The impact of isometric handgrip testing on left ventricular twist mechanics

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Key points

- Left ventricular twist (LVT) results from rotation of the LV apex and base in opposite directions.
- Although LVT is altered in various cardiac diseases, physiological factors that affect LVT remain incompletely understood.
- In an experimental model involving healthy humans, isometric handgrip testing (IHGT) was performed to produce a clinically relevant form of LV afterload increase. The impact of IHGT on LV twist mechanics was assessed using speckle-tracking echocardiography.
- IHGT produced significant increase in systemic blood pressure and acute reduction in LV stroke volume. In this setting, LV apical rotation and LVT significantly decreased.
- Impairment of LV twist mechanics may in part underlie the LV dysfunction that can occur in the clinical context of acute increase in afterload.

Abstract Left ventricular (LV) rotation occurs due to contraction of obliquely oriented myocardial fibres. Left ventricular twist (LVT) results from rotation of the apex and base in opposite directions. Although LVT is altered in various cardiac diseases, physiological factors that affect LVT remain incompletely understood. Isometric handgrip testing (IHGT), a well-established laboratory-based technique to increase LV afterload, was performed for 3 min at 40% maximum force generation in healthy human subjects ($n = 18$, mean age 29.7 ± 2.7 years). Speckle-tracking echocardiography was used to measure LV volumes, LV apical and basal rotation, peak systolic LVT and peak early diastolic untwisting rate (UTR) at rest and at peak IHGT. IHGT led to significant increase in systemic blood pressure (systolic, 120.6 ± 9.7 *vs.* 155.6 ± 14.5 mmHg, $P < 0.001$; diastolic, 67.5 ± 6.4 *vs.* 94.1 ± 21.1 mmHg, $P < 0.001$) and LV end-systolic volume (44.2 ± 7.8 *vs.* 50.5 ± 10.8 ml, $P = 0.005$), as well as a significant increase in heart rate (62.8 ± 11.7 *vs.* 84.7 ± 13.8 beats min^{-1}; $P < 0.001$). IHGT produced a significant acute reduction in LV stroke volume (63.9 ± 12.0 *vs.* 49.4 ± 7.8 ml, $P < 0.001$). In this setting, there was a significant decrease in peak systolic apical rotation (11.9 ± 3.0 *vs.* 8.6 ± 2.2 deg, $P < 0.001$) and a resultant 25% decrease in peak systolic LVT (16.6 ± 2.8 *vs.* 12.5 ± 2.8 deg, $P < 0.001$). The magnitude of peak early diastolic UTR did not change (-114.5 ± 26.4 *vs.* -110.6 ± 39.8 deg s^{-1}, $P = 0.71$). Peak systolic apical rotation and LVT decrease during IHGT in healthy humans. This impairment of LV twist mechanics may in part underlie the LV dysfunction that can occur in the clinical context of acute increase in afterload.

Introduction

Left ventricular (LV) rotation occurs due to contraction of obliquely oriented myocardial fibres and is characterized by rotation of the apex and base in opposite directions (Streeter *et al.* 1969; Sengupta *et al.* 2008). When viewed from the apical perspective, there is counterclockwise rotation of the apex and clockwise rotation of the base around the LV long axis. The apex-to-base difference in LV rotation is LV twist (LVT) (Mor-Avi *et al.* 2011). Although the importance of LVT in the settings of human performance (exercise) and cardiovascular disease is recognized (Stuber *et al.* 1999; Takeuchi *et al.* 2007; Sade *et al.* 2008; Stohr *et al.* 2011), physiological factors that affect LVT remain incompletely understood (Russel *et al.* 2009). Speckle-tracking echocardiography (STE) has emerged as a technology to make the study of LVT more accessible and feasible, and compares favourably to the reference standard of cardiac magnetic resonance imaging (Helle-Valle *et al.* 2005; Notomi *et al.* 2005).

Using STE, we previously demonstrated that LVT is a preload-dependent phenomenon in healthy humans (Weiner *et al.* 2010*a*). In terms of afterload dependence, animal studies consistently demonstrate that an acute increase in afterload results in decreased LVT (Gibbons Kroeker *et al.* 1995; MacGowan *et al.* 1996; Dong *et al.* 1999). In contrast, limited human data derived from the study of transplanted hearts suggest that LVT may not be affected by acute afterload manipulations (Hansen *et al.* 1991; Moon *et al.* 1994). More recently, a human investigation showed that nitroprusside infusion resulted in an increase in LVT (Park *et al.* 2010) and similar results were observed in children after interventional treatment of coarctation of the aorta (Laser *et al.* 2009).

To our knowledge, the impact of acute afterload increase on LVT in healthy human hearts has not been previously studied. Isometric handgrip testing (IHGT) produces an increase in mean arterial pressure (Hayashi *et al.* 1991) and thereby represents a safe and feasible method of imparting an acute increase in LV afterload. We hypothesized that the afterload challenge inherent in IHGT would result in a significant decrease in LVT. To assess this hypothesis, we utilized STE to study LV mechanics in healthy human subjects performing IHGT.

Methods

Ethical approval and study population

Healthy subjects were recruited from a hospital-wide email distribution advertisement at the Massachusetts General Hospital. Subjects were eligible if they were between ages 18 and 45 years and had a body mass index (BMI) of 18–29 kg m^{-2}. Exclusion criteria included any condition thought to impact ventricular function including but not limited to a history of myocardial infarction, coronary heart disease, cardiomyopathy, hypertension, aortic stenosis, valvular regurgitation greater than mild in severity or significant prior exercise training. Ethical approval for this study conformed to the standards of the *Declaration of Helsinki*. The study protocol was approved by the Partners Healthcare Institutional Review Board before study initiation. Written informed consent was obtained from all subjects.

Clinical assessment

The following clinical data were obtained on all subjects: age (years), height (m), weight (kg), and current/past medication use. Body surface area (BSA) was calculated using the Mosteller formula (Mosteller, 1987). Initial blood pressure was measured using a mercury column sphygmomanometer and an appropriately sized blood pressure cuff with the subject in the supine position after at least 10 min of quiet rest (at the completion of baseline echocardiography).

Experimental model for afterload increase

IHGT is a well-established laboratory-based technique to increase mean arterial pressure, heart rate, and muscle sympathetic nerve activity (Seals *et al.* 1991; Fu *et al.* 2002). IHGT was chosen as the haemodynamic perturbation in this study for logistical and scientific reasons. First, our inclusion of healthy humans imposes logistical limitations with regard to the invasiveness and manipulation that can be rightfully imposed on the subjects. IHGT is a safe, feasible, and validated method to produce acute after-load challenge and was therefore the perturbation used in this study. Second, IHGT is similar to the physiological afterload challenge that humans encounter clinically, in either exercise training (Lepley *et al.* 2010) or disease states (Rajagopal *et al.* 2007; Shingu *et al.* 2009).

In the current study, IHGT was performed using a commercially available digital hand-held dynamometer (North Coast Medical, Gilroy, CA, USA). To determine the maximum force generation, each subject performed three repetitive 1 s maximum-effort handgrip tests with the hand-held dynamometer in the right hand. The average value of the three maximum grip strength tests was computed and reported in newtons. In the situation where one of the three maximal efforts deviated from the peak effort by more than 25%, this value was excluded and the mean was derived from the remaining two values. Each subject then performed an endurance hand grip test at 40% maximum effort for a period of 3 min. This effort intensity was chosen in order to maximize fatigue but also to increase the likelihood that subjects would maintain the target effort level for the 3 min period and levels of

sustained IHGT force above 40% maximum have not been shown to result in additional increases in blood pressure (Seals *et al.* 1993). The individualized target force and real-time measurement of instantaneous force generation were displayed on a computer monitor to guide the 3 min effort. Subjects were instructed to breath regularly during IHGT to prevent effort-associated Valsalva physiology. Blood pressure and heart rate were measured every 1 min during IHGT and for 3 min into the recovery period. Echocardiography, as described below, was performed at rest prior to IHGT and during the peak-IHGT period, which was defined as the final minute of IHGT.

Standard two-dimensional echocardiography

Transthoracic echocardiography was performed using a commercially available system (Vivid-I, GE Healthcare, Milwaukee, WI, USA) with a 1.9–3.8 mHz phased-array transducer. Subjects were studied after >5 min of quiet rest at baseline and again during the final 1 min of the 3 min IHGT. Two-dimensional (2D), pulsed-Doppler and colour tissue Doppler imaging were performed from standard parasternal and apical positions with 2D frame rates of 60–100 frames s^{-1} and tissue Doppler frame rates >100 frames s^{-1}. For each subject we aimed to use the same frame rate for apical and basal 2D short-axis images to facilitate subsequent rotational analysis with STE. The peak-IHGT imaging protocol included the following: 2D parasternal short axis (base and apex), 2D apical four-chamber, pulsed-Doppler of mitral inflow and LV outflow tract, and tissue Doppler at the lateral and septal mitral annulus. All data were stored digitally, and off-line data analysis was performed (EchoPac, v. 7, GE Healthcare).

Cardiac parameters were measured in accordance with current guidelines (Lang *et al.* 2005). LV end-diastolic volume, LV end-systolic volume and LV ejection fraction were calculated from planar tracings of the LV end-ocardial border in the apical four-chamber view. LV length was measured in the apical four-chamber view and was defined as the end-diastolic length from the mitral valve hinge point plane to the most distal end-ocardium at the LV apex. Stroke volume was calculated as cross-sectional area$_{LVOT}$ × VTI$_{LVOT}$, where cross-sectional area $= \pi(\mathrm{radius}_{LVOT})^2$, LVOT is left ventricular outflow tract, and VTI is velocity–time integral. Cardiac output was calculated as the product of stroke volume and heart rate. Resting heart rates were obtained from the final loop of the resting echocardiogram and peak heart rate was defined as the highest heart rate during an image obtained during peak IHGT. Aortic valve opening/closure and mitral valve opening were measured from pulsed-wave Doppler images.

Peak systolic, early diastolic and late diastolic tissue velocities were obtained at the basal septal and lateral mitral annulus and were measured off-line from two-dimensional colour-coded tissue Doppler images and are reported as the average of three consecutive cardiac cycles. Longitudinal systolic strain measurements were made using speckle tracking analysis in the apical four chamber view, and the mean from six myocardial segments (basal septum, mid septum, apical septum, apical lateral, mid lateral and basal lateral) was reported.

Left ventricular rotation, twist and untwisting rate

For the purpose of LV rotation assessment, short-axis imaging standardization within and across subjects was maximized using the following criteria (Weiner *et al.* 2010*a,b*). The basal level was defined as the highest basal imaging plane at which uniform full thickness myocardium was observed surrounding the mitral valve at end-systole. As the location of apical imaging acquisition has been shown to confer significant variability in the measurement of apical rotation (van Dalen *et al.* 2008), we carefully standardized apical imaging. Specifically, from multiple apical acquisitions distal to the papillary muscles, the apical level was chosen as the imaging plane with no visible papillary muscles that most closely approximated an end-diastolic ratio of LV cavity diameter to total LV diameter (cavity + wall thickness) of 0.5 (Weiner *et al.* 2010*a,b*).

Speckle tracking analysis was used to measure LV rotation, LV twist (LVT) and untwisting rate (UTR). The highest-quality 2D basal and apical images that met the above pre-specified criteria were selected and the end-ocardium was traced. A full thickness myocardial region of interest (ROI) was selected. The software automatically segmented the LV short axis into six segments and selected suitable speckles for tracking. The reliability of tracking was confirmed by the reliability parameter of the system (V = valid tracking; X = unacceptable tracking). When the software signalled poor tracking efficiency, the observer readjusted the endocardial trace line and/or ROI width until an acceptable tracking score could be obtained. LV rotation at the basal and apical short-axis planes was determined as the average angular displacement of six myocardial segments. Curves of basal and apical LV rotation, LVT and UTR were automatically generated by the software (EchoPac, v. 7, GE Healthcare). Peak systolic LVT was calculated as the maximum instantaneous difference between peak systolic apical and basal rotation. The timing of peak systolic LVT was determined as a percentage of the systolic ejection period. Peak early diastolic UTR was defined as the peak untwisting velocity occurring in early diastole. The magnitude and timing of peak basal UTR and peak apical UTR were recorded

Table 1. Baseline (resting) subject characteristics and echocardiographic measurements

Height (m)	1.7 + 0.1
Weight (kg)	73.7 ± 9.3
Body surface area (m^2)	1.9 ± 0.2
Systolic blood pressure (mmHg)	120.6 ± 9.7
Diastolic blood pressure (mmHg)	67.5 ± 6.4
Heart rate (beats min^{-1})	62.8 ± 11.7
LV length (mm)	79.6 ± 0.5
LV end-diastolic volume (ml)	110.8 ± 20.1
LV end-systolic volume (ml)	44.2 ± 7.8
End-diastolic LV internal diameter (mm)	48.1 ± 3.2
Interventricular septum thickness (mm)	8.3 ± 1.0
Posterior wall thickness (mm)	8.5 ± 0.9
LV mass (g)	147.3 ± 22.7
Left atrial anterior-posterior dimension (mm)	34.0 ± 2.3

Data presented as means ± SD.

from the untwisting curves. The time difference between peak basal UTR and peak apical UTR was calculated as: time peak basal UTR – time peak apical UTR. Therefore, a *negative* value indicates that peak apical UTR occurred *after* peak basal UTR and *positive* value that peak apical UTR occurred *before* peak basal UTR. LV rotation, LVT and UTR are reported as absolute values. Intra- and inter-observer variability in our laboratory for LV rotation, peak systolic LVT and peak early diastolic UTR have been previously examined and published (Weiner *et al.* 2010a,b).

Statistical analysis

Measurements are presented as means ± standard deviations. Differences in physiological variables during IHGT were assessed using repeated measures ANOVA.

Baseline and peak-IHGT measurements were assessed for normality using the Shapiro–Wilk test and comparisons were then performed using Student's paired *t* test for continuous variables. A *P* value of <0.05 was considered significant.

Results

Subject characteristics and structural echocardiographic measurements

Twenty-two subjects completed the full protocol. Four subjects were excluded for technical factors that precluded complete LV rotation and LVT/UTR analysis: 2D image quality not adequate for STE at peak-IHGT ($n = 2$); frame rate differences between rest and peak-IHGT ($n = 1$); and dislodgement of ECG electrodes at peak-IHGT ($n = 1$). Therefore, 18 subjects (male = 15, female = 3) aged 29.7 ± 2.7 years were included in the final analysis. Baseline (resting) subject characteristics and echocardiographic measurements are shown in Table 1. All individuals had resting vital signs that were within normal limits and had structurally normal hearts. No subjects were taking prescription medications at the time of the study.

Effects of isometric handgrip testing

Cardiac and haemodynamic parameters. One-second maximal force IHGT and 3 min of sustained IHGT at 40% maximum effort was successfully completed in all 18 subjects used in the analysis. The mean right hand maximum force generation was 397.7 ± 89.0 N. The blood pressure response to IHGT was similar in each subject. Specifically, systolic and diastolic blood pressures increased throughout the IHGT period (Fig. 1) with a significant increase in the mean values of systolic
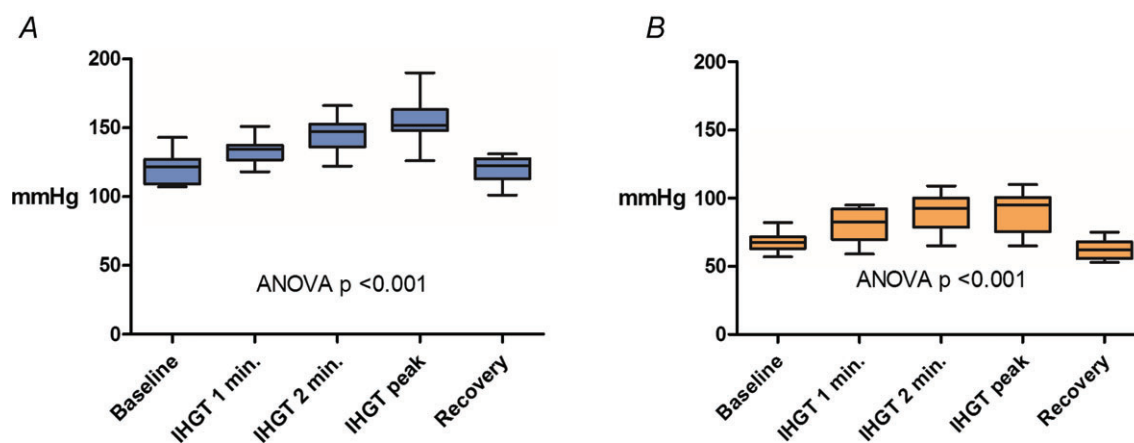

Figure 1 Blood pressure response during isometric handgrip testing
A, systolic blood pressure response during isometric handgrip testing. *B*, diastolic blood pressure response during isometric handgrip testing. IHGT: isometric handgrip testing. Box: mean ± 1 SD; whiskers: 5 and 95% confidence intervals.

(120.6 ± 9.7 *vs.* 155.6 ± 14.5 mmHg, $P < 0.001$) and diastolic (67.5 ± 6.4 *vs.* 94.1 ± 21.1 mmHg, $P < 0.001$) blood pressure when resting and peak IHGT values were compared. After completion of IHGT, blood pressures returned to baseline values by 3 min. Heart rate also increased significantly with IHGT (62.8 ± 11.7 *vs.* 84.7 ± 13.8 beats min; $P < 0.001$). There was no change in LV length (8.0 ± 0.5 *vs.* 8.0 ± 0.4 cm; $P = 0.95$) and LV end-diastolic volume (110.8 ± 20.0 *vs.* 110.0 ± 18.1 ml; $P = 0.79$). Consistent with increased afterload, LV end-systolic volume increased (44.2 ± 7.8 *vs.* 50.5 ± 10.8; $P = 0.005$) at peak-IHGT. This led to a significant decrease in stroke volume (63.9 ± 12.0 *vs.* 49.4 ± 7.8; $P < 0.001$; Fig. 2). The decrease in stroke volume and concomitant increase in heart rate resulted in no significant change in cardiac output (3.9 ± 0.5 *vs.* 4.2 ± 0.7 l min^{-1}; $P = 0.27$).

Systolic function. Baseline and peak-IHGT measures of systolic function are reported in Table 2. The increase in LV end-systolic volume with IHGT resulted in a decrease in LV ejection fraction, although the values at baseline and peak-IHGT are both considered within normal limits. Reductions in complementary measures of systolic function (peak systolic tissue velocity [S_m], longitudinal strain, and longitudinal strain rate) were also observed at peak-IHGT.

Diastolic function. IHGT produced relative diastolic dysfunction as evidenced by consistent changes in numerous complementary parameters of diastolic function (Table 2). Specifically, we observed reductions in early trans-mitral filling (E-wave) and tissue relaxation (E_m) velocities. This was accompanied by compensatory augmentation of late diastolic filling (A-wave) and tissue relaxation (A_m) velocities.
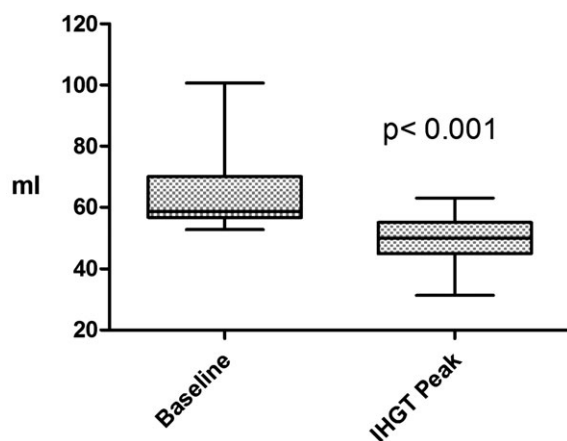

Figure 2. Stroke volume decreased with isometric handgrip testing
IHGT: isometric handgrip testing. Box: mean ± 1 SD; whiskers: 5 and 95% confidence intervals.

Table 2. Comparison of LV functional parameters at baseline and at peak isometric handgrip testing

	Baseline	Peak-IHGT	*P* value
Systolic function			
LV ejection fraction (%)	59.9 ± 3.1	54.3 ± 4.2	<0.001
LV peak lateral S_m (cm s^{-1})	7.4 ± 1.6	6.1 ± 1.2	<0.001
Longitudinal strain (%)	−20.6 ± 2.9	−18.2 ± 3.2	0.005
Longitudinal strain rate (% s^{-1})	−1.31 ± 0.2	−1.17 ± 0.2	0.01
Diastolic function			
Transmitral E-wave (cm s^{-1})	80.6 ± 15.3	70.0 ± 15.4	<0.001
Transmitral A-wave (cm s^{-1})	39.9 ± 8.0	55.2 ± 10.0	<0.001
E/A ratio	2.1 ± 0.6	1.3 ± 0.3	<0.001
E_m basal septum (cm s^{-1})	−9.7 ± 1.1	−7.7 ± 1.4	<0.001
A_m basal septum (cm s^{-1})	−5.2 ± 1.0	−6.7 ± 1.2	0.001
E_m basal lateral LV (cm s^{-1})	−12.0 ± 1.7	−8.7 ± 1.8	<0.001
A_m basal lateral LV (cm s^{-1})	−3.6 ± 1.3	−4.5 ± 1.6	0.03

A_m: late diastolic peak tissue velocity; E_m: early diastolic peak tissue velocity; IHGT: isometric handgrip testing; S_m: systolic peak tissue velocity.

Left ventricular rotation, twist, and untwisting rate. There was no significant change in LV length when rest was compared to peak-IHGT. Therefore, LV length correction did not change the findings and LV length-indexed values are not reported. Since correction for the increase in heart rate at peak-IHGT only intensified the results, raw values are reported due to the preference to report metrics that are familiar to the scientific community. Absolute values of LV rotation, LVT and untwisting parameters are detailed in Table 3. There was a significant 28% decrease in peak systolic apical rotation at peak-IHGT (Fig. 3*A*). In contrast, basal rotation was unchanged at peak-IHGT (Fig. 3*B*). This translated into a 25% reduction in peak systolic LVT (Fig. 4). Peak systolic LVT occurred earlier in the systolic ejection period due to peak systolic apical rotation occurring earlier at peak IHGT.

Unlike peak systolic LVT, peak early diastolic UTR did not significantly decrease at peak-IHGT. However, the relative timing of peak apical UTR and peak basal UTR changed with the haemodynamic perturbation. Specifically, apical UTR under resting conditions occurred after basal UTR (a negative value in Table 3) while at peak-IHGT apical UTR occurred before basal UTR (a positive value in Table 3; Fig. 5).

Discussion

We examined the impact of isometric handgrip testing on LV mechanics including LV rotation, LV twist (LVT) and LV untwisting rate (UTR). IHGT produced acute LV afterload increase as evidenced by increases in systemic blood pressure and LV end-systolic volume. In this context,

Table 3. Comparison of left ventricular rotation, twist, and untwisting at rest and at peak isometric handgrip testing

|	Baseline	Peak-IHGT	*P* Value
Systolic parameter			
Peak apical rotation (deg)	11.9 ± 3.0	8.6 ± 2.2	<0.001
Time to peak apical rotation (% SEP)	98.4 ± 2.7	93.8 ± 6.3	0.007
Peak basal rotation (deg)	-5.3 ± 2.3	-4.5 ± 2.6	0.19
Peak LVT (deg)	16.6 ± 2.8	12.5 ± 2.8	<0.001
Time to peak LVT (% SEP)	97.4 ± 2.7	93.9 ± 6.2	0.03
Diastolic parameter			
Peak apical UTR (deg s$^-$)	-85.8 ± 30.0	-81.9 ± 37.7	0.71
Peak basal UTR (deg s$^-$)	47.5 ± 25.2	55 ± 27.1	0.36
Time difference between peak apical and basal UTR (ms)	-37.6 ± 41.9	25.9 ± 28.9	<0.001
Peak UTR (deg s$^-$)	-114.5 ± 26.4	-110.6 ± 39.8	0.71

IHGT: isometric handgrip test; LVT: left ventricular twist; SEP: systolic ejection period; UTR: untwisting rate.

peak systolic apical rotation occurred earlier in the systolic ejection period and was decreased in magnitude. This resulted in a significant decrease in peak systolic LVT thus confirming the hypothesis that LVT is decreased in the setting of IHGT-mediated acute LV afterload increase.

Prior animal studies have demonstrated that manipulation of loading conditions influences the twisting motion of the heart (Gibbons Kroeker *et al.* 1995; MacGowan *et al.* 1996; Dong *et al.* 1999). Specifically, the afterload dependence of LVT was studied by magnetic resonance imaging in 10 isolated, blood perfused, ejecting canine hearts while preload was kept constant. Between low and high afterloads, there was a significant reduction in LVT (MacGowan *et al.* 1996). Similar results, namely a reduction in LVT with acute increase in LV afterload, were obtained from other elegant animal work (Dong *et al.* 1999).

Initial data characterizing the relationship between changes in acute loading conditions and LVT in human hearts suggest that LVT may not be afterload dependent. These studies included humans in whom radio-opaque beads had been inserted at the time of cardiac transplantation and no effect of methoxamine-induced afterload changes on LVT was found (Hansen *et al.* 1991; Moon *et al.* 1994). The study of heart transplant patients introduced several potential complicating factors including the use of fluoroscopic imaging to measure rotation/twist, altered innervation of transplanted hearts, and the lack of an intact pericardium (Tanaka *et al.* 2008). In contrast, more recent human studies have investigated the impact of a reduction in LV afterload, either with nitroprusside infusion (Park *et al.* 2010) or catheterization-based intervention for aortic coarctation (Laser *et al.* 2009), and document an increase in LVT with the decrease in afterload.

To our knowledge, our study is the first to examine the effect of IHGT-mediated acute afterload increase on LVT in healthy native human hearts. We have demonstrated a decrease in the magnitude of LV apical rotation and LVT with IHGT. Factors such as changes in LV geometry and intrinsic muscle fibre function may provide explanations for the mechanisms underlying the decreased LVT observed with IHGT. First, it has been shown that LVT is related to volume changes (as estimated by radial shortening) during ejection in canine hearts and that LVT is linearly related to volume during ejection (Beyar *et al.* 1989). There was an increase in end-systolic volume and a decrease in LV stroke volume at peak-IGHT in our study, thereby explaining some of the observed decrease in LVT. Second, fundamental muscle fibre physiology must be considered. It is well established that muscle fibres operate optimally when close to an ideal length (often their resting length) and that when stretched or shortened, generate less shortening and contractile force (Gordon *et al.* 1966). It is possible that IHGT altered myocardial fibre length sufficiently to impair function.
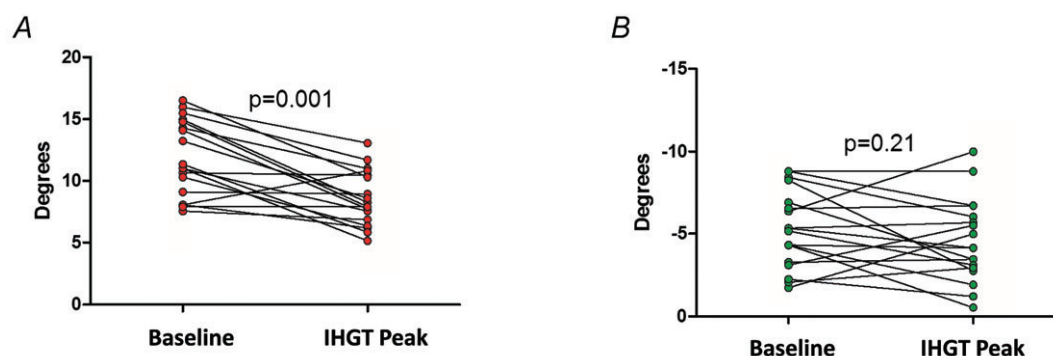
Figure 3 Left ventricular rotation and isometric handgrip testing
A, apical rotation decreased with isometric handgrip testing. *B*, there was no significant change in basal rotation with isometric handgrip testing. IHGT: isometric handgrip testing.
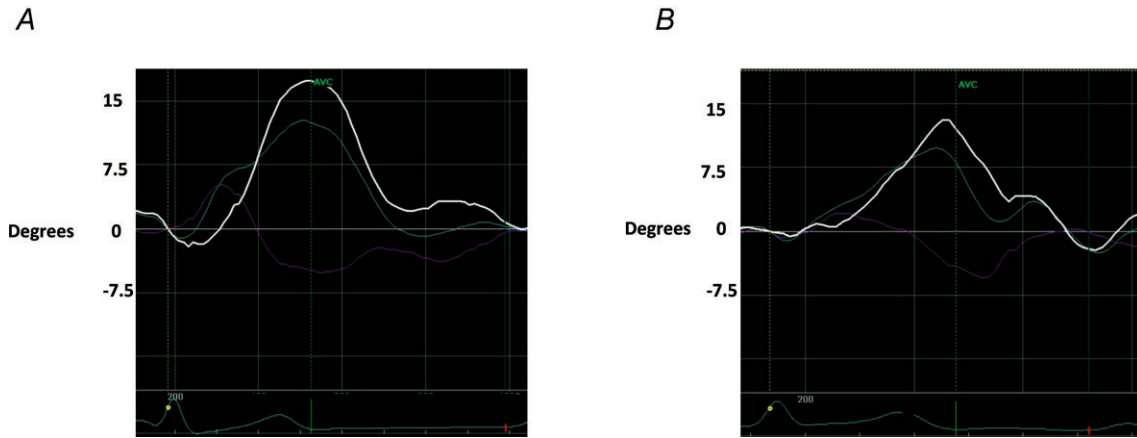
A   B

Figure 4 Representative example of left ventricular rotation and twist curves
A, representative example of left ventricular twist (LVT) *versus* time curve at rest. B, LVT *versus* time curve from the same study subject at peak isometric handgrip testing, demonstrating reduced apical rotation (light blue curve) and LVT (white curve). Peak systolic apical rotation and LVT both occur earlier in the systolic ejection period at peak afterload. Light blue curve: apical rotation; pink curve: basal rotation; white curve: twist; AVC: aortic valve closure.

Our finding that IHGT did not significantly reduce peak early diastolic UTR is somewhat unexpected. This finding suggests that IHGT produces an 'uncoupling' of systolic rotation/twist and diastolic untwisting. Previous investigations by our group (Weiner *et al.* 2010a,b), have demonstrated significant correlations between changes in LVT and UTR in response to haemodynamic stressors. Although precise mechanisms explaining this uncoupling observed in response to IHGT remain speculative, changes in the relative timing of peak apical and basal UTR may
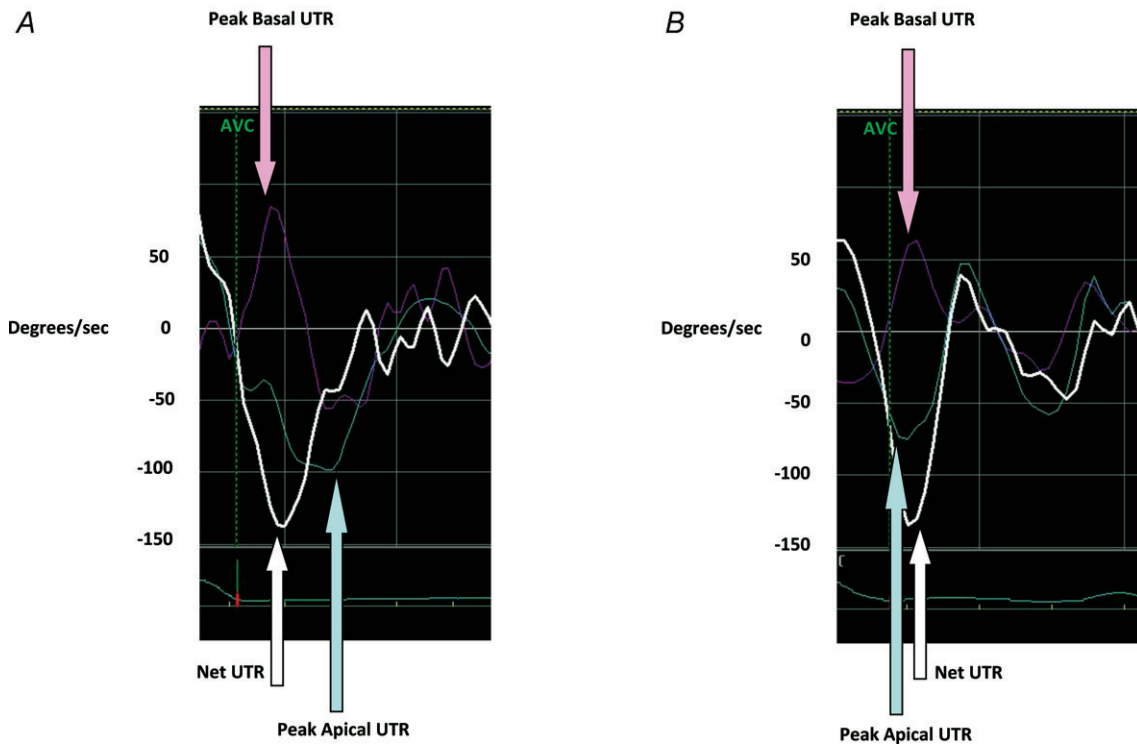

Figure 5. Representative example of untwisting rate (UTR) curves
A, at rest, peak apical UTR (light blue arrow) occurs after peak basal UTR (pink arrow). B, at peak isometric handgrip testing, peak apical UTR has shifted to the left (light blue arrow) and now occurs before peak basal UTR (pink arrow). This 'left-shift' of peak apical UTR, presumably the result of earlier termination of peak systolic apical rotation, leads to more synchronized apical and basal UTR with resultant preservation of net UTR. AVC: aortic valve closure; UTR: untwisting rate.

be explanatory. At rest, peak apical UTR occurs after peak basal UTR. In contrast, at peak-IHGT, peak apical UTR occurs earlier in diastole such that it occurs before peak basal UTR (Fig. 5). This 'left-shift' of peak apical UTR, presumably the result of pressure mediated, earlier termination of peak systolic apical rotation, leads to more synchronized apical and basal UTR with resultant preservation of net UTR. Untwisting may therefore serve as a relatively volume-independent index of relaxation since peak untwisting is normalized by the increased intraventricular pressure produced by IHGT. The fact that IHGT produced an increase in heart rate warrants mention in the context of interpreting a time-dependent parameter such as UTR. However, when corrected of heart rate (i.e. UTR/heart rate), the findings did not change.

There are several distinct implications of our findings. First, the present study is the initial *in vivo* assessment of LV twist mechanics in response to IHGT in healthy human hearts. Our results, consistent with previous animal work, demonstrate that IHGT-mediated acute LV afterload increase reduces apical rotation and LVT. This observation may provide an important mechanistic explanation for the clinically relevant LV dysfunction that can occur in the context of acute increases in LV afterload (Vlcek *et al.* 2008). Further studies examining the human myocardial response to IHGT in cardiomyopathic disease states are warranted and ongoing by our group. Second, our study provides an example of uncoupling of LVT and UTR characterized by decreased LVT but relative preservation of early diastolic UTR. We demonstrate that changes in the relative timings of apical and basal twist mechanics are explanatory. This may represent a compensatory mechanism by which the myocardium is able to preserve untwisting properties in the face of acute haemodynamic stress. Third, the current study highlights a potential important difference between the effects of acute and chronic LV afterload increase. Prior studies of LV twist mechanics indicate that LVT is increased in chronic high afterload conditions (Stuber *et al.* 1999; Nagel *et al.* 2000; Sengupta *et al.* 2008). Thus, it appears that initial pressure-mediated decline in LVT may ultimately transition to an adaptive increase in LVT if elevated afterload is sustained.

Study limitations

We evaluated young, healthy subjects. This limits the generalizability of our findings to specific cardiac disease states and to older subjects (Notomi *et al.* 2006). Second, we did not use invasive techniques to measure LV afterload. However, the observed increase in systemic blood pressure and LV end-systolic volume is consistent with IHGT serving as an effective method of augmenting LV afterload. Third, we acknowledge that IHGT does not produce an isolated increase in LV afterload given that heart rate increase and heightened sympathetic nervous system activity are also part of the integrated physiological response. However, both increases in heart rate and contractility (result of increased sympathetic tone) are known to *increase* the magnitude of LVT (Dong *et al.* 1999). Thus, our finding of decreased LVT despite increased heart rate only emphasizes the negative impact of acute afterload on LV apical rotation and LVT. Fourth, we recognize that normalizing LV twist by the ratio of the distance between basal and apical imaging planes to the radius of the LV may assist in comparing LV twist measurements across studies. However, variability produced when attempting to identify the same LV plane in the apical four-chamber and short-axis views did not allow us to normalize our data in this fashion.

Conclusions

Our results indicate that peak systolic apical rotation and LVT are decreased in response to IHGT-mediated LV afterload challenge in the healthy human heart. Defining the impact of IHGT on myocardial twist mechanics in the healthy heart serves as the foundation for future studies examining its impact in the settings of human exercise performance and cardiomyopathic disease states.

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Author contributions

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