Early Human Development 92 (2016) 51–55

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Heart rate variability in neonates of type 1 diabetic pregnancy

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ARTICLE INFO

Article history:
Received 16 July 2013
Received in revised form 2 November 2015
Accepted 8 November 2015

Keywords:
Diabetes
Fetal programming
Heart rate variability
Pregnancy

ABSTRACT

Background: Cardiomyopathy is a common finding in offspring of pre-gestational type 1 diabetic pregnancy. Echocardiographic and biochemical evidence of fetal cardiac dysfunction have also been reported. Studies suggest that offspring of diabetic mothers (ODM) undergo a fetal programming effect due to the hyperglycaemic intrauterine milieu which increases their risk of cardiovascular morbidity in adult life. Decreased neonatal heart rate variability (HRV) has been described in association with in-utero growth restriction, prematurity, sudden infant death syndrome and congenital heart disease. The effect of in-utero exposure to hyperglycaemia in diabetic pregnancy on neonatal HRV is unknown.
Aims: Our aim was to determine if neonatal HRV differs between normal and diabetic pregnancy.
Study design and subjects: This was a prospective observational study of 38 patients with pregestational type 1 diabetes and 26 controls. HRV assessment was performed using Powerlab (ADI Instruments Ltd).
Outcome measures: Heart rate variability assessment and cord blood sampling for pH and glucose were performed for all neonates. Maternal glycaemic control was assessed via measurement of glycosylated haemoglobin in each trimester in the diabetic cohort.
Results: Neonates of diabetic mothers had evidence of altered heart rate variability, with increased low frequency to high frequency ratio (LF: HF), suggestive of a shift towards sympathetic predominance ($p < 0.05$). This altered HRV was significantly related to fetal acidaemia, cord blood glucose values and maternal glycaemic control during pregnancy ($p < 0.05$).
Conclusion: Neonates of pregestational diabetic pregnancy have altered HRV which is related to maternal hyperglycaemia, fetal acidaemia and fetal glycaemia. Exposure of the developing heart to fluctuations in maternal glycaemia with subsequent alterations in HRV may explain why infants of diabetic mothers are at greater risk of cardiovascular disease in later life.

1. Introduction

Perinatal morbidity and mortality are increased in infants of diabetic mothers [1,2]. Altered cardiac structure is a common finding in this cohort with 38% having evidence of cardiomyopathy in the neonatal period, 5% of whom show clinical symptoms. [1,3,4] This is usually a transient finding, although cases of neonatal congestive cardiac failure have been reported [5,6]. Altered cardiac function in offspring of diabetic pregnancy has been reported as early as the first trimester of pregnancy [7] as well as in infants born to diabetic mothers [8]. Our group has also previously demonstrated biochemical evidence of cardiac dysfunction in this cohort which correlated with fetal cardiac structural abnormalities and poor perinatal outcome [9].

There have been many reports on the effect of the intrauterine life and subsequent adult disease, most famously the Barker hypothesis [10]. Offspring of diabetic mothers (ODM) appear to experience a fetal programming effect evidenced by increased cardiovascular morbidity, hypertension, aortic wall thickening, altered lipid profiles and impaired renal function in this population in later life [11–16].

Heart rate variability (HRV) is a measure of heart rate fluctuation around the mean heart rate. HRV assessment allows determination of low frequency (LF) and high frequency (HF) components and thus assessment of the sympathetic-parasympathetic balance. The assessment of infant HRV is well documented with decreased HRV found in association with prematurity, congenital heart disease and sudden infant death syndrome (SIDS) [17–19]. Interestingly, recent studies suggest that the in utero environment appears to have a lasting effect on HRV as persistent decreased HRV has been described in low birth weight babies at nine year follow up [20]. Persistent autonomic dysfunction may have a role in the increased cardiovascular risk seen in adult life in offspring of diabetic mothers.

The aim of this study was to examine heart rate variability in newborn infants of type 1 diabetic pregnancy to allow comparison with the non-diabetic population.

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http://dx.doi.org/10.1016/j.earlhumdev.2015.11.003
0378-3782/

2. Methods

This was a prospective observational study with institutional ethics approval and written parental consent. Thirty-eight consecutive patients with pre-gestational type 1 diabetes mellitus were recruited at 6 to 13 weeks' gestation from the multidisciplinary diabetic pregnancy clinic in a tertiary level maternal unit and followed longitudinally in pregnancy. Data on maternal glycaemic control was longitudinally collected during diabetic pregnancy. All infants had neonatal heart rate variability assessment performed in the first week of life. For comparison, twenty-four healthy controls were recruited prior to delivery by planned caesarean section and two were recruited prior to uncomplicated spontaneous vaginal delivery. Following informed written consent, both groups had cord blood sampling for arterial and venous pH, haematocrit and glucose followed by neonatal heart rate variability assessment in the first week of life.

2.1. Heart rate variability assessment

Heart rate variability (HRV) was defined as a measure of heart rate fluctuation around the mean heart rate. The parasympathetic system is associated with a high frequency peak in HRV whereas the sympathetic system is associated with a low-frequency peak in HRV. It is assessed via measurement of the RR interval, defined as the time difference between the R wave of one ECG complex and the R wave of the immediately preceding ECG complex. There are two elements involved in heart rate variability analysis; time domain analysis and frequency domain analysis. Time domain analysis is based on measurements directly related to the RR interval. Frequency domain analysis is assessed when power spectral analysis (using Fourier transformation) transforms the RR intervals into a spectrum with power as a function of frequency. With the neonate in the resting state heart rate variability was measured with Powerlab (ADI Instruments Ltd) which electronically recorded the neonatal ECG and the RR interval. To standardise conditions during this examination, the assessment was performed when the neonate was in the resting state, and ensuring a quiet external environment. The researcher (NR) remained in close proximity to identify any problems with neonatal ECG recording and to document movement patterns and crying. A 40 minute recording was reviewed by the researcher (NR) to determine the best quality 180 s of the reading. Data analysis was performed on 180 s long segments, which was chosen as a compromise between the demands of sufficient duration and signal stability. As recommended by the European task force document [21] the complete signal was carefully edited using visual checks and manual corrections of individual RR intervals. The derivative function was used to standardise all recordings and a 45 Hz low pass filter was used when the sample had a large proportion of "noise". Where visualisation of the tachogram revealed incorrectly identified R waves these short artefacts were manually deleted and R waves were added in if inappropriately missed. Post signal processing was kept to a minimum and there were no differences between the cohorts with respect to the number of beat analysed, duration of analysis and addition or removal of RR intervals. After post signal processing to clean the data, the RR interval is referred to as the normalized RR interval (NN).

(i) Time domain analysis
Beat-to-beat variation in the heart rate series was calculated from the NN (normalized RR) intervals is typically described by several statistical parameters, including

Mean NN the average RR interval after post signal processing

SDNN standard deviation of all NN intervals, reflecting overall variation in the heart beat series.

SDdeltaNN standard deviation of the differences in duration between adjacent NN intervals, reflecting instantaneous variation in the heart beat series

RMSSD square root of the mean of the sum of the squares of the differences between adjacent NN intervals, reflecting overall variation in the heart beat series.

(i) Frequency domain analysis
Frequency domain analysis is assessed when power spectral analysis (using Fourier transformation) transforms the RR intervals into a spectrum with power as a function of frequency. This allows determination of which frequencies in the RR series contain the heart rate variability power at a particular point in time and thus determine if high or low frequency signals predominate.

2.2. Establishing normal values

Since we are the first group to use the Powerlab software to assess neonatal heart rate variability, we used our cohort of normal neonates to define normal values for analysis settings and thus define mean RR interval (476.73 ms) with +/− 2SD used to define ectopic (395.49, 557.97) and +/− 5SD used to define artefact (273.63, 679.83). A bin size of 10 ms was used to define the time resolution for the analysis histograms. The ΔNN is the duration between successive NN (normalized RR intervals) and a ΔNN of 50 ms was defined as 'large difference' on the analysis settings. Fast Fourier transformation (FFT) size of 1024 was selected as the number of data points analysed in each segment of the FFT. The Welch spectrum window is the function applied to lessen the importance of points at the edge of the data segments used by the FFT and 1/2 was the chosen amount of overlap between successive data segments.

2.3. Frequency bands

In adults with a respiratory rate is 0.32 Hz (approximately 19 breaths per minute), thermoregulation-related heart rate variability (VLF) is defined as variability < 0.05 Hz, baroreflex-related heart rate variability is 0.05–0.1 Hz and respiratory sinus arrhythmia (HF) is 0.1–0.32 Hz.[1] Due to the higher neonatal respiratory rate of 0.5–1 Hz adjusted frequency bands had to be used. Values of <0.04 Hz for very low frequency (VLF), 0.04–0.15 Hz for low frequency and 0.15–1.1 Hz for high frequency (HF) were used in agreement with current literature [17,21].

2.4. Data analysis

Analysis was performed with the Powerlab (ADI Instruments Ltd) analysis software and data was examined in Poincaré Plot (each RR interval was plotted against the preceding RR interval in a scatter plot), Tachogram plot (each RR interval length was plotted against interval number, thus providing a good indication of misidentified R waves and artefacts) and a Spectrum plot (shows the power spectrum of the time-based tachogram using Fast-Fourier Transform analyses and thus displays the absolute and relative power measurements in the various frequency ranges).

2.5. Statistical analysis

SPSS version 12 was used to perform statistical analysis. The cohorts were compared using a student's *t* test for normally distributed data and Mann–Whitney U for non normally distributed data after investigation with Kolmogorov–Smirnov and Shapiro–Wilk to determine normality. Correlation with Pearson's or Spearman's coefficient was determined based on normality of data. Linear regression was utilized to determine the contribution of multiple factors to outcome data.