

A comparison of heart rate variability in women at the third trimester of pregnancy and during low-risk labour

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Abstract

Heart rate variability (HRV) has been recognised as a non-invasive method for assessing cardiac autonomic regulation. Aiming to characterize HRV changes at labour in women, we studied 10 minute ECG recordings from young mothers ($n = 30$) at the third trimester of pregnancy (P) or during augmentation of labour (L) ($n = 30$). Data of the L group were collected when no-contractions (L-NC) or the contractile activity (L-C) was manifested. Accordingly, the inter-beat interval (IBI) time series were processed to estimate relevant parameters of HRV such as the mean IBI (IBI), the mean heart rate HR, the root mean square of successive differences (RMSSD) in IBIs, the natural logarithm of high-frequency component (LnHF), the short-term scaling parameters from detrended fluctuation and magnitude and sign analyses such as ($\alpha 1$, $\alpha 1(\text{MAG})$, $\alpha 1(\text{SIGN})$), and the sample entropy (SampEn). We found statistical differences ($p < 0.05$) for RMSSD among P and L-NC/L-C groups (25 ± 13 vs. $36 \pm 14/34 \pm 16$ ms) and for LnHF between P and L-NC (5.37 ± 1.15 vs. 6.05 ± 0.86 ms²). Likewise, we identified statistical differences ($p < 0.05$) for $\alpha 1(\text{SIGN})$ among P and L-NC/L-C groups (0.19 ± 0.20 vs. $0.32 \pm 0.17/0.39 \pm 0.13$). By contrast, L-NC and L-C groups showed statistical differences ($p < 0.05$) in $\alpha 1(\text{MAG})$ (0.67 ± 0.12 vs. 0.79 ± 0.12), and SampEn (1.62 ± 0.26 vs. 1.20 ± 0.44). These results suggest that during labour, despite preserving a concomitant non-linear influence, the maternal short-term cardiac autonomic regulation becomes weakly anticorrelated (as indicated by $\alpha 1(\text{SIGN})$); furthermore, an increased vagally mediated activity is observed (as indicated by RMSSD and LnHF), which may reflect a cholinergic pathway activation owing to the use of oxytocin or the anti-inflammatory cholinergic response triggered during labour.

Keywords: Heart rate variability; Detrended fluctuation analysis Autonomic activity; Anti-inflammatory cholinergic pathway Oxytocin; Labour; Pregnancy

1. Introduction

Contractions during labour are generally associated with an increased maternal heart rate and mean arterial pressure as well as the subsequent increase in cardiac output resulting from increments in both stroke volume and heart rate [1–5]. The details of how these haemodynamic changes are driven by autonomic adaptations and, more-over, the actual role of the autonomic nervous system (ANS) during

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pregnancy remain to be fully elucidated [6]. In this regard, several findings prompt to consider labour as an inflammatory event that is not only initiated by hormonal factors [7]. In consequence, it can be assumed that labour may also introduce an anti-inflammatory response carried out by the autonomic activity [8].

Insights about the ANS activity of pregnant women have been studied by analysing the variation between the successive cardiac inter-beat intervals (IBIs), also referred to as heart rate variability (HRV) [9–11], which is a non-invasive approach to quantify the autonomous cardiac re-sponse to adrenergic and cholinergic influences [12]. In general, time-domain and spectral analysis, but also scaling methods (i.e. detrended fluctuation analysis: DFA) are applied to obtain measures that are used to estimate the autonomic response.

Although some authors have assumed that during pregnancy maternal autonomic conditions mainly reflect a sympathetic involvement [9–11] to the aortocaval compression of late gestation [13], the dynamic patterns of maternal heartbeat fluctuations have not been thoroughly explored, in particular during labour. In this regard, previous studies have mainly focused on changes of the mean maternal heart rate in relation to uterine contractions [2,4,5]. Recently, Suzuki et al. assessed maternal HRV during labour using a power spectral analysis to describe beat-to-beat changes associated with the particular presence of uterine contractions. Despite that no differences in high-frequency (HF) components between uterine contraction and non-contraction periods were found, the low-frequency (LF) and very-low-frequency (VLF) components during uterine contractions were significantly stronger during contraction periods. Authors concluded that the maternal sympathetic activity was apparently increased during uterine contraction periods [14].

In this study, we evaluate the use of linear and non-linear parameters to analyse heartbeat fluctuations during labour. In particular, we aimed to compare short-term IBI fluctuations registered from low-risk women during augmentation of labour with data collected during the third trimester of pregnancy to identify dynamic HRV changes.

We hypothesised that the autonomic adaptations during labour, either to facilitate haemodynamic requirements or even to restrain or counteract inflammation, are manifested on heartbeat fluctuations.

2. Methods

2.1. Subjects and data collection

Electrocardiogram (ECG) recordings were collected from 30 women, who developed term pregnancy (39.6 ± 1.2 weeks) and underwent low-risk labour. All recordings and procedures took place at Maternal and Childhood Research Center (CIMIGen) having obtained consent from each patient on a voluntary basis. For data collection we used an ECG portable device (Monica AN24 monitor, Monica Healthcare, Nottingham, UK), with a sampling frequency of 900 Hz. During recordings, subjects were free to choose their preferred posture due to the portability of the system, yet ECG segments to be analysed were only selected when women maintained a semi-Fowler's position. The general characteristics and the pregnancy outcome of this group are presented in Table 1; no major complications occurred in newborns as indicated by weights and Apgar scores.

The first and second stages of labour were identified by the presence of regular uterine contractions and cervix effacement and dilatation [15] (see values at Table 2). The ECG recordings during labour were classified into two distinct classes: the labour-contraction (L-C) included 10 min segments where the uterine activity was observable (with three or more contractions), and the other class, labour-no contraction (L-NC), included 10 min segments involving fewer uterine activity or no contractions at all. All studied women received intravenous oxytocin to improve contractility according to the Mexican guidelines for augmentation of labour [16]. For comparison, we also recorded 10 min segments of data collected during the last trimester of gestation (37–39 weeks) of other 30 women at the semi-Fowler's position not showing any clinical manifestation of the initiation of labour (P) (Table 1).

ECG recordings were visually analysed by using the software of the device, which displays values of maternal heart rate in conjunction with an ECG-derived uterine activity signal (Fig. 1). To ensure the proper selection of L-C segments accompanied by uterine contractions, we also identified unequivocal increments of the displayed maternal heart rate because during well-established frequent contractions the haemodynamic adjustments should generally involve a compensation of cardiac output by an increased heart rate [4,5,17]. L-C and L-NC segments were only selected if these segments involve none or few maternal gross movements.

2.2. Data analysis

Raw maternal ECG recordings were then processed using previous validated algorithms to generate IBI series which corresponded to episodes of contraction (L-C), no contraction (L-NC) or pregnancy (P) segments [18]. All series (L-C = 30, L-NC = 30 and P = 30) consisted of 600 IBIs for each subject (7 ± 1 minute duration), were reconditioned by a filtering approach and tested in line with previous studies [19] to exclude for ectopic beats and artefacts.

The maternal IBI fluctuation series were integrated by:

$$Y(k) = \sum_{i=1}^k [IBI(i) - \overline{IBI}] \quad (1)$$

where $Y(k)$ represents the k -th value of the resulting integration ($k = 1, 2, \dots, L$), $IBI(i)$ is the i -th RR interval, and $\overline{IBI}$ is the mean RR value of the IBI series (Eq. (1)).

Next, the integrated series were divided into boxes having equal numbers of n samples. The local trends Y_n were obtained for all boxes by a least-squared line fit and subtracted from $Y(k)$ to reduce, in principle, the non-stationary trends. The average root-mean-square fluctuation, $F(n)$, can then be calculated as Eq. (2):

$$F(n) = \sqrt{\frac{1}{L} \sum_{k=1}^L [Y(k) - Y_n(k)]^2} \quad (2)$$

The relationship on a double-log graph between $F(n)$ and time scales n was approximated by a linear model $F(n) \sim n^\alpha$, so providing the scaling exponent α as the slope of the plot covering the short-term range of n from 4 to 11 IBIs (in accordance with Peña et al. [21] and Yeh et al. [22]). The scaling exponent may vary from 0.5 (uncorrelated fluctuations, white noise) to 1.5 (smoother fluctuations) where a value near 1 indicates the existence of fractal-like correlations. The long-term scaling exponent (α_2) was not calculated in this study owing to well-known potential modifications of the scaling properties by periodic trends as reported by Hu et al. [23] (in our case uterine contractions during labour as well as the Braxton Hicks contractions presented at the third trimester of pregnancy).

Nonlinearity and linear time ordering scaling were assessed by MSA following earlier studies [24,25]. The original IBI series were processed to obtain new sequences of increments by taking the differences between adjacent intervals ($IBI_{i+1} - IBI_i$). These sequences (ΔIBI) were decomposed into magnitude, $|\Delta IBI|$, and sign series, $\text{sign}(\Delta IBI)$. After subtracting their respective means, magnitude and sign series were integrated and DFA was again applied as described above. The slope of $F(n)/n$ covering the range from 4 to 11 IBIs then provided magnitude and sign scaling exponents ($\alpha_1(\text{MAG})$ and $\alpha_1(\text{SIGN})$, respectively). Positive correlations in the magnitude series (i.e. finding $\alpha_1(\text{MAG}) > 0.5$) were identified as reliable markers of nonlinear properties [25]. The $\alpha_1(\text{SIGN})$ exponent provides information about the temporal directionality of the original series in relation to how series increments alternate, indicating if a positive or negative subsequent increment (decrement) is more likely to occur given a current increment (decrement) [24,25].

To assess the regularity/irregularity in relation to uterine contractions we also estimated the sample entropy (SampEn) calculated with $m = 2$ and $r = 0.2$, as described by Richman & Moorman [26].

2.3. Statistics

A discordant test was applied to the resulting values of all linear, scaling and nonlinear parameters for identifying potential outliers [27]. Having verified normality (by skewness, kurtosis and omnibus tests) and equal variance (using a modified-Levene equal-variance

test), statistical differences of IBI, HR, RMSSD, LnHF, α_1 , $\alpha_1(\text{MAG})$ and $\alpha_1(\text{SIGN})$ between L-NC and L-C segments were evaluated by a paired t-test with the NCSS software. Differences of same parameters between L-C and P segments (or L-NC and P) were evaluated by a t-test for independent measures. Because the test for SampEn reported no normality and rejected equal variance, a Kolmogórov-Smirnov test was applied to this parameter. Significance was considered by $p < 0.05$ for the paired t-test, and by $p < 0.025$ for the multiple independent comparisons.

3. Results

We found ANS-related differences in cardiac activity during labour vs. last trimester of pregnancy (L-C/L-NC vs. P), as well as during labour on the presence of contractions vs. no-contractions (L-C vs. L-NC).

Fig. 2 shows representative examples of the analysis of maternal heartbeat fluctuations during labour including segments of L-NC (Fig. 2a & c) and L-C (Fig. 2b & d). Whereas the raw IBI series are pre-sented at the top of the figure, the log-log $F(n)$ vs. n and log-log $F(n)/n$ vs. n relationships, providing the α_1 , $\alpha_1(\text{MAG})$ and $\alpha_1(\text{SIGN})$ exponents from a linear best-fit within the n range 4 to 11, are depicted below. This figure also includes results of the HR and RMSSD parameters (Fig. 2a & b). An increment of the HR owing to the presence of regular uterine contractions during the L-C segment is noticed. Yet the scaling parameters α_1 and $\alpha_1(\text{SIGN})$ maintain similar values for both segments regardless of such contractions, with exception of $\alpha_1(\text{MAG})$.

Fig. 3 shows a sign decomposition of typical data for P and L-NC segments. This figure illustrates a less anticorrelated pattern in heartbeat fluctuations during labour (L-NC) in comparison to data from the third trimester of pregnancy (P).

After applying a discordant test to all parameters, we found four RMSSD and LnHF discordant values from the P group and these values were discarded. Table 3 summarises principal findings for all studied parameters in relation with L-NC, L-C and P segments. Whereas the IBI and HR parameters show differences between L-C and L-NC segments, in accordance with our proposed experimental design for the selection of segments during labour, $\alpha_1(\text{SIGN})$ was the only scaling parameter that showed a dynamic effect of labour on heartbeat fluctuations as shown by differences between P and L-C/L-NC segments. In accordance with earlier findings, we found statistical differences in RMSSD among L-C/L-NC and P groups [28] as well as in LnHF among L-NC and P groups. By contrast, the parameters $\alpha_1(\text{MAG})$ and SampEn were influenced by the presence or absence of uterine contractions (Table 3).

4. Discussion

Our main finding is the identification of subtle but significant dynamic changes in the directionality of heartbeat fluctuations during childbirth at term, as indicated by the parameter $\alpha_1(\text{SIGN})$, which were not directly associated with the presence of uterine contractions. Thus, regardless of the uterine activity, maternal HRV at labour shows weaker anticorrelations in comparison with the stronger anticorrelated auto-nomic activity manifested by pregnant women at the third trimester. Following our previous results [21], this stronger anticorrelated condition of maternal heartbeat fluctuations seems in fact to be maintained prenatally during low-risk pregnancies. Our findings for $\alpha_1(\text{SIGN})$ may indicate that during labour the maternal cardiac regulation becomes less antagonistic in relation with short-term directionality (see Fig. 3b). Implying that, in terms of the mathematical framework of “random walks” [29], the autonomic interplay is manifested with different attracting levels for the heart frequency as opposed to the resulting strongly anticorrelated dynamics introduced, for instance, by a sympathetic pre-dominance during the third trimester [30].

The autonomic activity has been considered to offer an anti-inflammatory response through the direct action of acetylcholine inhibiting synthesis of pro-inflammatory cytokines, or indirectly via catecholamines stimulating the release of the anti-inflammatory cytokines, such as IL-10 [8]. Recent findings have provided insights into the correlation between heartbeat fluctuation parameters and inflammatory markers in accordance with the consideration of the so called anti-inflammatory reflex, mainly mediated by the vagus nerve [8,31, 32]. In this regard, the weaker anticorrelations of the maternal IBI fluctuations at labour (L-NC vs. P) could then reflect the participation of such anti-inflammatory autonomic pathway. This consideration is in accordance with the particular conceptualization of labour as an inflammatory event, either driven by exogenous or endogenous stimuli [7,28, 33,34]. This position is supported by evidence identifying that some important labour processes, such as cervix remodelling, rupture of membranes, and rhythmic contractions, appear to be mediated by inflammatory processes [34]. Besides, the release of inflammatory cytokines during labour probably contributes to the expelling of placenta's fragments and, eventually, to contend with pathogens in the post-partum period as well [35]. Furthermore, the activation of the anti-inflammatory autonomic pathway may also be attributed to the role of exogenous oxytocin that embraces functional effects as cardiovascular and the autonomic modulating neuroimmunoendocrine peptide [36–39]. Clodi et al. have found that oxytocin decreases the neuroendocrine and cytokine activation caused by bacterial endotoxin in men. Given that the effect of oxytocin was not identified for monocytes and peripheral blood mononuclear cells in vitro, they concluded that such decrease is possible due to the modulation of the cholinergic anti-inflammatory pathway [40]. Notwithstanding that the administration of intranasal oxytocin did not alter the circulating levels of pro-inflammatory cytokines or stress hormones, Norman et al. found that oxytocin also influences the autonomic cardiac control as indicated by an increased HF parameter and decreased pre-ejection period [37]. Similarly, Kemp et al. have reported that the acute administration of intra-nasal oxytocin increases the HRV in male humans during rest as indicated by changes in the power of the HF component at trend levels [41]. Oxytocin for the purposes of augmentation of labour is one of the most frequently used medications in obstetrics. Recent studies have showed that oxytocin is used in 40% of labouring women in Latin American countries [42].

Our results for the RMSSD and LnHF parameters during labour seem also consistent with the possible manifestation of a cholinergic mechanism to attenuate inflammation as we found increased values of both parameters at L-NC episodes as compared with the P group, suggesting the participation of the vagal cholinergic pathway [43], and the subsequent dynamic manifestation of diverse heart frequency attracting levels from the mathematical standpoint of “random walks” [29].

The autonomic condition of pregnant women has been mainly evaluated by quantifying the spectral power, or by assessing the structure of irregularity of the heartbeat fluctuations through the use of scaling exponents [21,22,44]. In this regard, some authors have identified autonomic changes in the heartbeat fluctuations during pregnancy; these have been generally associated with the particular response to undertake the aortocaval compression of late gestation [13]. Yeh et al. reported that the heartbeat fluctuations of late pregnant women involve lower magnitude and an increased short-term fractal scaling exponent α_1 as compared with data collected 3 months after delivery, which in return show similar values of non-pregnant controls [22]. Similarly, Baumert et al. [45] have found increased α_1 values in comparison with the first half of pregnancy at the end of gestation, perhaps coinciding with the reduced vagal outflow reported during pregnancy [46]. Yet, no changes in low-risk pregnant women during gestation for the scaling exponents α_1 and $\alpha_1(\text{SIGN})$ have also been reported [21]. Corresponding to these studies, we observed that no changes in α_1 , RMSSD and LnHF were in fact introduced by the uterine activity, despite provoking a significantly different mean heart rate. This finding is in accordance with a recent study reporting no differences in high-frequency HRV components during periods with uterine contractions [14]. Actually, α_1 at labour showed here similar values with the abovementioned prenatal studies [21]. In the case of $\alpha_1(\text{MAG})$, we also failed to find differences when comparing L-C and P groups. Thus, according to the dynamic meaning that can be considered for these parameters, the short-term heartbeat fluctuations maintain irregular fractal-like correlations ($\alpha_1 \approx 1$) and non-linearity ($\alpha_1(\text{MAG}) > 0.5$) regardless of the increased hemodynamic demands of labour. Using the interpretation adopted from our previous study [21], both dynamical conditions can thus be considered as evidence that the ANS regulation of the cardiovascular system does not become hampered at low-risk labour.

Similar dissociation between changes in the magnitude of HRV parameters and their α_1 scaling invariance has been described in other physiological scenarios. For example, the well-known reduction of the IBI fluctuations that occurs during ageing was not found to be accompanied by changes of the fractal (scale-invariant) behaviour [47]. This finding suggests that the alterations in the cardiac control mechanisms with advance age differ from the mechanistic changes in the autonomic regulation associated with pathological conditions. Such results appeared in accordance with Pikkujämsä et al. who reported that children show lower overall HRV, despite presenting similar IBI short-range correlation properties as healthy adults [48]. Likewise, despite that the heart rate and other short-term indexes of HRV are affected by physical activity during free-running ambulatory conditions [49], this influence, by contrast, did not appear significant for α_1 . In the same way, Tulppo et al. have reported that an enhanced vagal outflow did not change α_1 values [50].

Regarding clear heartbeat dynamic effects provoked by the manifestation of contractions during labour, it is important to mention that, in addition to the differences in the mean heart rate and SampEn2 (see below), we did find differences in the $\alpha_1(\text{MAG})$ parameter, which probably indicate a contraction-driven increment of the nonlinear properties involved in the cardiovascular regulation.

These properties have been linked to the complexity of the feedback mechanism of neurohormonal cardiac regulation [24,47], which increases for pregnant women after mid pregnancy possibly owing to new control influences or to modifications of feedback interactions [21]. Given the pain perception dynamics associated with uterine activity [52,53], the contraction-driven increment of complexity (indicated by $\alpha_1(\text{MAG})$) that we report here appears relevant to be explored in more detail as we did not find any study yet reporting an association of this parameter with pain.

5. Limitations

Labour introduces changes in ventilation that may also affect the respiratory-driven IBI fluctuations. All studied women here were under spontaneous respiration, and we calculated the central frequency of the HF band to estimate the mean respiration frequency between labour and third trimester groups. Yet, as no statistical differences were found [28], an important influence of ventilation in the results found for labour in this study is not likely.

The mean time elapsed between the onset of labour and the beginning of the collection of ECG data was 5.8 ± 7.1 h. The total time of labour was 13 ± 8 h. As a high variation in such beginning and duration of labour was observed, it would be appropriate as well to consider their potential effects for our analysis. However, we found no significant time-dependence on the estimation of HRV parameters, which would be strongly associated with that variation.

Despite that it was not possible for us to make a longitudinal study to avoid potential individual differences between subjects in the HRV values, the general characteristics of the study population (5-minute Apgar score, birth weight, gestational age and others, reported at Table 1) support the manifestation of quite similar conditions between the L and P groups, both reflecting a low-risk pregnancy status.

In future work, we will consider investigating HRV data obtained during pre- and post-partum stages at immediate periods before and after labour.

6. Conclusion

In summary during normal childbirth the maternal short-term cardiac regulation shows a concomitant nonlinear dynamics that should provide stable and adaptive capabilities [54]. Yet such regulation becomes weakly anticorrelated (as indicated by $\alpha_1(\text{SIGN})$) and involves an increased vagally-mediated fluctuations (as indicated by RMSSD and LnHF), which may reflect an activation of the cholinergic pathway owing to the use of oxytocin or the anti-inflammatory response triggered during labour. We consider that dynamic changes in maternal heartbeat fluctuations could then become potential features to identify the physiological onset of labour.

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