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Left ventricular isovolumic relaxation and renin-angiotensin system in the growth restricted fetus

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Abstract

Objective: To determine left ventricular isovolumic relaxation time (LV IRT) in normally developing and growth restricted fetuses (FGR) as an indicator of fetal cardiac afterload and neonatal systolic blood pressure.
Study design: A prospective longitudinal study in 124 normally developing and 47 growth restricted fetuses (FGR). LV IRT, fetal heart rate (FHR) and umbilical artery pulsatility index (PI) were determined at 2–3 week intervals starting at 22–26 weeks of gestation until delivery. Renin and angiotensin I levels were measured by radioimmunoassay in umbilical venous blood after delivery. Systolic blood pressure was measured at day 1 and day 5 of postnatal life. To evaluate the association between LV IRT, gestational age and FHR, bivariate regression analyses were performed.
Results: Mean LV IRT (62 ± 8 ms) was 29 percent longer in FGR as compared to the normal subset (47 ± 6 ms) at all gestational ages ($p < 0.001$). Mean postnatal active plasma renin level ($7.78 \pm$ S.D. 1.03 ng/ml) and postnatal angiotensin I level (4.21 ± 0.70 ng/ml) in the FGR subset were significantly higher ($p < 0.001$) than in the normal subset (4.81 ± 1.04 ng/ml, renin and 2.69 ± 0.44 ng/ml, angiotensin I). There was a significant difference ($p < 0.01$) in systolic blood pressure between the two subsets on postnatal day 1 (FGR 52 ± 6 mmHg vs. normal 46 ± 4 mmHg) and day 5 (FGR 76 ± 5 mmHg vs. normal 60 ± 6 mmHg).
Conclusion: Left ventricular isovolumic relaxation time may act as a sensitive index of increased arterial afterload in the growth retarded fetus and may herald raised systolic blood pressure in the early neonatal period.

Keywords: Isovolumic relaxation time; Growth restricted fetus; Renin; Angiotensin

1. Introduction

Fetal growth restriction (FGR) complicates 10%–15% of all pregnancies [1]. The cause of FGR is multifactorial. Pregnancy induced hypertension (PIH), preeclampsia and maternal nutritional deficiencies are among the most common causes of FGR [1,2]. Although perinatal complications of FGR are well documented, it is only recently that researchers are focused on the long-term morbidity which is associated with this phenomenon. Numerous epidemiological studies have described the relationship between low birth weight and high blood pressure in adult life. It was proposed that factors associated with FGR could program the development of the cardiovascular system and act as a risk for essential hypertension, hyperlipidemia and death from cardiovascular disease in later life [3–5]. However, there is no information about the mechanisms of this programming. Whether these mechanisms start during intrauterine life or factors of intrauterine life could serve

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as a background for the early development of hypertension in adults and adolescents is still unknown.

Current management of FGR fetuses consists of serial ultrasound examinations to assess growth as well as Doppler velocimetry in the umbilical artery and several other vessels [6–8]. FGR is usually characterized by an elevated umbilico-placental vascular resistance which may also affect the afterload of the fetal heart [7]. The specific sequence of Doppler changes and hemodynamic modifications in FGR fetuses has been shown, including a change in peripheral arterial impedance resulting in redistribution of blood flow to the vital organs (heart and brain) which is followed by progressive impairment of cardiac function and abnormal venous flow patterns [6,8].

The effects of experimental restriction of placental function and fetal growth on fetal arterial blood pressure regulation during late gestation have been investigated in fetal sheep [9]. A special role of endogenous renin-angiotensin system in the maintenance of blood pressure in growth restricted fetus was determined by captopril infusion [9].

Earlier we have shown the increase in left ventricular isovolumic relaxation time (LV IRT) in FGR fetuses [10]. It is well known that the main determinant of IRT is ventricular afterload [11]. Direct measurements of intraventricular pressure and time course of isovolumic relaxation demonstrated a strong correlation between LV IRT and end-systolic LV pressure (afterload) in sheep [12]. A higher end-systolic pressure value means longer period of isovolumic relaxation. During this time intraventricular pressure should decay from end-systolic pressure (systolic blood pressure) to the value about zero mmHg, which is essential for the initiation of ventricular filling.

We speculated that LV IRT could serve as a noninvasive index of human fetal cardiac afterload. To test this hypothesis we studied the changes of fetal left ventricular isovolumic relaxation time in normally growing and growth restricted fetuses and measured the activity of the renin-angiotensin system which could be involved in the maintenance of arterial blood pressure in the normal sized and growth restricted newborn.

2. Patients and methods

A total 171 consecutive singleton pregnancies was enrolled in the study which was approved by the local Ethics Review Board of the Mother and Child Care Institute. All women consented to participate. The gestational age at enrolment ranged between 22 and 26 weeks of gestation. Gestational age was determined from the patient's last menstrual period and was confirmed by a first-trimester fetal crown-rump length or early second-trimester fetal biparietal diameter measurement. Fetal biometry and Doppler velocimetry measurements were carried out at 2–3 week intervals until delivery.

Biometry and Doppler measurements were performed using a real-time pulsed Doppler ultrasound system (Aloka SSD 1400, Aloka Industry Corp., Tokyo). The Doppler carrier frequency was 3.5 MHz. The four-chamber view of the heart was visualized on a transverse cross-section. The Doppler sample was then placed immediately distal to the mitral valve leaflets. The high-pass filter was set at 100 Hz. Doppler tracings were accepted when the angle between the Doppler cursor and the assumed flow direction was 10^0 or less. On the Doppler waveform traces the left ventricular isovolumic relaxation time (LV IRT; ms) was determined from the artifact of aortic valve closure to the onset of transmitral flow [10] (Fig. 1). The latter was taken as the point where the signal rose above the filter. Fetal heart rate (bpm) was calculated from the time difference between the onsets of transmitral flow in two consecutive cardiac cycles.

Doppler flow velocity waveforms were recorded from the umbilical artery [6,7].

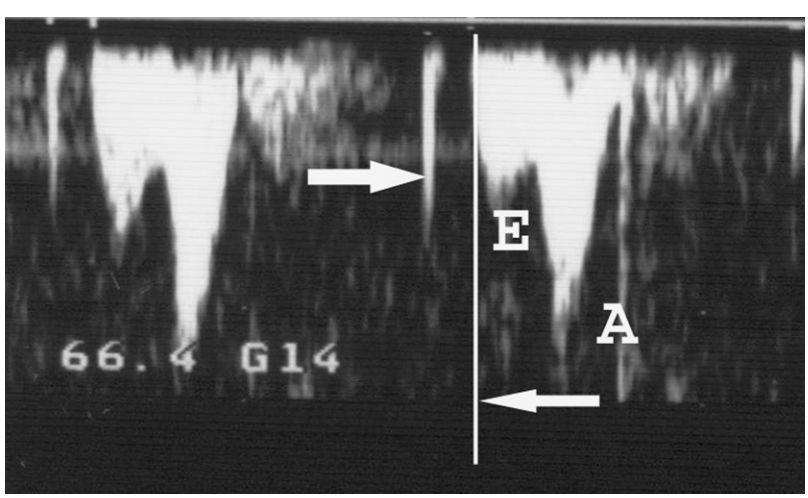

Fig. 1. Pulsed Doppler velocity waveforms from normally developing fetus at 34 weeks of gestation. Left isovolumic relaxation time is determined from the interval between aortic valve closure artifact and the onset of E component of transmitral flow.