specific period of funding for our work this was not feasible in the present study. We did not assess heart rate-corrected QT and were thus not able to comment on the likely determinants of QT interval shortening at this early stage of pregnancy.

Conclusion

The early stages of pregnancy are associated with substantial changes in cardiac autonomic control, with reductions in parasympathetic tone and increases in sympathetic activity. Whether these changes influence ventricular myocardial repolarisation and thus predispose women to arrhythmogenic events is yet to be determined. We have shown that QTVI is a sensitive marker of not only physiological state but also of gestational age. The use of QTVI as a marker of arrhythmia risk during pregnancy is feasible and could provide clinically important information regarding the need for prophylactic anti-arrhythmia treatment. We

have used unique and novel concepts to assess cardiovascular responses to early pregnancy. These non-invasive methods have great clinical potential in predicting and identifying normal and abnormal responses to increased physiological stress, such as occur during orthostatic manoeuvre and light intensity exercise.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. R Carpenter received a NISCHR (Welsh Government National Institute for Social Care and Health Research) PhD studentship, and The Cooperative Pharmacy (UK) provided financial support for project consumables.

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