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Ivabradine improves left ventricular twist and untwist during chronic hypertension☆

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ABSTRACT

Background: Left ventricular (LV) dysfunction develops during LV hypertrophy and particularly during tachycardia. Thus we investigated the effects of heart rate (HR) reduction with ivabradine, an I_f-channel blocker, on LV twist and untwist which represents myocardial deformation occurring during the overall systole and diastole and therefore provide valuable evaluation of global LV systolic and diastolic function.
Methods: Eight chronically instrumented pigs receiving continuous angiotensin II infusion during 28 days to induce chronic hypertension and LV hypertrophy. Measurements were performed at Days 0 and 28 after stopping angiotensin II infusion in the presence and absence of ivabradine.
Results: At Day 0, reducing HR from 75 ± 3 to 55 ± 2 beats/min with ivabradine did not affect LV twist but slowed LV untwist along with an increase in LV end-diastolic pressure. At Day 28, LV posterior and septal wall thickness as well as the estimated LV mass increased, indicating LV hypertrophy. LV twist and untwist were significantly reduced by 33 ± 4% from 16 ± 1° and 32 ± 6% from −154 ± 9°/s, respectively, showing global LV systolic and diastolic dysfunction. In this context, ivabradine decreased HR by 25% from 86 ± 5 beats/min and significantly improved LV twist from 11 ± 1 to 14 ± 1° and LV untwist from −104 ± 8 to −146 ± 5°/s.
Conclusions: Administration of ivabradine during chronic hypertension and LV hypertrophy improved LV twist and untwist. This further supports the beneficial effect of this drug on both LV systolic and diastolic function during the development of LV hypertrophy.

1. Introduction

The development of left ventricular (LV) hypertrophy is accompanied by abnormalities in left ventricular (LV) function and particularly during tachycardia [1]. Therefore heart rate (HR) reduction represents an attractive strategy to improve LV function in this setting. Using a model of chronic infusion of angiotensin II, we previously demonstrated the restoration of a normal profile for isovolumic contraction and relaxation by reducing HR with ivabradine [2]. However, these isovolumic periods do not reflect the whole cycle and represent only a small part of the overall cardiac cycle. Furthermore, these time periods are very difficult to assess in humans with the current clinical imaging approaches. For all these reasons and to provide stronger proofs for concluding that LV function can be improved by the HR reducing agent ivabradine, a more complete and simultaneous assessment of LV systolic and diastolic functions is needed.

Interestingly, LV twist and untwist are myocardial deformations that occur during the overall systole and diastole, respectively, which can be assessed in humans with echocardiography. They result from the helical LV myocardial fibers architecture [3] and represent respectively LV myocardial deformation during the systole and diastole [4]. In systole, the counter-coiled helix of subepicardial and subendocardial fibers generates rotation of the apex and base of the LV around LV longitudinal axis in opposite directions, resulting in LV twist [5]. LV untwist occurs during diastole before filling [6]. It is also an important component of the early diastolic LV filling [7] and contributes to the diastolic suction [8].

Accordingly, we investigated the effects of heart rate (HR) reduction induced by ivabradine, an I_f-channel blocker, on LV twist and untwist in a pig model of chronic hypertension. Ivabradine has the advantage that it does not modify atrioventricular or LV conduction and it is devoid of any intrinsic negative inotropic or lusitropic effects [9–12].

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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2. Methods

The experiments were agreed by the local animal ethical committee [ComEth AFSSA-ENVA-UPEC agreement #11-0059].

2.1. Surgical instrumentation and hemodynamic measurements

As previously described [1,2], eight female pigs (3 ± 1 months old Landrace Large White crossed, 22 ± 1 kg, Lebeau, Gambais, France) underwent left thoracotomy under anesthesia and were instrumented with fluid-filled Tygon catheters introduced in the aorta and left atrium. Three of these pigs were also included in a previous study [13]. A catheter was also inserted in the pulmonary artery for angiotensin II infusion. Six of them were instrumented with a solid-state pressure transducer inserted in the LV (P5A, Konigsberg Instruments, Pasadena, CA, USA) and an aortic flow probe (Transonic Systems Inc., Ithaca, NY, USA). Postoperative care was performed as previously described [1,2].

All hemodynamic data were recorded (1 kHz), digitized and analyzed using HEM v4.2 software (Notocord Systems, Croissy sur Seine, France). Aortic and left atrial pressures were measured with P23XL pressure transducers (Becton-Dickinson, Franklin Lakes, NJ, USA). Cardiac output was measured using a T206 blood flow-meter (Transonic Systems Inc., Ithaca, NY, USA). LV pressure was cross-calibrated with the left atrial and aortic pressures. The change in LV pressure over time (LV dP/dt) was computed from the LV pressure signal. LV end-diastole was defined as the initiation of the upstroke of LV pressure tracing after atrial contraction and indicated by the initial increase in LV dP/dt.

2.2. Echocardiographic data acquisition and analysis

Images were obtained using a Vivid 7 echocardiograph (GE Healthcare, Horten, Norway) with a 3.5-MHz transducer at high frame rates (range 68–80 frame/s). Care was taken to record the short-axis views at the same HR and acquisition frame rate. Videos were recorded in parasternal short-axis views (base, apex). Mitral valve leaflets identified the basal view and the apical view was defined by no papillary muscle visible and end-systolic obliteration. For all measurements, three consecutive cardiac cycles were stored digitally for blinded offline analysis (EchoPac 6.0, GE Healthcare). The LV mass was estimated from LV linear dimensions, acquired from the short-axis views [14].

2.3. Speckle tracking analysis

Speckle tracking analysis was performed offline using dedicated software (EchoPac, GE Medical Systems). LV rotation and rotational velocities were assessed from short-axis views at basal and apical levels. The total cycle time was measured from the start of the systole.

Rotation raw data derived from a single cardiac cycle were exported for analysis in specific data sheet (Excel, Microsoft Corp, Seattle, WA). To allow temporal analysis with isochronal points, the time sequence was normalized to total cycle time [15] and cubic interpolation was carried out (Burns et al., [16]). The onset and the end of the cardiac cycle represented respectively 0% and 100% of the total cycle time.

Next LV twist was calculated as the instantaneous difference between the maximum apical and basal rotations and was expressed in degrees [5]. The LV twisting rate and LV untwisting rate, which represents respectively the maximum velocity of the systolic and diastolic myocardial LV deformation were also calculated and expressed in degrees·s^{-1}. The extent of untwist during the isovolumic relaxation time (UT_{IVRT}) was also calculated. UT_{IVRT} was expressed as percentage of LV twist as follow: $UT_{IVRT} = 100 \times (\text{peak of twist} - \text{twist}_{MVO})/\text{peak of twist}$, where twist_{MVO} represented the LV twist at the mitral valve opening.

2.4. Protocol

All animals were studied four weeks after surgery (Day 0, body weight: 30 ± 1 kg) and after induction of hypertension by four weeks of continuous angiotensin II infusion at 30 ng/kg/min using an external portable peristaltic pump (Day 28, body weight: 34 ± 1 kg) [1,2]. Hemodynamic and echocardiographic measurements were carried out in animals lying in upright position in a sling with spontaneous breathing under sedation with intravenous injection of a mixture of ketamine (1.5 mg/kg), butorphanol (0.2 mg/kg) and diazepam (0.8 mg/kg). These measurements were performed at Day 0 in basal condition and after ivabradine infusion (1 mg/kg). At Day 28, measurements were performed 1 h after stopping the angiotensin II infusion in order to minimize the impact of changes in loading conditions, *i.e.*, to evaluate the intrinsic LV contractile properties and after ivabradine infusion (1 mg/kg). Each animal served as his own control.

2.5. Statistical analysis

Variables are expressed as mean ± SEM. Comparisons were performed using 2 way ANOVA for repeated measures followed by paired Student's *t*-test with Bonferroni correction if needed. Correlations were studied using linear regression and correlations between variables were tested by Pearson's coefficient correlation. Statistical analysis was performed using GraphPad Prism 6 (GraphPad Software, La Jolla, CA, USA). Statistical significance was fixed at $p < 0.05$.

3. Results

3.1. General hemodynamic and left ventricle characteristics

Administration of ivabradine significantly decreased HR (−27 ± 2% from 75 ± 3 beats/min at Day 0 *vs.* −25 ± 5% from 86 ± 5 beats/min at Day 28) (Fig. 1) (Table 1.). At Day 0 under ivabradine, HR was <60 beats/min. As a consequence, cardiac output was significantly reduced but stroke volume was slightly but significantly increased (Fig. 1). At Day 0 and Day 28, a significant increase in LV end-diastolic pressure was observed.

At Day 28, LV posterior (12.1 ± 0.2 mm at Day 28 *vs.* 5.7 ± 0.2 mm at Day 0) and septal (11.7 ± 0.2 mm at Day 28 *vs.* 5.4 ± 0.2 mm at Day 0) end-diastolic wall thickness, the estimated LV mass (157 ± 15 g at Day 28 *vs.* 74 ± 5 g at Day 0) and LV to body weight (4.6 ± 0.5 g/kg at Day 28 *vs.* 2.5 ± 0.1 g/kg at Day 0) significantly increased, suggesting LV hypertrophy as previously demonstrated in this experimental model [1].

3.2. LV twist

There was global systolic dysfunction after four weeks of chronic angiotensin II infusion as shown by significant reductions in LV twist (11 ± 1° at Day 28 *vs.* 16 ± 1° at Day 0) as well as its apical (7 ± 1° at Day 28 *vs.* 9 ± 1° at Day 0) and basal (−5 ± 1° at Day 28 *vs.* −8 ± 1° at Day 0) components. Twisting rate significantly raised but its extent was not sufficient to preserve LV twist (Fig. 2, upper panel).

At Day 0, administration of ivabradine altered neither LV twist with its apical and basal components nor twisting rate. At Day 28, administration of ivabradine improved LV systolic function as indicated by significant increases in LV twist (14 ± 1° under ivabradine *vs.* 11 ± 1° at baseline at Day 28) and its basal component (−6 ± 1° under ivabradine *vs.* −5 ± 1° at baseline at Day 28) without significant changes in twisting rate (Fig. 2, lower panel).

3.3. LV untwist

After four weeks of chronic angiotensin II infusion, LV untwist was significantly reduced as indicated by decreased LV untwisting rate (−104 ± 8°/s at Day 28 *vs.* −154 ± 9°/s at Day 0), UT_{IVRT} and LV untwisting velocity at mitral valve opening, showing LV diastolic dysfunction (Fig. 2, lower panel).

At Day 28, LV untwist was improved by ivabradine as indicated by increased LV untwisting rate (−146 ± 5°/s under ivabradine *vs.* −104 ± 8°/s at baseline at Day 28), UT_{IVRT} and LV untwisting velocity at mitral valve opening (Fig. 2, lower panel), noting that at Day 0, administration of ivabradine reduced all the three parameters of LV untwist (LV untwisting rate: −117 ± 7°/s under ivabradine *vs.* −154 ± 9°/s at baseline at Day 0).

3.4. Relationship between LV twist, untwist and heart rate

As shown in Fig. 3, no significant correlation was found between LV twist and different levels of HR with ivabradine both at Day 0 and Day 28 (Fig. 3, upper panel). In contrast, HR and LV untwisting rate were correlated when ivabradine was administered at Day 0 but this relationship was lost at Day 28 (Fig. 3, lower panel).

4. Discussion

The present study investigated the effects of ivabradine on LV twist and untwist during chronic hypertension and LV hypertrophy induced by four weeks of angiotensin II infusion. In hypertrophied hearts, ivabradine improved both LV systolic and diastolic functions as assessed by improved LV twist and untwist. These beneficial effects of ivabradine at Day 28 seemed not be related to HR reduction as there was no

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