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● *Original Contribution*

EFFECT OF HYPOXEMIA WITH OR WITHOUT INCREASED PLACENTAL VASCULAR RESISTANCE ON FETAL LEFT AND RIGHT VENTRICULAR MYOCARDIAL PERFORMANCE INDEX IN CHRONICALLY INSTRUMENTED SHEEP

AMAR BHIDE,[*†] OLLI VUOLTEENAHO,[‡] MERVI HAAPSAMO,[§] TIINA ERKINARO,[¶] JUHA RASANEN,[‖#] and GANESH ACHARYA[*†**]

[*] Women's Health & Perinatal Research Group, UiT—The Arctic University of Norway, Tromsø, Norway; [†] Department of Obstetrics and Gynecology, University Hospital of Northern Norway, Tromsø, Norway; [‡] Biomedicine Unit, Department of Physiology, University Hospital of Oulu, Oulu, Finland; [§] Department of Obstetrics and Gynecology, University Hospital of Oulu, Oulu, Finland; [¶] Department of Anesthesiology, University Hospital of Oulu, Oulu, Finland; [‖] Department of Obstetrics and Gynecology, University of Eastern Finland, Kuopio, Finland; [#] Oregon Health and Sciences University, Portland, Oregon, USA; and [**] Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institute, Stockholm, Sweden

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Abstract—Myocardial performance index (MPI) is increased in growth-restricted fetuses with placental insufficiency, but it is unknown if this is due to fetal hypoxemia or increased placental vascular resistance (R_{plac}). We used chronically instrumented sheep fetuses (n = 24). In 12 fetuses, placental embolization was performed 24 h before experiments. On the day of the experiment, left (LV) and right (RV) ventricular MPIs were obtained by pulsed Doppler at baseline and in the hypoxemia and recovery phases. At baseline, R_{plac} was greater and fetal pO_2 lower in the placental embolization group, but RV and LV MPIs were comparable to those of the control group. During hypoxemia, mean LV MPI increased significantly only in fetuses with an intact placenta (0.34 vs. 0.46), returning to baseline during the recovery phase. Right ventricular MPI was unaffected. We conclude that fetal LV function is sensitive to acute hypoxemia. Exposure to chronic hypoxemia could pre-condition the fetal heart and protect its function with worsening hypoxemia. (E-mail: abhide@sgul.ac.uk)

Key Words: **Cardiovascular function, Hypoxemia, Sheep model.**

INTRODUCTION

The myocardial performance index (MPI) was originally described in the evaluation of dilated cardiomyopathy (Tei et al. 1995). It reflects combined systolic and diastolic cardiac function in both adults and children and is independent of age, ventricular geometric assumptions, heart rate (HR) and blood pressure (Tei et al. 1995, 1996). This observation has been extended to fetuses, and MPI has been studied as a possible marker of fetal cardiac dysfunction. However, the fetal circulation is quite different from the adult circulation. Fetal systemic and pulmonary circulations work in parallel rather than in series, as in adults. The dominant ventricle in adult life is the left ventricle. In the fetus, it is the right ventricle, which supplies blood to most of the body and the placenta. The fetal left ventricle preferentially perfuses the brain. In the setting of increased placental vascular resistance, the afterload on the right ventricle can be elevated. Vascular resistance in the cerebral circulation, however, remains relatively low. Fetuses that are growth restricted because of placental insufficiency appear to have increased left ventricular MPI (Crispi et al. 2008). However, it is uncertain whether the change in MPI is a reflection of hypoxemia, changes in cardiac loading conditions or a direct effect of myocardial cell damage. There have been a few previous attempts to study the relationship between hypoxemia and MPI. One such study (Guorong et al. 2007) reported

Address correspondence to: Amar Bhide, Fetal Medicine Unit, 4th Floor, Lanesborough Wing, St. George's Hospital, Blackshaw Road, SW17 0 QT, United Kingdom. E-mail: abhide@sgul.ac.uk

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elevated left as well as right ventricular MPIs in hypoxemia caused by acute cord occlusion. To our knowledge, the effect of acute hypoxemia (without changes in preload or afterload) and the effects of chronic hypoxemia with elevation of placental vascular resistance (R_{plac}) on fetal right and left ventricular MPIs have not been studied.

We hypothesized that increased R_{plac} and chronic fetal hypoxemia caused by placental embolization lead to global myocardial dysfunction and increased fetal left and right ventricular MPI. Furthermore, we wanted to investigate whether fetuses with increased R_{plac} and chronic hypoxemia respond differently to an acute reduction in fetal pO_2 compared with fetuses with intact placenta.

METHODS

All experiments were performed in accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Council of Europe 1986) and European Union Directive ETS 123 (1997). The Animal Care and Use Committee of the University of Oulu approved the study protocol.

Surgical preparation and instrumentation

Data from 24 chronically instrumented pregnant sheep at 115–129/145 d of gestation were used for this report. The details of the instrumentation have been described previously (Erkinaro et al. 2004, 2009). In brief, a laparotomy was performed under general anesthesia and endotracheal intubation. The fetal lower body was exteriorized through a hysterotomy, and 18G polyurethane catheters were introduced into the descending aorta and inferior vena cava *via* the femoral artery and vein. A 4-mm-transit-time ultrasonic flow probe (Transonic Systems) was placed around the umbilical arteries to measure placental volume blood flow (Q_{Plac}). After replacement of amniotic fluid with 0.9% warm saline and closure of the surgical wounds, all catheters and probes were tunneled subcutaneously and exteriorized through a small skin incision in the ewe's flank. Post-operative analgesia was provided with a fentanyl patch (50 mcg/h) attached to the ewe's tail, with additional intramuscular injections of fentanyl 1.5 to 2 mcg/kg twice daily. After 4 d of recovery and 24 h before the experiment, placental embolization was performed in 12 sheep using 45- to 150-mm microspheres (Contour Emboli, Target Therapeutics, Fremont, CA, USA) to simulate placental pathophysiology in pregnancies complicated by placental insufficiency. A dry volume of 0.25 mL of microspheres was suspended in 0.5 mL of 20% albumin and diluted with 10 mL of 0.9% saline. This solution was injected into the fetal descending aorta in 1-mL increments every 15 min until fetal arterial oxygen saturation decreased by 30% from pre-embolization values. The control group included 12 sheep with intact placental circulation.

Throughout the recovery period of 4–5 d, the ewes received daily intravenous infusions of 1 L of Ringer's lactate solution with ampicillin 1 g, and the fetuses were given intravenous injections of benzyl penicillin 1×10^6 IU.

Experimental protocol

On the fifth postoperative day, general anesthesia was induced with propofol 4–7 mg/kg and maintained with isoflurane 1–1.5% in an oxygen/air mixture via an endotracheal tube and mechanical ventilation. Muscle relaxation was induced with rocuronium 20 mg and monitored with a neurostimulator, with additional boluses given as needed. A 16G polyurethane catheter was inserted into the maternal descending aorta through a femoral artery.

When all hemodynamic parameters were stabilized, both invasive and Doppler ultrasonographic baseline measurements were obtained (baseline). After this, maternal and fetal hypoxemia, defined as maternal oxyhemoglobin saturation of 80%, was induced by replacing oxygen with medical air in the rebreathing circuit, and a set of measurements identical to those at baseline were obtained after 15 min of maternal hypoxemia (hypoxemia). Thereafter, the maternal inhaled oxygen concentration was returned to baseline, and the ewe and her fetus were allowed to recover from hypoxemia for 15 min before obtaining the recovery phase measurements (recovery).

Invasive measurements

Maternal arterial pressures and heart rate were measured with disposable pressure transducers (DT-XX, Ohmeda, Hatfield, UK). The transducers used for fetal arterial and venous blood pressure measurements were reusable (Biopac Systems, Santa Barbara, CA, USA). Maternal and fetal mean arterial pressures (MAPs) were computed arithmetically (MAP = diastolic pressure + [systolic pressure–diastolic pressure]/3), and HRs were computed from the arterial waveforms. Placental (R_{Plac}) vascular resistance was computed by dividing fetal MAP by Q_{Plac}. All variables were recorded continuously at a sampling rate of 100 Hz using a polygraph (UIM100 A, Biopac Systems, Santa Barbara, CA, USA) and computerized data acquisition software (Acqknowledge, Version 3.5.7 for Windows, Biopac Systems, Santa Barbara, CA, USA). The recordings were later analyzed at 1-min periods, and the median value of the 6,000 measurements per variable was chosen to represent