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Can We Use Vertical Bore Magnetic Resonance Scanners for Murine Cardiovascular Phenotype Characterization? Influence of Upright Body Position on Left Ventricular Hemodynamics in Mice

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ABSTRACT

High resolution magnetic resonance (MR) imaging is uniquely suited for cardiovascular phenotype characterization in transgenic mice. Experimental MR scanners with the high magnetic field strength are commonly built with a vertical bore design. The hemodynamic consequences of a prolonged upright body position in anesthetized mice are, however, unknown. Thus, the purpose of this work was to investigate the influence of a vertical body position on murine systemic blood pressure and left ventricular (LV) hemodynamics over time. We studied six C57Bl/6 mice at 14–16 weeks of age (body weight, 24–28 g) under isoflurane anesthesia. Positioned supine on a 37°C warming pad, a microtip catheter was advanced via the right carotid artery into the left ventricle. Continuous registration of LV hemodynamics was performed at rest and after tilting of the table to a 90-degree vertical position. After tilting, there was a transient decrease of LV systolic pressure to 96% of initial values immediately after tilting with return to baseline level within 6 min. Tilting to vertical

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position had no influence on LV end-diastolic pressure, heart rate, maximal rate of left ventricular pressure increase, and maximal rate of left ventricular pressure decrease. Over a follow-up period of 60 min in vertical position, there were no significant changes in murine hemodynamics. An acute change of body position is fully compensated by a normal orthostatic response in anesthetized mice. Prolonged upright body position exerts no significant changes in murine LV hemodynamics. Hence, high resolution MR studies for cardiovascular phenotype characterization in transgenic mice performed on vertical bore MR scanners allow measurements under physiologic conditions.

Key Words: *Magnetic resonance imaging; Mouse hemodynamics; Orthostatic response; Vertical bore MR scanner*

INTRODUCTION

Magnetic resonance imaging (MRI) is a noninvasive imaging modality that allows for high temporal and spatial resolution and hence meets the imaging requirements of the small and rapidly beating mouse heart. As an intrinsically three-dimensional method, MRI allows for volumetric quantification without relying on geometric models (1). This renders the MRI method uniquely suited for the assessment of volumetric and functional changes in hearts with shape distortions and asymmetric ventricular dilatation, as they occur in dilated cardiomyopathy or during ventricular remodeling after myocardial infarction (2,3).

We recently demonstrated high accuracy and reproducibility of MRI in the assessment of left ventricular (LV) volumes and mass in adult (4) and in new-born and juvenile mice (5). Furthermore, MRI in mice may provide information on regional myocardial torsion and strain (6) and reflects acute geometric and functional changes of the murine heart evoked by inotropic stimulation.

Cardiac MR studies in mice performed on experimental MR scanners operating at 300 MHz (corresponding to 7.05 T) offer sufficient temporal and spatial resolution. However, to further increase the signal-to-noise ratio and hence gain even higher resolution for applications such as vessel wall characterization or three-dimensional angiography in mice, there is currently a trend in murine MRI toward magnets with field strengths such as 11.7 T or higher. However, although most of these high field MR scanners are built in a vertical bore design, the effects of sustained orthostasis on the murine cardiovascular system have not yet been investigated.

Because far-reaching conclusions regarding potential pathomechanisms or therapeutic strategies might be drawn from these MR studies in genetically engineered mice, the orthostatic response to sustained vertical body position has to be characterized. Given the rapidly increasing interest of the cardiovascular MR community for this subject, the purpose of this work was to systematically investigate the murine orthostatic response as it would occur during prolonged MR studies on a vertical bore experimental MR scanner.

MATERIALS AND METHODS

Six male C57Bl/6 mice (body weight, 24–28 g; Charles River, Sulzfeld, Germany) were studied at 14–16 weeks of age. Studies were performed in accordance with the *Guide of the Care and Use of Laboratory Animals* (National Institutes of Health 85-23, revised 1985) and were approved by the University and government authorities (protocol number 621-2531.01-10/98). Mice were anesthetized by isoflurane inhalation (1.5 to 2 vol% with 1 l/min oxygen flow) via a nose cone. Mice were then positioned supine on a 37°C electrical warming pad and were fixed to the pad at the four paws by tape.

To measure LV hemodynamics, a high-fidelity microtip catheter transducer (1.4 F, Millar Instruments, Houston, TX) was inserted into the right carotid artery and was then carefully advanced into the left ventricle. Continuous registration of heart rate, LV pressures, and dP/dt was performed for 10 min at baseline conditions in the supine position and during tilting of the warming pad into the 90-degree vertical position (Fig. 1). The orthostatic response was then followed for 60 min. All pressure signals were digitized at a sampling rate of 4000 Hz and recorded with a PowerLab system (ADInstruments, Castle Hill, Australia).

Statistical Analysis

Statistical analysis was performed using Prism software (GraphPad Software, San Diego, CA). All results

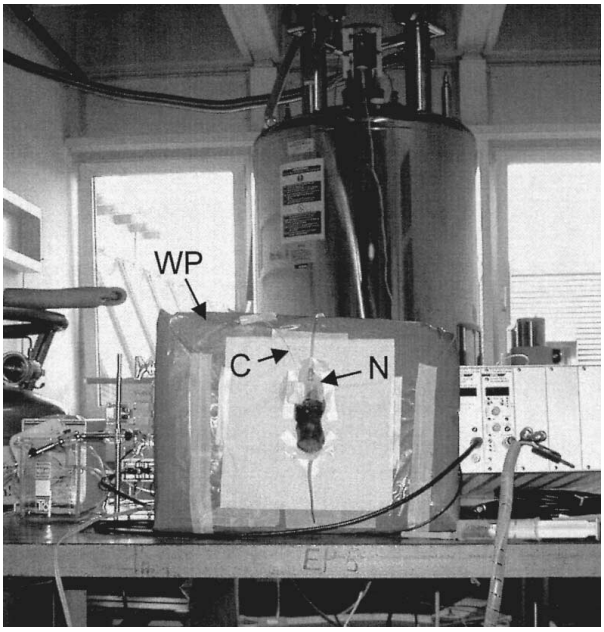

Figure 1. Experimental setup for in vivo measurement of LV hemodynamics with a microtip catheter. The magnet in the background is a 11.7-T vertical MR system. N, nose cone for isoflurane anesthesia; C, catheter lead connected to the pressure transducer; WP, warming pad.

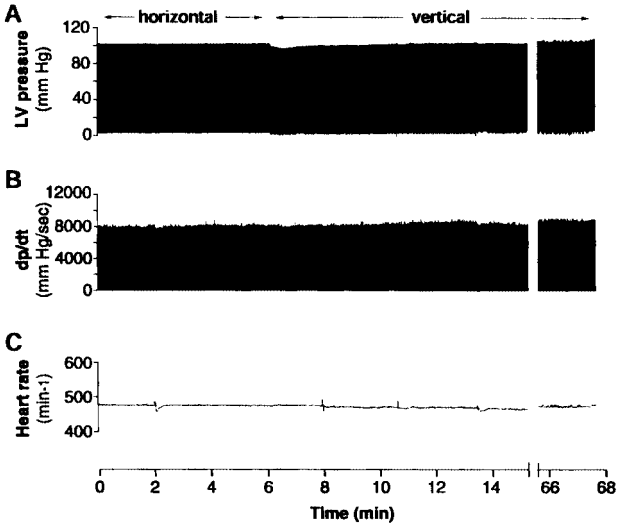

Figure 2. Hemodynamic response of a C57Bl6/J mouse to change from horizontal to vertical position. The mouse was anesthetized with isoflurane, fixed on a warming pad, and a microtip catheter was advanced through the right carotid artery into the left ventricle. Parameters displayed are LV pressure (A), contractility (dp/dt; B), and heart rate (C). Shortly after tilting the warming pad to the vertical position, a small and transient drop in LV systolic pressure was observed (A). However, all hemodynamic parameters remained stable for up to 1 hr.

are given as means ± SEM. Comparisons of parameters over time were done with analysis of variance for repeated measurements. Differences were considered statistically significant at $p < 0.05$.

RESULTS

LV hemodynamic parameters in the horizontal body position of the mice were stable for at least 90–120 min (data not shown). After blood pressure and heart rate were stabilized in the horizontal position, the warming table was tilted into a vertical position. This acute change in position resulted in a small drop in LV systolic pressure (vertical 106 ± 14 mm Hg vs. horizontal 111 ± 12 mm Hg; Figs. 2 and 3B) without any significant alteration in heart rate, LV end-diastolic pressure, or cardiac contractile and relaxation parameters (Figs. 2 and 3). After 10 min in the vertical position, there were no significant changes of heart rate nor end-systolic and end-diastolic pressure (Table 1). Furthermore, parameters of LV contractility (dP/dt_{max}) and relaxation (dP/dt_{min}) were unchanged. Heart rate, cardiac contractility, and LV pressure both at systole and end-diastole were essentially

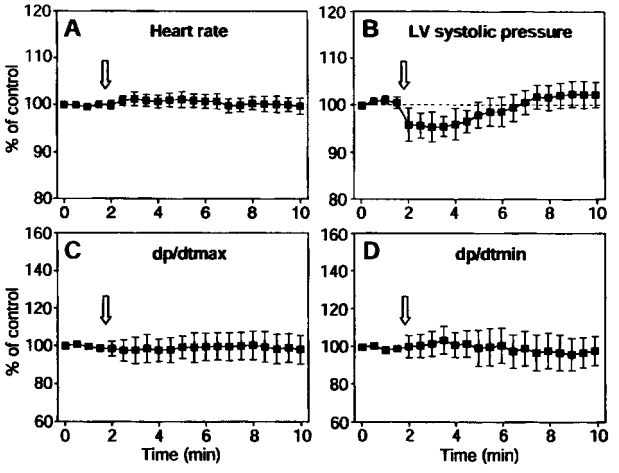

Figure 3. Mean values for cardiac function of C57Bl6/J mice in the vertical position. Mice were anesthetized and the left ventricle was catheterized as described in Materials and Methods. After switching to the vertical position, heart rate (A), cardiac contractility (dp/dt_{max}; C), and relaxation (dp/dt_{min}; D) remained unchanged. However, the maximal LV systolic pressure dropped below baseline for several minutes (B). Data are from six male mice aged 14–16 weeks (means ± SD).

unaltered for up to 60 min in the vertical position (Fig. 2), indicating the absence of orthostatic dysfunction occurring during prolonged vertical body position.

DISCUSSION

This work characterizes for the first time the orthostatic response of mice to sustained vertical body position, to which mice are typically exposed on high field MR scanners with vertical bore design. Although a growing number of MR groups are currently starting with experimental MR studies in either genetically or surgically manipulated mice on vertical bore magnets, there is a lack of information on the murine hemodynamic response to prolonged upright body position.

The main reason for building high field MR scanners with a vertical bore design derives from the superconducting coil within the magnet. Because these magnet coils are exceptionally heavy due to the number of windings necessary to achieve high field strength, a standing position of the coil resulting in a vertical bore guarantees much higher stability of the magnet construction compared with a superconducting coil suspended around a horizontal bore. This coil stability comes even more into account when the magnet is up to field. Because of the high field strength, the coil develops massive forces that exert deformation effects on the magnet and its casing. Furthermore, supply and diversion of liquid nitrogen or helium for superconductive conditions can be achieved much more easily with this coil design. Because experimental MR scanners at field strengths of 9 T and higher are mainly used for both MRI and spectroscopy experiments, the vertical bore design is required to allow for investigation of fluids or objects in MR glass tubes. All these reasons for a constructor's choice of a vertical bore design of a high field scanner result in lower costs of such a scanner compared with a horizontal bore design.

Particularly in basic cardiovascular research, comprehensive information on hemodynamic effects of the murine upright body position is required to avoid misinterpretation of MR data. Because both cardiac geometry (e.g., LV volumes at systole and diastole) and function (represented by, e.g., stroke volume, cardiac output, or ejection fraction) are highly influenced by hemodynamic parameters such as preload, afterload, or heart rate, the consequences of prolonged orthostasis on the murine cardiovascular system have to be fully predefined before embarking on MR studies in transgenic mouse lines. This is a crucial prerequisite for an understanding of murine cardiac physiology and for a correct interpretation of findings in mice with potential pathologic phenotype.

Measurements of hemodynamic parameters can be achieved with high accuracy by high-fidelity micromanometer catheters (7). At present, these catheter tip transducers are available in different diameters down to 1.4 F and are typically inserted into either a carotid or femoral artery. For ventricular pressure registration, the catheter is advanced into the aorta and, after retrogradely passing through the aortic valve, is placed in the left ventricle.

In human physiology, orthostatic response to an upright body position is characterized by a vasomotor action aimed to maintain systemic vascular resistance or venous return, or both (8). However, in some individuals, standing still in an upright position can provoke a vasovagal (or orthostatic) syncope. The normal orthostatic response in humans after 10 min in the upright posture comprises a rise in heart rate of about 30% but constant blood pressure with increase of diastolic blood pressure of less than 5% and change of systolic blood pressure in either direction of less than 5%.

In our experiments, mice showed no significant changes of heart rate, systolic and diastolic LV pressure, or contractility and relaxation. These parameters re-

Table 1

Hemodynamic Parameters of C57B16/J Mice Anesthetized with Isoflurane (n = 6)

	Position	
	10 min Horizontal	10 min Vertical
Heart rate, min^{-1}	516 ± 29	514 ± 9
End-systolic pressure, mm Hg	111 ± 12	114 ± 11
End-diastolic pressure, mm Hg	5.6 ± 0.6	5.9 ± 0.4
dP/dt_{max}, mm Hg/sec	9041 ± 759	8854 ± 1090
dP/dt_{min}, mm Hg/sec	−10,034 ± 899	−9322 ± 840

None of the parameters measured differed significantly after changing from horizontal to vertical position.

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mained stable both in the first minutes of upright body position and during the follow-up time of 60 min in the vertical position. Particularly the absence of any alteration of LV end-diastolic pressure due to upright posture represents an important finding, because LV end-diastolic pressure is directly governed by preload and should therefore be the most sensitive parameter to a corresponding change of preload. One reason for the different degree of decline in central venous pressure and hence preload might come from the different size between humans and mice. Whereas the liquid column from toe to heart in humans is around 1 m (depending on the individuals height), it comprises only a few centimeters in the mouse. Therefore, even if the mouse is kept in a straight upright posture, the gravitational effects and hence effects on preload are to some extent smaller.

The cardiovascular reaction to tilting into the vertical position did not depend on the type of anesthesia. When mice were anesthetized with tribromethanol (9) instead of isoflurane, a similar transient decrease in LV systolic pressure was observed that returned to baseline rapidly. In addition, blood pressure and cardiac contractility were stable for at least 60 min in the vertical position (data not shown).

The findings of this study represent valuable information on murine cardiovascular physiology, because for studies of cardiac morphology and function in mice by high resolution MRI it typically takes 40 to 60 min to acquire all the data required. Interestingly, the duration of the upright posture is also crucial for the sensitivity of the clinical tilting test, because syncope in patients often occurs not early but after a time delay of more than 20 min (10,11).

In conclusion, we demonstrated an absence of hemodynamic changes and hence a normal response of mice to prolonged upright body position. However, due to minor changes of systolic pressure within the first few minutes after of upright body position, it is recommended that MR data acquisition is delayed until 8 to 10 min after the vertical positioning. We could show the stability of the measured hemodynamic parameters over a time period comparable with the typical scan time for murine cardiac MR studies. Therefore, high resolution MRI in mice performed on a vertical bore MR system allows the study of the murine cardiovascular phenotype under physiologic conditions.

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