CARDIAC STRAIN DURING UPRIGHT CYCLE ERGOMETRY IN ADOLESCENT
MALES

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Running Head: Cardiac Strain During Exercise

Abstract

Little evidence exists with regard to changes in cardiac strain that occur during submaximal exercise in young males. The aims of the study were to evaluate the changes that occur in longitudinal (L), radial (R) and endocardial circumferential (EC) strain during submaximal upright cycle ergometry and to examine the test-retest reproducibility of these measurements. Fourteen recreationally active, adolescent (age: 17.9 ± 0.7 years), males volunteered for the study. All subjects underwent an incremental (40W) submaximal cycle ergometer test. L, R, and EC strain values were obtained using speckle tracking, from two-dimensional B-mode images of the left ventricle (LV) during rest and the initial stages of submaximal exercise (40W and 80W). The average of 6 LV segments was used to determine both peak wall deformation (%) and the time to peak deformation (ms). There was a statistically ($P<0.05$) significant increase from rest to submaximal exercise for peak deformation for L, R and EC strain. There was a statistically significant ($P<0.05$) decrease from rest to submaximal exercise for time to peak for L and R and EC strain and between submaximal workloads for time to peak for L strain and EC strain. Coefficients of variation demonstrated reproducibility for upright strain and strain rate measurements similar to published supine measurements. This study has demonstrated that changes in left ventricular wall deformation (L, R and EC strain) that occur during the transition from rest to submaximal exercise can be reliably measured and confirm that a healthy left ventricle has a hyperdynamic response to exercise.

KEY WORDS: Regional, Myocardial, Function, Exercise, Adolescents

Introduction

Quantification of regional planes of movement of the myocardium were originally derived from tissue Doppler technology and permitted the first calculations of regional displacement (strain) and rate of displacement (strain rate).[1] . This technique has been largely superseded by speckle tracking echocardiography,[2] which has the advantages of not being affected by translation or tethering of adjacent segments and minimally affected by angle of insonation in standard views[3,4].   Myocardial mechanics can be measured in multiple planes, with longitudinal, radial and circumferential strains standardized and shear planes still under investigation. Application of speckle-tracking derived strain and strain rate data have been proven to be useful for the assessment of systolic function in individuals with cardiovascular disease[5] and to evaluate regional wall motion during strenuous acute exercise[6].

To date, almost all of the investigations into the pattern of left ventricular strain changes during exercise has been limited to supine and semi-supine exercise[7,8]. Increases in systolic longitudinal strain have been noted from rest to exercise, but with no subsequent change with increasing exercise intensity, whereas, circumferential strain continued to increase with increasing exercise intensity[8]. In the one study in which the subjects exercised in an standing treadmill protocol Reuss et al.,[9] demonstrated an increase in strain and strain rate from rest to peak exercise in a group of healthy, adults. However, strain data were acquired within one minute after the cessation of exercise and with the subjects returned to the left-lateral decubitus/horizontal position. It is unclear whether

this same pattern of change would be present while the subject continued to exercise and was maintained in the upright exercise position for cycle ergometry.

Previous work from our laboratory[10] has demonstrated an orthostatic effect upon cardiac structure and function that could influence strain and strain rate responses during exercise. These data[10] demonstrated decreases in the left ventricular myocardial relaxation velocity (TDI-E') in the upright compared to the supine position. Along with this velocity reduction, decrements in ventricular volume were noted, while left ventricular mass remained unchanged, resulting in a relative concentric hypertrophy with an associated increase in wall stiffness. Interrogation of these wall stiffness effects and the impact of altered loading conditions that accompany exercise in the upright position has not been fully explored via cardiac strain measurements with advanced speckle tracking techniques. One of the unique aspects of the present study was therefore to acquire strain and strain rate data during exercise and with the subject maintained in the upright position.

Prior to evaluating the pattern of strain data with upright exercise, the stability (test-retest reproducibility) of these data needed to be determined. Currently, there are limited data in the literature with regard to the test-retest reproducibility of cardiac strain data[11] acquired during exercise.

Consequently, the primary aim of the study was to evaluate the changes that occur in longitudinal, radial and endocardial circumferential strain during upright submaximal cycle ergometry in a group of adolescent males and it was hypothesised that the healthy

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left ventricle would demonstrate a hyper-dynamic response to submaximal exercise. The secondary aim was to evaluate the test-retest reliability of these data during exercise and it was hypothesised that acceptable levels of reproducibility of cardiac strain data would be derived from upright cycle ergometry exercise.

Methods

Subjects

The subjects (age: 17.9 ± 0.7 years; mass: 72.1 ± 8.2 kg and stature: 182 ± 7 cm) were recruited from a local school. All participants were recreationally active, but were not undergoing any systematic training . The subjects were of similar maturity status (4-5) as measured by Tanner self-assessment[12].

All subjects performed an incremental exercise test to volitional exhaustion on a cycle ergometer (Lode Excalibur Sport, Groningen, The Netherlands). Initial and incremental loads were 40W, with 3-minute stages and a constant cadence of 60rpm. Subjects performed two progressive cycle ergometer tests to exhaustion, with a 3-day gap between test sessions. Previous work from our laboratory[13] demonstrated no time-of-day effect on cardiovascular responses to cycle ergometer exercise to exhaustion in a group of adolescent males. Therefore, the subjects in the present study were not tested at the same time of day on both visits.

Echocardiographic imaging of the left ventricle was performed during the last 30 seconds of each stage from parasternal short axis (at the level of the mitral papillary muscles) and

apical four-chamber views with the subject in an upright but forward-leaning position on the cycle ergometer. A standard clinical echocardiographic system with a 5 MHz phased array transducer was used for all subjects (Model iE33, Philips Medical Systems, Eindhoven, the Netherlands). Imaging parameters were set to maximize 2D frame rate, gated to real-time ECG tracings and digitally stored without compression. Due to the limited time available for image acquisition and respiratory artifact from subject tachypnea, the cardiac cycle with the best-defined endocardium was chosen for analysis to limit confounding effects of regional dropout or excessive cardiac translation with hyperpnea.

Post-exercise test analysis was performed using a feature and speckle tracking algorithm on the two-dimensional B-mode images (Velocity Vector Imaging 2.0, Siemens Medical Solutions, Mountain View, CA, USA) by a single, experienced observer (PB). Average peak longitudinal and average peak circumferential strain and strain rate were calculated from the average of 6 cardiac segments. Average peak radial strain and strain rate were calculated from combined simultaneous endocardial and epicardial tracings averaged for 6 cardiac segments. Average time to peak strain and strain rate was calculated similarly using the average of 6 cardiac segments (Figure 1). Peak strain and strain rate were defined as the maximum negative (longitudinal, circumferential) or positive (radial) deflection of the strain curve. Peak strain and strain rate were not normalized to Doppler-derived aortic valve closure, to avoid error introduced from using non-simultaneous Doppler information at elevated heart rates. Analyses of strain and strain rate measurements were limited to rest, 40W and 80W during the incremental exercise

protocol to limit subject artifacts that could arise from tachycardic responses at higher exercise intensities.

Statistical Analysis

A one-way repeated measures ANOVA was used to test for any workload effect. If this was identified for any of the dependent variables, Bonferroni adjusted paired t-tests were used to identify the source of the differences. Coefficients of variation (%) were derived for peak strain for longitudinal, circumferential and radial measurements at rest, 40W and 80W. Data are presented as mean ± standard deviation and statistical significance was accepted at the $p \leq 0.05$. SPSS Version 20 was used to perform all statistical analyses.

Results

Imaging success

Peak systolic strain and strain rate were calculated successfully in all myocardial segments and views, for each individual, at each pre-defined workload (rest, 40W and 80W). No segments were excluded from analysis due to inadequate tracking.

Strain

With respect to peak: longitudinal, radial and circumferential strain, there was a statistically significant ($p < 0.05$) increase from rest to both submaximal workloads for all three variables (Table I). Analyses of the time to peak for: longitudinal, radial and circumferential strain demonstrated that there was a statistically significant ($p < 0.05$) decrement from rest to both submaximal workloads for all three variables (Table I). In

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addition, time to peak for circumferential strain also decreased ($p < 0.05$) with increasing exercise intensity (40W to 80W).

Strain Rate

With regard to peak: longitudinal, radial and circumferential strain rate, there was a statistically ($p < 0.05$) significant increase from rest to both submaximal workloads for all three variables (Table II). Evaluation of the time to peak for: longitudinal, radial and circumferential strain rate illustrated the following trends. There were statistically ($p < 0.05$) significant decrements between rest and 40W for time to peak for longitudinal and circumferential strain rates (Table II). Statistically significant ($p < 0.05$) decrements were also noted between rest and 80W for time to peak for radial strain rate and circumferential strain rate (Table II). Furthermore, a statistically significant ($p < 0.05$) decrease in time to peak for circumferential strain rate was also noted (Table II) with an increase in exercise intensity (40W to 80W).

Test-retest reproducibility

The mean and SD for the test-retest values are stated in TableIII. The coefficient of variation data (CV) derived from the longitudinal and circumferential analyses were the most stable data from rest to 80W. Greater variability was noted for the CV obtained from the radial analyses (Table III). These absolute workloads also represented, approximately the same ($p > 0.05$) relative exercise intensity (expressed as a percentage of VO_2peak) for the two sets of measurements (**Visit 1 40W:** 30 ± 8 %VO_2peak vs**. Visit 2 40W:** 28 ± 6%VO_2peak) **and (Visit 1 80W:** 41 ± 9%VO_2peak vs**. Visit 2 80W:** $39 \pm$

6% VO_2peak). Peak oxygen uptake at the end of the cycle ergometer test was: 3.20 ± 4.9 L·min^{-1}.

Discussion

During upright cycle ergometry exercise, statistically significant changes were noted from rest to submaximal exercise for longitudinal, circumferential and radial strain and strain rate. The coefficients of variation generated in this study for the test-retest reproducibility of longitudinal and circumferential strain demonstrated that it was also possible to obtain reliable cardiac strain data during upright cycle ergometer exercise. Greater variation was noted for radial strain and strain rate measurements, consistent with the greater variability reported with radial measurements reported in the extant literature. The findings from the present study have particular relevance, as most cycle ergometry exercise evaluations in clinical and sporting environments are performed in an upright position.

The present study demonstrated that peak wall deformation of both longitudinal and circumferential strain increased from rest to the first submaximal workload and then plateaued, even after there was an increase in exercise intensity. A similar phenomenon was noted by[8] during semi-supine cycle ergometry in young healthy adults (26 years of age). These authors created an incremental workload protocol of 20, 30 and 40% of maximal aerobic power and demonstrated that longitudinal strain remained unchanged after the initial workload of 20% of maximal aerobic power. Longitudinal strain appears to be sensitive to both pre-load and after-load, but the evidence from both human[15] and

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animal models[16,17] suggests that pre-load has a slightly greater influence on longitudinal strain. Therefore, any increase in venous return, as seen at the onset of exercise, will lead to an increase in longitudinal strain with the onset of exercise[18]. Longitudinal strain is considered to be a surrogate measure of sub-endocardial contractility and there is limited evidence to suggest that the sub-endocardium is more sensitive to local tissue de-oxygenation. Consequently, any lack of change in longitudinal strain could also stem from a higher sensitivity to local ischemia and a blunted response to increasing exercise intensity[19]. The only comparable study, by Reuss et al[9] demonstrated changes in strain and strain rate with peak exercise, as measured by tissue Doppler imaging, but with the peak exercise measurements performed with the subjects off the treadmill and returned to a supine/left lateral decubitus position. The present study built upon the orthostatic differences imposed by exercising in a seated position[10] (i.e. upright cycle ergometry) that better represent the physiologic state of typical exercise.

Equivocal findings were noted with respect to circumferential strain responses during exercise. Doucende et al[8]., noted increased circumferential wall deformation with increasing exercise intensity during semi-supine exercise, but this pattern of change was not noted during upright cycle ergometer exercise, where a plateau in responses were noted with increasing exercise intensity. It is possible, that orthostatic factors could have influenced the differential, circumferential strain responses when comparing upright and semi-supine exercise. Concomitant, with an increase in peak deformation with the onset of exercise, a statistically significant reduction in time to peak deformation was noted for

longitudinal and circumferential strain, from rest to exercise. This pattern of data was also noted with increasing exercise intensity in the present study.

There are no comparable data available in the literature with regard to the test-retest reproducibility of obtaining cardiac strain data during upright cycle ergometer exercise. It is encouraging that the coefficients of variation for longitudinal and circumferential strain derived from this study with the subjects in an upright "normal"position are similar to those obtained at supine rest by Oxborough et al.,[11]. These researchers[11] also demonstrated within-day, intra-observer coefficients of variation at rest (peak longitudinal strain: 6%, circumferential strain: 7% and radial strain: 19%), again similar with the exercise-derived data derived from the present study. The coefficients of variation for peak deformation in radial strain during upright exercise in the present study were also larger (16-20%) than both longitudinal and circumferential strain. These findings were not unusual, as it has been previously demonstrated that radial strain is only weakly correlated with sonomicrometry[14] and is also dependent upon the poorer lateral image resolution that is required to capture radial strain data.

The findings from this study are delimited to a group of healthy, adolescent males, with echo imaging performed using a single vendor platform and with strain measured using a single vendor-neutral analysis tool. Further work with respect to regional myocardial deformation and the rate at which this occurs in the adolescent, female population and highly trained youth athletes, and how these results may compare to other vendor solutions, is warranted.

The methodological implications, however, of the findings from this present investigation are multiple. This study has demonstrated that it is possible to obtain reliable strain data when individuals are exercising in a normal upright body position and these findings may help to remove the constraint of exercising in the semi-supine position chosen for imaging convenience in previous strain studies. As with all studies incorporating feature and speckle tracking imaging, it is crucial to maximize acquired frame rates without storage compression, as the systolic time interval shortens at higher heart rates. While it is ideal to perform cardiac measurements during breath-holding to minimize cardiac translation or respiratory-induced changes in cardiac filling, this is not feasible at increasing levels of exercise. From a practical standpoint, however, end-expiratory-phase consistency is possible, as the best image quality will coincide with the least-lung expansion obscuring transthoracic windows. It is also not possible to obtain simultaneous Doppler and 2D imaging with an accelerating heart rate to permit accurate measurement of timing of aortic valve closure or systolic duration. Novel approaches to determining this simultaneous information will be helpful to future investigations.

In conclusion, the evidence from this novel investigation suggests that reliable longitudinal and circumferential strain data can be obtained during upright, submaximal cycle ergometer exercise. Also, significant changes in left ventricular wall deformation occur during the transition from rest to submaximal upright exercise and these changes confirm that a healthy left ventricle has a hyperdynamic response to exercise.

Author Contributions

Professor V.Unnithan helped to develop the concept and design of the study, helped

collect the data and conducted the statistical analyses and interpreted the findings. He

also wrote all drafts of the paper. Dr Piers Barker helped to develop the concept of the

study, collected and analysed the data and made contributions to various drafts of the

manuscript. Dr Rowland helped design the study and collect the data. He also critically

reviewed the manuscript. Doctors Lindley and Roche helped with data collection and

critically reviewed the manuscript. Mr Garrard helped with the data collection.

References

1. Abram TP, Nishimura RA: Myocardial strain: can we finally measure contractility. J Am Coll Cardiol 2001: 37: 731-734.

2. Dandel M, Lehmkuhl H, Knosalla C,et al: Strain and strain rate imaging by echocardiography-basic concepts and clinical applicability. Current Cardiol Rev 2009: 5: 133-148.

3. George KP, Naylor LH, Whyte GP, et al: Diastolic function in healthy humans: non-invasive assessment and the impact of acute and chronic exercise. Eur J Appl Physiol 2010: 108: 1-14.

4. Marwick TH: Measurement of strain and strain rate by echocardiography: ready for prime time? J Am Coll Cardiol 2006: 47: 1313-1327.

5. Ishii K, Imai M, Suyama T, et al: Exercise-induced post-ischemic left ventricular delayed relaxation or diastolic stunning: is it a reliable marker in detecting coronary artery disease? J Am Coll Cardiol 2009: 53: 698-705.

6. George K, Shave R, Oxborough D, et al: Left ventricular wall segment motion after ultra-endurance exercise in humans assessed by myocardial speckle tracking. Eur J Echocardiogr 2009: 10: 238-243.

7. Stohr EJ, McDonnell B, Thompson J, et al: Left ventricular mechanics in humans with high aerobic fitness: adaption independent of structural remodeling, arterial haemodynamics and heart rate. J Physiol 2012: 590: 2107-2119.

8. Doucende G, Schuster I, Rupp T, et al: Kinetics of left ventricular strains and torsion during incremental exercise in healthy subjects. The key role of torsional mechanics for systolic-diastolic coupling. Circ Cardiovasc Imaging 2010: 3: 586-594.

9. Reuss CS, Moreno CA, Appleton CP, et al: Doppler tissue imaging during supine and upright exercise in healthy adults. J Am Soc Echocardiogr 2005: 18: 1343-1348.

10. Rowland TW, Unnithan VB, Barker P, et al: Orthostatic effects on echocardiographic measures of ventricular function. Echocardiography 2012: 29: 523-527.

11. Oxborough D, George K, Birch KM: Intraobserver reliability of two-dimensional ultrasound derived strain imaging in the assessment of the left ventricle, right ventricle and left atrium of healthy human hearts. Echocardiography 2012: 29: 793-802.

12. Matsudo S, Matsudo V: Self-assessment and physician assessment of sexual maturation in Brazilian boys and girls: concordance and reliability. Am J Human Biol 1994: 6: 451-455.

13. Rowland T, Unnithan V, Barker P, et al: Time-of-day effect on cardiac responses to progressive exercise. Chronobiol Int 2011: 28: 611-616.

14. Amundsen BH, Helle-Valle T, Edvardsen T, et al: Non-invasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol 2006: 47: 789-793.

15. Burns AT, La Gerche A, D'hooge J, et al: Left ventricular strain and strain rate: characterization of the effect of load in human subjects. Eur J Echocardiogr 2010: 11: 283-289.

16. A'Roch A, Gustafsson U, Johansson G, et al: Left ventricular strain and peak systolic velocity: responses to controlled changes in load and contractility, explored in a porcine model. Cardiovasc Ultrasound 2012: 10:22: P1-9.

17. Rosner A, Bijens B, Hansen M, et al: Left ventricular size determines tissue-Doppler derived longitudinal strain and strain rate. Eur J Echocardiogr 2009: 10: 271-277.

18. Choi JO, Shin DH, Cho SW, et al: Effect of pre-load on left ventricular longitudinal strain by 2D speckle-tracking. Echocardiography 2008: 25: 873-879.

19. Henein MY, Gibson DG: Long axis function in disease. Heart 1999: 81: 229-231.

TABLES

Table I: Left ventricular longitudinal, radial and circumferential strain data at rest and submaximal exercise

	Rest		40W		80W	
	Average Peak Strain (%)	Time to peak (ms)	Average Peak Strain (%)	Time to peak (ms)	Average Peak Strain (%)	Time to peak (ms)
Longitudinal	-15.4 ± 1.9*	357.1 ± 37.7*	-18.3 ± 1.9	312.2 ± 40.0†	-20.5 ± 2.7	275.3 ± 44.5
Radial	37.5 ± 13.1*	304.6 ± 48.7*	49.5 ± 11.0	263.8 ± 46.7	47.0 ± 15.9	232.4 ± 33.4
Circumferential	-21.6 ± 3.0*	329.5 ± 44.4*	-28.7 ± 3.9	275.1 ± 33.3†	-28.2 ± 6.6	249.0 ± 28.2

*denotes a statistically ($P<0.05$) significant difference between rest to both submaximal exercise intensities for average peak strain and time to peak deformation. † denotes a statistically significant ($P<0.05$) difference between submaximal workloads (40W and 80W) for time to peak deformation for Longitudinal Strain.

Table II: Longitudinal, radial and endocardial circumferential strain rate data at rest and submaximal exercise

	Rest		40W		80W	
	Average Peak Strain Rate (1/s)	Time to peak (ms)	Average Peak Strain Rate (1/s)	Time to peak (ms)	Average Peak Strain Rate (1/s)	Time to peak (ms)
Longitudinal	-1.18 ±0.25*	180.9 ±50.4$^\diamond$	-1.55 ±0.26	147.7 ±34.2	-1.86 ±0.43	143.6 ±46.8
Radial	2.47 ±0.69*	142.4 ±64.9$^\Delta$	3.14 ±0.63	107.7 ±31.8	3.40 ±0.87	100.6 ±36.0
Circumferential	-1.75 ±0.39*	187.9 ±25.1	-2.41 ±0.51	165.6 ±23.9†	-2.67 ±0.92	141.0 ±21.5

*denotes a statistically (P<0.05) significant difference between rest to both submaximal exercise intensities for average peak strain rate and time to peak deformation. $^\diamond$denotes a statistically significant (p<0.05) difference between rest and 40W for time to peak deformation. $^\Delta$denotes a statistically significant (p<0.05) difference between rest and 80W for time to peak deformation. † denotes a statistically significant (P<0.05) difference between submaximal workloads (40W and 80W) for time to peak deformation.

Table III: Mean and SD for longitudinal, circumferential and radial strain peak data measured while: sitting, upright, at rest on the cycle ergometer and at 40W and 80W on visits 1 and 2. Derived coefficients of variation (CV) at rest, 40W and 80W

	Rest		40W		80W	
	Visit 1	Visit 2	Visit 1	Visit 2	Visit 1	Visit 2
Peak Longitudinal (%)	-15.4 ± 1.9	-16.1 ± 1.5	-18.3 ± 1.9	-19.2 ± 2.1	-20.5 ± 2.7	-19.5 ± 3.5
Peak Radial (%)	37.5 ± 13.1	40.9 ± 10.5	49.5 ± 11.0	42.2 ± 10.7	47.0 ± 15.9	42.8 ± 9.6
Peak Circumferential (%)	-21.6 ± 3.0	-23.2 ± 3.0	-28.7 ± 3.9	-25.4 ± 3.0	-28.2 ± 6.6	-27.2 ± 3.9
Longitudinal CV (%)		9.2		8.2		13.8
Circumferential CV (%)		8.2		10.4		12.1
Radial CV (%)		20.5		16.7		20.4

FIGURES

Figure 1: Representative analysis plot of speckle tracking of longitudinal strain data at 80W for an individual subject. RA denotes Right Atrium, RV denotes Right Ventricle, LA denotes Left Atrium and LV denotes Left Ventricle