Impact of Afterload Increase on Left Ventricular Myocardial Deformation Indices

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Background: Left ventricular (LV) afterload could be associated with reduced myocardial contractility. The aim of this study was to evaluate the relative impact of increased afterload on LV myocardial deformation indices in chronic aortic constriction, with regard to hypertrophy, myocardial fibrosis, and mitochondrial function, and to differentiate acute versus chronic afterload effect.

Methods: Young pigs underwent aortic banding (n = 11) or sham (n = 7) operations. Nineteen weeks later, LV morphology and systolic function, including myocardial deformation, were assessed by echocardiography before and after banding release or acute aortic constriction (in the sham group). After the animals were euthanized, mitochondrial function and LV interstitial fibrosis were assessed.

Results: The chronic banding group (n = 8) presented with significant LV hypertrophy compared with the sham group (n = 7), and longitudinal strain (LS) was significantly altered (16.9 ± 0.7% vs 20.3 ± 0.7%, P = .001) while circumferential, radial strain, and ejection fraction were not. LS abnormalities were situated mostly on the basal and mid segments and on the septal wall. There was also significantly more myocardial fibrosis in the chronic banding group compared with the sham group, while mitochondrial function was preserved. The relative contributions of hypertrophic and fibrotic remodeling and of afterload to alter global LS were 62%, and 38%, respectively. Acute aortic banding also significantly altered LS. The ratio of LS to septal wall thickness enabled differentiation between chronic and acute afterload increase (1.9 ± 0.2 in the chronic group vs 2.9 ± 0.3 in the acute group, P = .001).

Conclusions: LS is susceptible to both hypertrophic and fibrotic remodeling and afterload increase, particularly on the basal and mid LV segments of the septum. The ratio of LS to septal wall thickness enables differentiation of acute from chronic afterload LS alteration. (J Am Soc Echocardiogr 2016;■:■-■.)

Keywords: Animal model, Aortic stenosis, Left ventricular afterload, Echocardiography, Left ventricular hypertrophy, Myocardial strain

Left ventricular (LV) pressure chronic overload secondary to chronic progressive moderate to severe aortic valve stenosis or systemic hypertension leads to morphologic hypertrophic remodeling of the left ventricle. It also generates impairments of longitudinal myocardial deformation, although LV ejection fraction (LVEF) may be preserved. LV hypertrophy and myocardial fibrosis are reported to be cofactors of LV deformation alteration.[1,2] LV hypertrophic remodeling induces a decrease in coronary flow reserve and an increase in oxygen myocardial consumption and consequently myocardial ischemia, which results in interstitial myocardial fibrosis.[1,2] Moreover, myocardial hypertrophy is considered an adaptive response to increased workload, while compelling evidence also suggests mitochondrial (dys)function to mechanistically contribute to heart failure development.[3,4]

However, it has been demonstrated that an acute increase in LV afterload alone could also result in a significant reduction in LV longitudinal strain (LS), as well as circumferential strain (CS), radial strain (RS), and LVEF.[5]

The main rationale of this study was that the relative roles of afterload, myocyte bioenergetics, LV hypertrophy, and myocardial fibrosis in global LS reduction, in the presence of chronic afterload increases, are not precisely understood. Moreover, to date, no experimental model has attempted to differentiate the effects of chronic or

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Abbreviations

ADP = Adenosine diphosphate

CO = Cardiac output

CS = Circumferential strain

LS = Longitudinal strain

LV = Left ventricular

LVEF = Left ventricular ejection fraction

RS = Radial strain

progressive afterload increases from those pertaining to acute afterload increases.

We hypothesized, in the event of chronic aortic stenosis, that afterload increases and hypertrophic remodeling should contribute to a higher extent to reduced LV deformation than either myocardial fibrosis or myocyte mitochondrial function, at least at an early stage. Releasing chronic afterload would allow us to evaluate the relative contribution of each factor. Moreover, in the event of acute aortic constriction, only afterload increases and, although to a lower extent, myocyte mitochondrial function are likely to be involved. Consequently, indices taking in account both deformations and LV wall thickness should be of interest and enable us to differentiate between the effects of chronic and acute afterload increases on myocardial deformation.

The main aim of this study was to evaluate the relative contribution of increased afterload on LV global and regional myocardial deformations assessed by strain in chronic aortic constriction, with regard to hypertrophic and fibrotic myocardial remodeling, as well as expected mitochondrial myocyte metabolism alterations. A debanding (afterload release) experiment was also performed to evaluate the respective participation of LV remodeling (hypertrophy and fibrosis) and impairment on residual deformation abnormalities. Furthermore, an acute aortic constriction experiment was produced to assess the effects of afterload taken out of the context of LV remodeling and to differentiate between acute and chronic afterload effects on myocardial deformations.

METHODS

The study was conducted as a prospective intervention (chronic banding) versus control (sham operation) study on male piglets with a mean body weight of 13.0 ± 1.5 kg (mean age, 10.3 ± 0.7 weeks). All experiments were conducted in agreement with the National and European Research Council Guide for the care and use of laboratory animals, and the protocol used was accepted by our local committee (No. 50120208-A).

In the chronic banding group ($n = 11$), we induced a progressive increase in afterload by placing a Teflon band around the supracoronary ascending aorta (initially without any constriction), which became stenosing during growth. In the control group ($n = 7$), we performed sham operations.

At a median 19.0 weeks' follow-up, animals in the two groups were compared at baseline after median thoracotomy. The study protocol is presented in Figure 1.

Initial Surgical Procedure

The piglets were preanaesthetized with an intramuscular injection of ketamine hydrochloride and medetomidine. Propofol 1% was then given in an ear vein. The animals were intubated and ventilated in volume-controlled mode (Cato M33285; Dräger, Lübeck, Germany). During the surgical procedure, the maintenance of anesthesia was ensured by 1.5% isoflurane sufentanil. A continuous infusion of fluids (Ringer's acetate) was administered. Surgical procedure consisted in a left lateral minithoracotomy in the fourth intercostal space. After pericardial opening and interaorticopulmonary space dissection, the ascending aorta was exposed. The circumference of the supracoronary ascending aorta was estimated by placing a suture around it. A nonstenosing Teflon band was placed and sutured around the aorta. The thoracic wall was closed in layers. Prophylactic antibiotics and analgesics were intravenously administered. Finally the animals were extubated and transported back to the farm. A sham operation was performed on the control animals. Instead of banding the aorta, the procedure consisted only of pericardial opening and then closure of the thoracic wall.

Follow-Up Protocol

After a median of 19 weeks, the animals were anesthetized and intubated per the initial procedure and cisatracurium was added. A 4-Fr fluid-filled catheter was advanced into the proximal aorta via the left carotid artery for continuous monitoring of systemic arterial pressure. An 8-Fr fluid-filled catheter was advanced into the left jugular vein for fluid infusion. An 8-Fr fluid-filled catheter was advanced into the right jugular vein, and a Swan-Ganz catheter (Swan-Ganz CCO; Edward Lifesciences, Irvine, CA) was advanced into the pulmonary artery, under echocardiographic guidance. After injection of heparin, an 8-Fr dual field micromanometer-tipped pressure-conductance catheter (Millar Ventri-Cath 510; Millar Instruments, Houston, TX) was introduced along the long axis of the left ventricle, via the right carotid artery and through the ascending aorta (and through the banding if present), with the pigtail tip in the apex of the left ventricle. The correct position was confirmed echocardiographically. The animals were then stabilized for 30 min before thoracic surgery. After midline sternotomy, the heart was suspended in a pericardial cradle and the aorta localized. After 30 min of stabilization (baseline), hemodynamic and echocardiographic recordings were digitally acquired during brief suspension of mechanical respiration (10–15 cardiac cycles). In the chronic banding group, the next step consisted to release the aorta by sectioning the Teflon banding. Hemodynamic and echocardiographic recordings were performed after 30 min of stabilization in this condition (debanding).

In the sham group, acute banding was applied by a monitored constriction of the aorta, producing hemodynamically a ≥20 mm Hg peak-to-peak LV-aortic pressure gradient. Hemodynamic and echocardiographic recordings were made after a stabilization period of 10 min, and aortic banding was then released.

At the end of the protocol, the animals were euthanized during deep anesthesia, and the heart was excised for postmortem examinations. Each heart was collected in the operating room and immediately perfused with and stored in cold cardioplegic solution at 4°C during transport and dissection. The cardioplegic solution contained 110 mmol/L NaCl, 1.2 mmol/L $CaCl_2$, 16 mmol/L KCl, 16 mmol/L $MgCl_2$, and 10 mmol/L $NaHCO_3$, as previously described.[6]

Hemodynamic and Echocardiographic Evaluation

In each condition (baseline, debanding, and acute banding [sham]), heart rate, systolic and diastolic blood pressures, LV maximal, minimal, and end-diastolic pressures, cardiac output (CO), dP/dt_{max}, and dP/dt_{min} were recorded and stored digitally (IOX; Emka Technologies, Paris, France). After midline thoracic and pericardial opening, the transducer, fixed in a saline-filled latex bag, was placed on the epicardium. The echocardiographic recordings were performed with a 4.0-