

● *Original Contribution*

## REGIONAL MYOCARDIAL FUNCTION AND RESPONSE TO ACUTE AFTERLOAD INCREASE IN CHRONICALLY ANEMIC FETAL SHEEP: EVALUATION BY TWO-DIMENSIONAL STRAIN ECHOCARDIOGRAPHY

LI XIONG,<sup>\*†</sup> LEAH S. BERNARD,<sup>†</sup> JASON N. HASHIMA,<sup>†</sup> YOU-BIN DENG,<sup>‡</sup>  
ZHIWEN ZHOU,<sup>†</sup> MUHAMMAD ASHRAF,<sup>†</sup> A. ROGER HOHIMER,<sup>†</sup> LOWELL E. DAVIS,<sup>†</sup>  
WEIHUI SHENTU,<sup>‡</sup> DAVID J. SAHN,<sup>†</sup> and JUHA RASANEN<sup>†</sup>

\* Wuhan General Hospital of Guangzhou Command, Wuhan, China; <sup>†</sup> Oregon Health & Science University, Portland, OR, USA; and <sup>‡</sup> Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

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**Abstract**—We hypothesized that in chronic fetal anemia, remodeling of the myocardium is related to abnormalities in regional wall motion and acutely increased afterload further disturbs myocardial strain. Chronic anemia was induced in one fetus of each of seven sheep twin pregnancies. The fetuses were studied by two-dimensional (2-D) strain echocardiography at baseline and during increased afterload via angiotensin II (AT II) infusion. At baseline, the peak systolic longitudinal, radial and circumferential strains in the left ventricular lateral wall in anemic fetuses were lower than those in the controls (all  $p < 0.05$ ). During AT II, the circumferential strain of right ventricular free wall decreased significantly both in the control and anemic fetuses. Left ventricular free wall systolic strains were not affected by AT II. Fetal myocardial remodeling in chronic anemia decreases left ventricular systolic free wall strains. The myocardial adaptation does not change ventricular responses to acutely increased afterload. (E-mail: [sahnd@ohsu.edu](mailto:sahnd@ohsu.edu)) © 2010 World Federation for Ultrasound in Medicine & Biology.

**Key Words:** Fetal anemia, Two-dimensional strain, Myocardial function, Afterload, Speckle tracking.

### INTRODUCTION AND LITERATURE

In the chronically anemic fetal sheep, stroke volume, cardiac output and coronary blood flow increase and systemic vascular resistance decreases (Davis and Hohimer 1991; Davis et al. 1996, 1999). In addition, chronic fetal anemia leads to remodeling of the myocardium both by means of hyperplasia and hypertrophy (Jonker et al. 2009). Experimental studies on sheep fetuses with chronic anemia have shown that the sensitivity of the right ventricle to increasing afterload remains unchanged suggesting that fetal myocardial adaptation in chronic anemia is successful (Davis et al. 1996).

Two-dimensional (2-D) strain imaging is an echocardiographic technique that uses standard B-mode images for speckle tracking analysis. Two-dimensional strain echocardiography offers a more reproducible and

less time-consuming measurement of regional strain in longitudinal, circumferential and radial directions that are site specific and angle independent (Notomi et al. 2005; Teske et al. 2007). Regional myocardial strain measured by 2-D strain echocardiography has been demonstrated to be a sensitive parameter for the evaluation of regional myocardial function in patients with preserved global left ventricular systolic function, including those with diastolic heart failure, hypertension and coronary heart disease without visual regional wall motion abnormality (Liang et al. 2006; Wang et al. 2008; Yip et al. 2002).

In this experimental sheep model of chronic fetal anemia, we tested the hypothesis that remodeling of the ventricular myocardium is related to abnormalities in regional wall motion and an acute increase in afterload further disturbs regional myocardial strain measured by 2-D strain echocardiography.

### MATERIALS AND METHODS

#### *Animal preparation*

Studies were performed in time-bred fetal sheep of mixed breeding obtained from a local source. The

Address correspondence to: David J. Sahn, M.D., L608, Pediatric Cardiology, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239-3098 USA. E-mail: [sahnd@ohsu.edu](mailto:sahnd@ohsu.edu)

Institutional Animal Care and Use Committee, Oregon Health & Science University approved all procedures and operations.

Seven twin pregnant ewes at  $113 \pm 1$  days gestation (term 145 days) were instrumented under general anesthesia induced by a diazepam ketamine mixture and maintained with 1.5% to 2.5% isoflurane in a 1 to 3 nitrous oxide to oxygen mix. Under sterile conditions, the fetuses were partially externalized in the normal surgical fashion. Polyethylene catheters were introduced into the internal jugular vein and carotid artery of each fetus. A three-lead EKG wire was placed subcutaneously on the fetal chest. Catheters were then tunneled to the ewe's flank. The uterus and abdomen were closed and the ewe was allowed to recover for 3 to 4 days. Chronic anemia was induced in one of the randomly selected fetus of each pair by removing 30 to 120 mL of blood and replacing it with isotonic saline to achieve an arterial oxygen content of 2 mL/dL in the absence of acidosis by day 6 to 7 of daily bleeding as previously described (Davis *et al.* 1999). The fetuses were then studied on day 8 or 9 after induction of anemia. Heart rate was monitored with a cardiometer triggered from the arterial pressure waves. Fetal blood pressure was referenced to amniotic fluid pressure.

#### *Echocardiography studies*

Echocardiographic studies were performed with the ewe anesthetized. Anesthesia was induced with propofol and the ewe was intubated. Anesthesia was maintained with 1% to 2.5% isoflurane mixed with room air. Echocardiographic images were obtained using a Vivid 7 ultrasound system (GE Medical Systems, Norten, Norway) with a 7S phased array probe, for obtaining high frame rate (circa 180 frames/s) 2-D gray-scale images. Left and right ventricular end-diastolic dimensions were measured from the four-chamber view. Left ventricular ejection fraction was also calculated from M-mode echo as previously described (Teichholz *et al.* 1976). For speckle tracking analysis, four-chamber view and short-axis view at the papillary muscle level were obtained using conventional 2-D gray-scale echocardiography by a single investigator. Three stable and well-defined consecutive cardiac cycles were acquired digitally for each view. The scan line data for these images were processed using acoustic-tracking software (EchoPac 6.1, GE Medical Systems, Norten, Norway), allowing off-line semi-automated analysis of speckle-based strain.

The off-line analysis was performed by a single independent observer, who was blinded to the fetal arterial blood gases and hemodynamic data. Myocardial endocardial surface was manually traced at the end-systolic frame and an automated tracking algorithm outlined the myocardium in successive frames throughout

the cardiac cycle. After the tracking quality was verified for each segment (with subsequent manual adjustment of the region of interest if necessary), myocardial motion was analyzed by speckle-tracking within the region-of-interest bound by endocardial and epicardial borders. Myocardial longitudinal, circumferential and radial strain curves were obtained and peak systolic strain values were measured. The peak systolic longitudinal strain was measured from four-chamber views and the peak systolic radial and circumferential strains were measured from short-axis views at the papillary muscle level.

#### *Study protocol*

Echocardiographic data were collected at baseline and during the afterload increase *via* infusion of 2 mcg/mL (Bachem, Torrance, CA, USA) of angiotensin II (AT II) with the rate titrated to increase blood pressure by 15 mm Hg in each fetus.

#### *Statistical analysis*

Data were expressed as mean  $\pm$  SD. An unpaired *t*-test was used to compare parameters between the control and anemic fetal hearts. A paired *t*-test was used for comparisons of measurements obtained at baseline and during increased afterload. The tests used in statistical analysis were performed using the SPSS 13.0 software and *p* value of less than 0.05 was considered statistically significant.

## RESULTS

#### *Arterial blood gases and hemodynamic data*

Arterial blood gases and hemodynamic data at baseline and during increased afterload are listed in Table 1. Both at the baseline and during the increased afterload by AT II, hemoglobin, hematocrit and oxygen content in anemic fetal sheep were significantly lower than those in controls (all  $p < 0.05$ , Table 1). At baseline,  $P_{O_2}$  was less in anemic fetuses compared with the controls ( $p < 0.05$ , Table 1). In anemic fetuses, mean arterial blood pressure was lower at baseline than in the control fetuses. During AT II infusion, fetal heart rate was higher in anemic fetuses compared with the controls ( $p < 0.05$ , Table 1). Fetal mean arterial blood pressure increased significantly in both control and anemic fetuses during AT II infusion compared with the baseline (all  $p < 0.05$ , Table 1).

#### *Conventional echocardiographic data*

Comparisons of the conventional echocardiographic parameters at baseline and during AT II infusion are shown in Table 2. Left and right ventricular end-diastolic dimensions and left ventricular ejection fraction did not significantly differ between the two groups at the

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