Left Ventricular Adaptation to Acute Hypoxia: A Speckle-Tracking Echocardiography Study

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Background: Hypoxia depresses myocardial contractility in vitro but does not affect or may even improve indices of myocardial performance in vivo, possibly through associated changes in autonomic nervous system tone. The aim of this study was to explore the effects of hypoxic breathing on speckle-tracking echocardiographic indices of left ventricular function, with and without β_1-adrenergic inhibition.

Methods: Speckle-tracking echocardiography was performed in 21 healthy volunteers in normoxia and after 30 min of hypoxic breathing (fraction of inspired oxygen, 0.12). Measurements were also obtained after the administration of atropine in normoxia (n = 21) and after bisoprolol intake in normoxia (n = 6) and in hypoxia (n = 10).

Results: Hypoxia increased heart rate (from 68 ± 11 to 74 ± 9 beats/min, P = .001), without changing mean blood pressure (P = NS), and decreased total peripheral resistance (P = .003). Myocardial deformation magnitude increased (circumferential strain, −19.6 ± 1.9% vs −21.2 ± 2.5%; radial strain, 19.2 ± 3.7% vs 22.6 ± 4.1%, P < .05; longitudinal and circumferential strain rate, −0.88 ± 0.11 vs −0.99 ± 0.15 sec^{-1} and −1.03 ± 0.16 vs −1.18 ± 0.18 sec^{-1}, respectively, P < .05 for both; peak twist, 8.98 ± 3.2° vs 11.1 ± 2.9°, P < .05). Except for peak twist, these deformation parameters were correlated with total peripheral resistance (P < .05). Atropine increased only longitudinal strain rate magnitude (−0.88 ± 0.11 vs −0.97 ± 0.14 sec^{-1}, P < .05). The increased magnitude of myocardial deformation persisted in hypoxia under bisoprolol (P < .05). In normoxia, bisoprolol decreased heart rate (73 ± 10 vs 54 ± 7 beats/min, P = .0005), mean blood pressure (88 ± 7 vs 81 ± 4 mm Hg, P = .0027), without altering deformation.

Conclusions: Hypoxic breathing increases left ventricular deformation magnitude in normal subjects, and this effect may not be attributed to hypoxia-induced tachycardia or β_1-adrenergic pathway changes but to hypoxia-induced systemic vasodilation. (J Am Soc Echocardiogr 2013;26:736-45.)

Keywords: Left ventricular strain, Left ventricular function, Hypoxia, Myocardial deformation, Autonomic nervous system

Acute hypoxia may result from different situations, such as asphyxia and airway obstruction, and is associated with a rapid depletion in available oxygen at all tissue levels as well as in the myocardium. Hypoxia has been reported to decrease myocardial fiber contractility under in vitro experimental conditions[1,2] and in intact animal preparations,[3] but it does not affect[4,5] or even improves indices of myocardial performance, such as left ventricular (LV) ejection fraction (LVEF)[6] and cardiac output,[7] in vivo in human studies. The discrepancies between these in vivo and in vitro studies could be explained by hypoxia-associated sympathetic activation.[8-11] In addition to direct inotropic effects of catecholamines,[8] hypoxia-associated tachycardia[12] could in itself be a cause of increased contractility.[13,14] In addition, previous human studies have used echocardiography-derived LVEF measurements, which inherently have poor reproducibility and sensitivity to detect subtle changes in LV function.[15,16] Speckle-tracking echocardiography (STE) may overcome these limitations.[17]

We therefore explored in healthy volunteers the effects of acute hypoxic exposure on conventional echocardiographic and STE-derived measurements of LV function. To characterize the role of the sympathetic nervous system in the myocardial effects of hypoxia, we evaluated the effects of β-blockade on myocardial function in hypoxia.

We assessed the effects of atropine in normoxia to explore the possibility of a chronotropic-related myocardial effect.

METHODS

Study Population

Twenty-one participants (mean age, 27 ± 7 years) were studied in normoxia, in hypoxia, and in normoxia after atropine administration. In a second stage, 10 subjects (five of whom were new participants;

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This work was supported by Fonds Erasme, Université Libre de Bruxelles (Brussels, Belgium) (Dr. Dedobbeleer); Fonds Pour la Chirurgie Cardiaque (Brussels, Belgium) (Drs. Dedobbeleer and Unger); Fonds Docteur et Madame René Tagnon (King Baudouin Foundation, Brussels, Belgium) (Dr. Dedobbeleer); and Fondation M. Horlait-Dapsens King (Brussels, Belgium) (Dr. Dedobbeleer).

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0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2013.04.012

Abbreviations

BP = Blood pressure

GSCirS = Global left ventricular peak systolic circumferential strain

GSCirSR = Global left ventricular peak systolic circumferential strain rate

GSLS = Global left ventricular peak systolic longitudinal strain

GSLSR = Global left ventricular peak systolic longitudinal strain rate

GSRadS = Global left ventricular peak systolic radial strain

GSRadSR = Global left ventricular peak systolic radial strain rate

HR = Heart rate

LV = Left ventricular

LVEF = Left ventricular ejection fraction

PAP = Pulmonary arterial pressure

RV = Right ventricular

SaO_2 = Arterial oxygen saturation

STE = Speckle-tracking echocardiography

TPR = Total peripheral resistance

mean age, 26 ± 7 years) were studied in normoxia and in hypoxia under β-blockade, and six of these subjects were also studied in normoxia under β-blockade.

Inclusion criteria were as follows: age 20 to 40 years; normal results on physical examination, 12-lead electrocardiography, and standard echocardiography; and resting heart rate (HR) > 55 beats/min (>60 beats/min in the β-blocker substudy).

Exclusion criteria were contraindication to the use of atropine or bisoprolol, smoking, and physical training of >2 hours per week.

The study protocol was approved by our local ethics committee (P2009/304, P2010/270). All participants provided written informed consent.

Study Design

Normoxia, Hypoxia and Normoxia with Atropine (n = 21). *Normoxia and Normobaric Hypoxia.* The study was carried out as diagrammed in Figure 1. Comprehensive echocardiography and STE were performed in normoxia and after 30 min of hypoxic breathing. The hypoxic test was performed using a tightly adapted mask permitting inspiration of a mixture of 12% oxygen in nitrogen (Messer Belgium NV, Machelen, Belgium). This degree of hypoxia, corresponding to an altitude of 4,500 m, has been shown to be well tolerated, with minimal changes in P_{CO_2}.[18] HR, blood pressure (BP), arterial oxygen saturation (SaO_2) (Datex, Aartselaar, Belgium) and expired P_{CO_2} (PNT Digital; Medical Electronic Construction, Brussels, Belgium) were continuously monitored.

Echocardiography was performed in a stable state, after a plateau SaO_2 had been reached for ≥20 min. The maximal duration of the hypoxic test, including echocardiography, was 90 min.

Atropine Infusion in Normoxia. Imaging data were acquired in normoxia after an intravenous bolus (0.5 mg, with a maximum of 1 mg) of atropine (Sterop Laboratories, Brussels, Belgium), ≥1 hour after the hypoxic test, allowing the return to baseline of HR, SaO_2, and BP.

Hypoxia under β-blockade (n = 10) and Normoxia under β-blockade (n = 6). Echocardiographic measurements were obtained in normoxia without β-blockade and in hypoxia after administration of bisoprolol (a β_1-blocking agent with a minimal effect expected on total peripheral resistance (TPR)[19] in 10 subjects. Bisoprolol (Mylan SPRL, Overijse, Belgium) was administered at

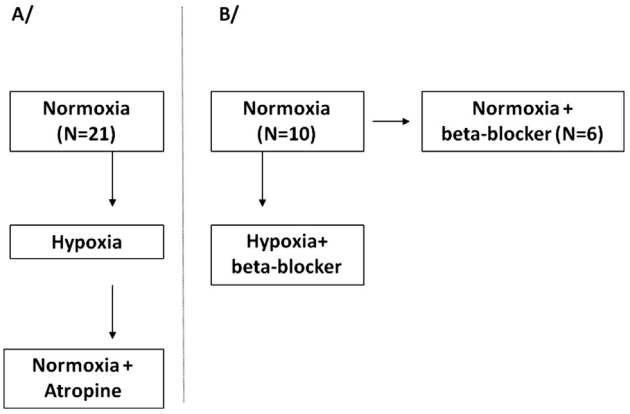

Figure 1 Study flowchart.

a dose of 5 mg/day for 48 hours. In a preliminary study, a higher dose of bisoprolol could not be used, because of the occurrence of lipothymia during hypoxia. In a second set of experiments in six subjects, the same echocardiographic measurements were obtained under β-blockade in normoxia.

Echocardiography

Images were acquired using an iE33 echocardiographic system (Philips Medical Systems, Andover, MA). LVEF and LV volumes were evaluated using the apical biplane method of disks.[20] LV stroke volume was calculated as LV stroke volume = Π × (LV outflow tract diameter/2)^2 × LV outflow tract velocity-time integral and was indexed to body surface area. TPR was estimated as TPR (Wood units) = mean BP/cardiac output.[21]

Mitral annular systolic velocity (mitral S wave) was obtained by spectral tissue Doppler and averaged from septal and lateral values. The LV myocardial performance (Tei) index was obtained from a single cardiac cycle using the following formula: [(interval between cessation and onset of the mitral inflow velocity−ejection time)/ejection time].[22] The ratio of isovolumic relaxation time to RR time interval was calculated as described by Huez *et al.*[7]

Right ventricular (RV) fractional area change, tricuspid annular plane systolic excursion, RV myocardial performance (Tei) index, myocardial isovolumic acceleration, and peak systolic velocity at the tricuspid valve (tricuspid S wave) were measured as previously described.[23] The transtricuspid pressure gradient was obtained using the Bernoulli equation using the peak velocity of the regurgitant jet. Systolic pulmonary arterial pressure (PAP) was calculated as the sum of the transtricuspid pressure gradient and the estimated right atrial pressure, on the basis of the collapsibility of the inferior vena cava.[24]

The mean PAP was calculated as 0.61 × systolic PAP + 2 mm Hg.[25] Pulmonary vascular resistance (Wood units) was calculated as [(peak velocity of the tricuspid regurgitant jet/RV outflow tract velocity-time integral) × 10 + 0.16].[26]

All Doppler measurements were averaged from three consecutive beats.

STE

Strain, strain rate, and LV twist parameters were analyzed offline using two-dimensional speckle-tracking echocardiographic software (QLAB Advanced Quantification Software version 7.1; Philips Medical Systems).