**In vivo** human cardiac shortening and lengthening velocity is region-dependent and not coupled with heart rate

‘Longitudinal’ strain rate markedly underestimates apical contribution

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What is the central question of this study?
Regulation of cardiac function is typically achieved by changes in heart rate (HR) and cardiac shortening velocity (strain rate, SR), but their interdependence \textit{in vivo} remains poorly understood.

What is the main finding and its importance?
Using resistance exercise to physiologically increase heart rate and arterial resistance in humans, and measuring regional cardiac SR (at the base and apex), we found that HR and SR were not strictly coupled because SR at the base and apex responded differently, despite the same HR. Importantly, our data show that the region-averaged 'longitudinal' SR, which is currently popular in the clinical setting, markedly underestimated the contribution of the apex.
Abstract
The fundamental importance of cardiac shortening and lengthening velocity (=strain rate, SR) has been demonstrated in vitro. Currently, the interdependence between in vivo SR and HR is poorly understood because studies 1) have typically assessed region-averaged ‘longitudinal’ strain rate, which likely underestimates the apical contribution, and 2) have used non-physiological interventions that may have also been influenced by multi-collinearity caused by concomitant reductions in arterial resistance. Resistance exercise acutely raises HR, blood pressure and arterial resistance and transiently disassociates these cardiovascular factors following exercise. Therefore, we measured SR, HR, BP and arterial resistance in nine healthy men (Age: 20±1 years) immediately before, during and after double leg press exercise at 30% and 60% of maximal strength. Resistance exercise caused a disproportionate SR response at the left ventricular (LV) base and apex (Interaction effect: p<0.05). Consequently, associations between HR and regional peak SR were inconsistent and mostly very weak (r²: 0.0004–0.24). Similarly, the areas under the curve for systolic and diastolic SR and their relationship with systolic and diastolic duration were variable and weak. Importantly, region-averaged ‘longitudinal’ SR was identical to basal SR, thus, markedly underestimating apical contribution. In conclusion, in vivo HR and SR are not strictly coupled in healthy humans; which is explained by the region-specific responses of SR that are not captured by ‘longitudinal SR’. This novel observation emphasizes the independent role of in vivo SR in overall cardiac function during stress and may cause a ‘revival’ of SR as a marker of regional LV (dys)function.

Non-standard Abbreviations and Acronyms: 1RM: one repetition maximum, an indicator of muscular strength; HR: heart rate; LV: left ventricle; SR: strain rate; BP: blood pressure.
Introduction
A fundamental task of the cardiovascular system is to match the cardiac output with the peripheral metabolic and non-metabolic blood flow demand. Regulation of cardiac output is achieved by adjustment of 1) the frequency of cardiac contraction, commonly termed heart rate (HR), and 2) of the intrinsic cardiac muscle force and deformation. One of the most sensitive parameters of the latter contributor is the shortening velocity of cardiac myocytes (Daniels et al., 1984). The importance of both HR and the shortening velocity of cardiac myofibres has been demonstrated in vitro and is undisputed, yet the in vivo interdependence between HR and the velocity of myofibre shortening is surprisingly poorly understood (Brouha et al., 1936; Sonnenblick, 1962; Brutsaert et al., 1971; Daniels et al., 1984). Data exist to show that the in vivo velocity of cardiomyofibre shortening and lengthening – also referred to as ‘strain rate’ (SR) – is related to the sympathetically-mediated HR (Weidemann et al., 2002). Initially, this concept appears logical because an increase in HR could be expected to cause a faster rate of cardiac tissue deformation as reflected by enhanced SR. Further agreement with this idea is evidenced by the reduced survival rate in cardiac patients who have a blunted SR response to sympathetic and chronotropic stimulation (Bjork Ingul et al., 2007). However, a close relationship between SR and HR eliminates the use of SR as an independent marker of contractile function (Greenberg et al., 2002). While a recent investigation has suggested that SR is “less likely to be confounded by chronotropic responses” (Mak et al., 2012), the study used atrial pacing and failed to elicit any changes in SR, thereby limiting the possibility to study the natural coupling between SR and HR. More importantly, the regional SR responses associated with increased HR in vivo have not been examined previously. Instead, an average ‘longitudinal’ strain rate was presented. This measurement has imposed the concept that SR is greater at the LV base compared with the apex (Wilkenshoff et al., 1998). From an anatomical perspective, this is surprising because the left ventricle (LV) is more ‘free’ at the apex as it is not tethered to the right ventricle and could therefore be expected to shorten more than the base. This is further supported by studies that have shown a more dynamic and more plastic function at the LV apex (Doucende et al., 2010; Stöhr et al., 2011; Stöhr et al.,
Consequently, previous studies measuring HR and longitudinal SR may not have captured the contribution of the LV apex. Showing differences in regional SR at the base vs. apex would provide strong evidence that the overall HR cannot be strictly coupled with in vivo SR because regional differences in shortening and lengthening velocities would occur within the same heart beat independently of the frequency of contractions. Taken together, it is clear that presently the physiological in vivo interdependence of SR and HR is still poorly understood because extrapolation of patient data and inference from pharmacological and/or electrophysiological pacing interventions does not permit a confident conclusion on whether in vivo SR is related (or not related) to HR in humans. At present this theory is lacking empirical evidence obtained from healthy individuals undergoing physiological stress, which would respect the integrative nature of cardiovascular regulation beyond artificial isolated stimulation. In fact, some existing data are suggestive of the hypothesis that HR and SR may not be coupled in vivo. For example, Sengupta et al. (2006) demonstrated that different regions of the left ventricle (LV) are activated for different periods of time. These different activation times could be indicative of region-dependent SR to ensure an overall well-coordinated contraction of the whole LV muscle. A comprehensive investigation into the in vivo interdependence of SR and HR in healthy humans will advance our current understanding of fundamental cardiac function and may help to revisit the role of regional cardiac function in various conditions and populations.

An important aspect to consider when evaluating the in vivo interdependence between HR and SR are false associations caused by confounding factors, such as a concomitant decrease in peripheral resistance. SR has been shown to be reduced when afterload is increased and consequently an increase in SR is expected when afterload is reduced (Burns et al., 2010). This means that any condition that raises HR but that is concomitantly also associated with a reduction in afterload or peripheral arterial resistance may result in enhanced SR that is potentially falsely associated with HR. Thus, a physiological stimulus that acutely raises HR but that does not concomitantly reduce peripheral vascular resistance may help to improve our understanding of HR and SR coupling. One such stimulus is resistance...
exercise, which is known to acutely increase systemic vascular resistance and transiently disassociate HR and blood pressure immediately following physical effort (Rezk et al., 2006), making it a suitable model to verify the coupling between HR and SR in vivo. Accordingly, the aim of this study was to examine the integrated physiological response of HR, SR, blood pressure and vascular resistance before, during and immediately following resistance exercise.

Methods

**Ethical approval and study population.** Following ethical approval from the Cardiff Metropolitan University School of Sport ethics committee, twelve healthy, non-smoking males provided verbal and written informed consent to take part in the study. Two volunteers did not complete the trial because of poor echocardiographic windows at baseline. Due to insufficient quality of echocardiographic images in another volunteer, the final study group consisted of nine participants (Age: 20±1 years; height: 178±6 cm; weight: 82.2±15.8 kg; 1 repetition maximum (1RM): 313±81 kg). This study conforms to the standards set by the latest revision of the Declaration of Helsinki and procedures used were in agreement with institutional guidelines.

**Experimental protocol.** Participants attended the laboratory twice; for initial testing of their maximal leg strength as reflected by their one repetition maximum, 1RM, (ref) during double leg press exercise and on the experimental day for the assessment of SR, HR, blood pressure and arterial resistance. All exercise was performed on a commercially available leg press machine (Linear Leg Press, Life Fitness, Cambridgeshire, UK). During visit one, participants’ one repetition maximum (1RM) for the 45° inclined double-leg press exercise was determined according to the guidelines set by the National Strength and Conditioning Association (Baechle et al., 2008). Following a warm-up set with a light resistance that allowed 5-10 repetitions, participants were given a two min rest period. The first attempt was performed using a load equal to ~50% of the participant’s estimated 10 RM, allowing 3-5 repetitions. After 3-5 min the load was increased to be somewhat more difficult, based on the ease with which
the previous trial was performed. This process continued by increasing or decreasing the load until the participants could perform only one complete repetition with proper exercise technique. Between four and six trials were typically required for determining each participant’s 1RM. Participant position was noted and repeated during the experimental condition described as follows.

On the experimental day, participants were weighed and then asked to sit down on the leg press machine. In this position, a 3-lead ECG was attached and recorded within the ultrasound (Vividq, GE Medical Systems Israel LTD, Israel) and a continuous blood pressure monitor (FinometerPRO, Finapres Medical Systems FMS, Arnheim, Netherlands) was used to capture the change in blood pressure over time (Schutte et al., 2003). Participants were then asked to raise their legs and place their feet onto the weight-bearing platform of the leg press machine to perform a brief warm-up that consisted of six repetitions at 10 and 20% of 1RM to familiarise participants with the postural position. Following the warm-up participants rested for two minutes. Then, participants performed one double leg extension. Exercise was performed with an assistant releasing the weight, the participant receiving it and performing a near complete leg extension followed by an immediate, consistent leg flexion to a 90 degree knee angle. There, participants were asked to hold the weight isometrically for 3-5 seconds before participants were released of the weight. Participants’ feet remained raised on the leg press platform for post-exercise assessment until 12 seconds following exercise, after which every participant was asked to put their feet on the ground and rest for 2 minutes. 90 seconds into this recovery period, participants were asked to raise their legs again and put their feet on the double leg press platform in preparation for the next double leg press exercise. Because only one echocardiographic image can be acquired per double leg press exercise and this investigation was part of a bigger study, participants performed a total of ten leg extensions, interspersed with 2 minutes of recovery. Following ten repetitions, participants rested for ten
minutes with their feet on the ground. Thereafter, the same previous exercise performed at 30% 1RM was repeated at 60% 1RM (see figure 1 for a schematic of the protocol).

**Data collection and analysis.**

**Blood pressure.** Blood pressure was measured using photoplethysmography (FinometerPRO, Finapres Medical Systems FMS, Arnheim, Netherlands) on the middle finger of the right hand, with the right arm rested on a cushioned box positioned next to the participant. Blood pressure was recorded throughout the entire experiment (PowerLab, ADInstruments, Oxford, UK). To align the beat-by-beat blood pressure waveforms with cardiac SR measurements, an assistant added markers into the blood pressure recording software (LabChart 7 Pro v7.2, ADInstruments, Oxford, UK) upon instruction from the cardiac sonographer, who simultaneously recorded three consecutive cardiac cycles as outlined in detail below. The three blood pressure waveforms preceding the marker in the data capture were then analysed for peak systolic blood pressure and results were averaged.

**Echocardiography.** One specialist cardiac sonographer acquired all images with a phased-array probe (M4S, GE Medical Systems Israel LTD, Israel) on a commercially available ultrasound system (Vividq, GE Medical Systems Israel LTD, Israel). For the purpose of this study, three out of ten recorded images were relevant; the apical 4-chamber view and the parasternal short-axis view at the LV base and the parasternal short-axis view at the apex. The LV base was defined as the short-axis window that showed the mitral valve leaflets in early diastole. The LV apex was obtained by moving the transducer along the long-axis of the LV as close to the true apex as possible, ensuring that the lumen remained circular across the entire cardiac cycle and avoiding obliteration of the lumen at the end of systole. LV base and apex short-axis images were recorded during successive leg press repetitions. For each image, five consecutive cardiac cycles were recorded during gentle end-expiration. For all three of the echocardiographic windows, the same image was recorded immediately before, during and 7 seconds following each leg press repetition, resulting in a total of 18 images per participant (3 x base, 3x apex, 3x longitudinal, each at 30% and 60% of 1RM, respectively,
totalling 54 cardiac cycles per participant). Echocardiographic images were analysed in accordance with current guidelines (Gorcsan & Tanaka, 2011) using a commercially available computer platform (EchoPAC, GE Medical Systems, Version 112). Stroke volume was calculated from the difference between the end-diastolic and end-systolic areas in apical 4-chamber views as previously described (Lang et al., 2006). Flow propagation velocity, a surrogate of intra-ventricular pressure gradients and LV suction (Carrick-Ranson et al., 2013) was measured from colour M-mode images of the LV chamber (Garcia et al., 2000). SR data were obtained by tracing the endocardial border of the LV. The region of interest width was then adjusted to cover the entire myocardium, excluding valves and trabeculations. Raw speckle tracking data of longitudinal, circumferential and radial SR were saved and imported into custom software (2D Strain Analysis Tool, Version 1.0beta14, Stuttgart, Germany). The software applied a cubic spline algorithm to interpolate the raw speckle tracking data to 600 data points in systole and diastole, respectively. All SR data in this manuscript are based on interpolated results and are reported as either peak SR in systole and diastole, respectively, or the systolic and diastolic areas under the curve (see Figure 1). AUC was calculated because associations between SR and HR relate peak values (=SR) with a metric of duration (HR), whereas AUC of SR and HR cover the same time periods. All SR data represent the average SR for six (longitudinal and base) and four (apex) myocardial segments, except for some exclusions when speckles could not be tracked in less than 5% of the cases (Cerqueira et al., 2002). If a segment was excluded in one condition, it was removed for all conditions for this individual, to maintain within-subject comparability.

**Systolic arterial resistance.** In order to determine the resistance the heart was facing during the contraction phase, systolic arterial resistance were estimated as peak systolic blood pressure (mmHg) divided by stroke volume (ml).

**Statistical analyses.** All data are reported as means ± SD unless otherwise stated. Two-way analysis of variance (ANOVA) was used to determine main effects for time (pre, during and post exercise), exercise intensity (30% vs. 60% of 1RM) and the interaction between these. Data that showed significant main effects (p<0.05) were analysed post hoc with the Bonferroni
test. Relationships were determined using linear regression analysis. Statistical analyses were performed with GraphPad Prism (GraphPad Prism for Windows, Version 5.0.1, San Diego, California, USA).

**Results**

Within each of the two exercise trials, HR, cardiac output, systolic blood pressure, diastolic blood pressure and systolic arterial resistance increased during exercise (p<0.0001, Figure 2). HR and cardiac output remained elevated following exercise while systolic blood pressure, diastolic blood pressure and systolic arterial resistance declined back to baseline levels. Stroke volume declined during resistance exercise but increased back to baseline levels immediately after (ANOVA main effects P<0.002). Flow propagation velocity was mildly reduced during resistance exercise, although this change did not reach statistical significance (30%: baseline 103±33 cm/s, exercise 82±16 cm/s, recovery 92±43 cm/s, respectively; 60%: baseline 95±28 cm/s, exercise 84±22 cm/s, recovery 88±32 cm/s, respectively ANOVA p=0.11). Peak circumferential, radial and longitudinal SR changed significantly over time across the three conditions (ANOVA main effects p<0.0001, p<0.0001 and p<0.0042, respectively). Importantly, there were significant interaction effects between the peak SR responses at the LV base compared with the LV apex (Figure 3). Accordingly, relationships between peak systolic circumferential and radial SR and HR were mostly weak and non-significant, except for peak radial SR at the base during the 30% trial (r²: 0.24, p=0.01, Figure 4). Even longitudinal SR, which represents a global average over six myocardial segments from base to apex, only explained between 35 and 42% of the variance of HR. With the exception of peak radial SR during the 30% trial (r²: 0.30, p=0.005), there were no significant relationships between SR and stroke volume (P>0.05). To check the possibility that by choosing peak SR we may have underestimated the influence of the pattern of SR across the entire cardiac cycle, we also determined the area under the curves (AUC) for systolic and diastolic SR and examined their relationships with systolic and diastolic duration, respectively.
However, these associations were even weaker, as illustrated in Figure 5. Similarly, peak SR and areas under the curve for SR were weakly associated with blood pressure or arterial resistance (Figure 6). There were no differences between the responses at 30% and 60% of 1RM (all main effects for exercise intensity p>0.05). With the exception of radial SR at the base during the 30% trial ($r^2$: 0.30, p<0.05), SV also did not correlate with SR (p>0.05).

**Discussion**

The aim of this study was to verify the common assumption that the *in vivo* shortening and lengthening velocity of human cardiac tissue is closely related to the prevailing HR. Our measurements of systolic and diastolic strain rate (SR) – *in vivo* indicators of cardiac shortening and lengthening velocity – show that there can be substantial regional variation in the SR response to acute stress and that consequently the *in vivo* SR is not coupled with HR. These data indicate a more complex regional adjustment of the *in vivo* contractile state of the human heart than previously thought and suggest that SR is not simply related to chronotropic state. Future studies should examine the exact cause for the regional disparities in SR as these may be important for the general understanding of normal human cardiac function and may help in the diagnosis of malfunction.

**Potential mechanisms for regional SR differences**

It is well known that the shortening velocity of the human heart is influenced by several fundamental determinants of cardiac function including inotropic and chronotropic state, as well as preload and afterload (Sonnenblick, 1962; Colan *et al.*, 1984). The key finding of this study was that *in vivo* SR differed between the LV base and apex and that SR in these two regions responded differentially to an acute rise in HR. Consequently, the composite measurement of longitudinal SR, although showing good correlations with HR in some instances in this study, cannot be a true reflection of regional SR. The observation that SR is regionally different agrees with several fundamental cardiac principles. In the following paragraph, three potential mechanisms for the regional disparities in LV SR will be discussed:
1) Differential electrical activation times, 2) the shape of the left ventricle and the associated tension on the wall, and 3) intra-ventricular pressure gradients.

**Electrical activation times.** The contraction of the human heart is initiated and controlled by an intrinsic pacemaker that typically originates in the sinoatrial node and then spreads across the entire heart in a well-described sequence. In the healthy human heart this electrical propagation is translated into mechanical work, characterised by sequential contraction of all cardiomyocytes during each heart beat (Bers, 2002). The overall frequency of contraction is also controlled by the sinoatrial node, and by circulating sympathetic and parasympathetic hormones. However, owing to the variable cardiac chamber sizes and the different distances that each sinoatrial signal needs to ultimately cover across each chamber, different regions of the heart are electrically activated at different time points within one cardiac cycle (Sengupta et al., 2006). Recently, Sengupta et al. (2006) showed that the LV apex is activated for longer during systole. Our data agree with this finding by showing a consistently greater circumferential SR at the apex compared with the base. These regional differences also explain why longitudinal SR was only moderately associated with HR, because the basal and apical segments will have contributed disproportionally to the average longitudinal SR. As such, the authors believe that longitudinal SR represents an artificial value not in agreement with the natural LV shortening velocity, mostly by underestimating the contribution of the LV apex as evidenced by its low absolute values shown in figure 3. This is further supported by the observation that despite a within-subject design, longitudinal SR explain at most 42% of the variance of HR, which the authors consider too weak to reflect a true coupling between these parameters. Instead, the present results suggest that the longer activation time at the apex enables the development of a greater rate of shortening at the apex, which is in agreement with previous data highlighting regional differences in LV function (Stöhr et al., 2012; Weiner & Baggish, 2012; Stöhr et al., 2014). Whether regional cardiac activation times change when HR increases is not known to the authors of this article. However, because SR did not change to the same magnitude at the base and apex in the present study, the present data provide evidence for at least one physiological condition during which SR and HR are not
coupled. It could be postulated that regional activation times during the present study changed disproportionately at the LV base and apex when HR increased. Future research may seek to determine whether changes in the regional activation pattern underpin regional changes in SR during stress.

**Shape of the left ventricle and regional wall tension.** In addition to the previously discussed regional differences in duration of cardiomyocyte activation, the shape of the LV may also explain why SR in the present study differed between the LV base and apex. The tension of the LV wall and the associated tension of myofibres is dependent on the shape (the curvature) of the wall and the internal and transmural pressures (Choi et al., 2010). Although one of the main reasons for the regulation of LV wall thickness is to minimise LV wall stress and equalise wall stress evenly from the endocardium to the epicardium (Vendelin et al., 2002), some differences may still persist as reflected by the non-uniform wall thickness of the LV. Typically, the LV myocardium is thinner at the LV apex compared with the base (Dong et al., 1994; Lee et al., 2013). These regional differences are likely caused by a different tension on the wall of the LV base compared with the LV apex. Since wall tension and shortening velocity are related (Brutsaert et al., 1971) and the role of end-systolic wall stress in circumferential shortening velocity has been highlighted (Colan et al., 1984), the present observation that SR differs between the LV base and apex may be explained by differences in LV shape and wall tension along the long-axis of the human LV. It is likely that acute LV shape changes caused by altered preload and afterload during resistance exercise explain some of the differential adjustment of SR at the LV base and apex. Future studies may wish to investigate this more in-depth, as shape changes occur in many difference physiological and pathological conditions.

**Intra-ventricular pressure gradients.** Intra-ventricular pressure gradients exist in the human LV (Popovic et al., 2006). These pressure differences have been mostly associated with diastolic LV function and have been suggested to create a suction effect that aids LV filling. Similarly, intra-ventricular pressure gradients are present during ventricular ejection (Yotti et al., 2005). Resistance exercise is known to cause large increases in arterial blood pressure (Haykowsky et al., 2001), which was confirmed by the large rise in systolic blood pressure
during sub-maximal effort in the present study. Such changes in arterial pressure are likely to also impact on ventricular pressures and the intra-ventricular pressure gradient during ejection. While we did not measure intra-ventricular pressure gradients during ejection in the present study, our analysis of diastolic flow propagation velocity, which has been associated with intra-ventricular pressure gradients and LV suction (Carrick-Ranson et al., 2013), revealed no difference across the six exercise conditions. This is in agreement with diastolic SR data which were consistent throughout the experiment (Figure 6b). In contrast, the significant interaction effect between SR at the base and apex suggests that ejection pressure gradients may have changed. We and others have previously highlighted the importance of regional LV differences and the implications for ejection of blood at rest (Eriksson et al., 2011) and for LV function during exercise (Stöhr et al., 2014). A change in the ejection pressure gradient and SR during resistance exercise, similar to that seen in aortic stenosis (Bauer et al., 2004), would cause different wall tension on the LV base compared with the apex and hence differently impact regional cardiac shortening velocity (Colan et al., 1984). The following paragraph will discuss this and the other findings in relation to the potential clinical significance.

**Clinical significance**

When technological advances first enabled the easy assessment of SR with tissue Doppler and then speckle tracking ultrasound, there was hope that this new parameter would provide a regional index of myocardial contractile state (Edvardsen et al., 2002; Greenberg et al., 2002) and provide superior prediction of patient outcome (Bjork Ingul et al., 2007). More recently, the influence of cardiac preload and afterload on SR has been shown (Burns et al., 2010; Weiner et al., 2012). Together with the assumption that SR is dependent on the prevailing HR, these data have somewhat reduced the interest in assessing SR as an independent marker of cardiac function. By showing that SR is independent of HR, the present study advances our current understanding of regional cardiac contractile function in healthy individuals and suggests that SR may indeed be a sensitive local measurement of cardiac function.
contractile state. In particular the contractile function of the LV apex is highlighted by the present study, which would be missed by exclusive examination of the global ‘longitudinal SR’. These findings suggest that a more focused assessment of regional SR in patient populations may be beneficial, with the ultimate aim to generate normal reference ranges. As such, the authors believe that the present findings extend beyond conditions with enhanced afterload. Rather, the results show that the shortening behaviour of the LV is highly region-dependent, irrespective of HR. This could have multiple implications for the clinical setting, where many cardiac diseases such as myocardial infarctions, myocarditis and even some forms of asymmetric cardiomyopathies are characterised by a local impairment in cardiac function. For some, if not many, cardiac diseases the local evaluation of contractile behaviour measured from SR may provide an indication of the disease progression and thus inform treatment plans. Finally, the present data suggest that assessing regional myocardial contractile state by using pharmacological stimulation with chronotropic agents may not be as successful at detecting regional contractile function compared with using a physiological stress such as exercise or isometric handgrip testing, which can be employed in humans (Doucende et al., 2010; Stöhr et al., 2011; Stöhr et al., 2012; Weiner et al., 2012).

Conclusions

By using resistance exercise as a model to examine whether in vivo HR and SR are closely related, the present study reveals that the in vivo shortening and lengthening velocity of the healthy human heart is not strictly coupled with HR. SR in different regions across the LV can respond differentially to an integrated physiological stimulus, suggesting that region-specific SR may be important in the regulation of cardiac function during acute stress. The findings highlight the independent role of SR in cardiac regulation and may therefore lead to a ‘revival’ of SR as a valuable (patho)physiological marker of regional contractile function.
Additional information

Competing interests

None of the authors have any competing interests to report.

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Author contributions

All data collection was performed in the physiology laboratory of the Cardiff School of Sport, Cardiff Metropolitan University, Cardiff, United Kingdom.

E.J.S. conceived the research and wrote the manuscript. All authors contributed to the design of the experiment and pilot work, data collection, data analysis, interpretation of the data as well as the critical revision of the manuscript for its intellectual content. All authors have approved the final version of the manuscript.

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References


Figure legends

**Figure 1. Schematic of the experimental protocol.** Following a warm-up, blood pressure and echocardiographic images were taken before, during and immediately after double leg press exercise at 30% (A) and 60% (B) of maximal strength (1RM).

**Figure 2. Example of circumferential strain rate (SR) curves.** The graphs show the group average circumferential SR curves (n=9) at the LV base (top) and apex (bottom) during the 30% (left) and 60% (right) resistance exercise trial. For the purpose of clarity, error bars have been omitted.

**Figure 3. Heart rate (HR), systolic blood pressure (BP) and systolic arterial resistance before, during and immediately after resistance exercise.** HR, systolic BP and systolic arterial resistance increased markedly during exercise compared with rest. Following exercise, HR remained elevated at exercise levels while systolic BP declined back to baseline. Note: HR increased during resistance exercise solely due to a reduction in diastolic duration, which suggests that HR cannot be associated with systolic SR. There were no significant differences between exercise at 30% and 60% of 1 repetition maximum (1RM). *: p<0.05; ***: p<0.001.

**Figure 4. Regional peak strain rate (SR).** Peak SR was significantly different at the base and apex of the LV. Moreover, the pattern of responses differed between regions as evidenced by significant interaction effects, suggesting that the overall HR cannot be strictly related to peak SR. Note that the absolute longitudinal SR was almost identical to basal circumferential SR, indicating that this parameter is unsuitable for the detection of regional LV function as it markedly underestimates the contribution of the apex. *: significant interaction between base and apex; †: significant difference between pre, during and post; Number of symbols reflects p<0.05, p<0.01 and p<0.001.
Figure 5. Relationships between peak strain rate (SR) and heart rate (HR). Overall, associations between peak SR and HR were weak. The most consistent relationship was observed between peak longitudinal SR (an average longitudinal parameter that includes basal, apical and other segments) and HR, although SR only explained 35 - 42% of the variance of HR.

Figure 6. Associations between the area under the curve (AUC) for strain rate (SR) and A) systolic and B) diastolic duration. Similar to the relationships with peak SR and HR, associations between SR AUC were mostly weak. Note that diastolic longitudinal SR and diastolic duration were negatively associated. AUC<sub>sys</sub>: area under the curve during systole; AUC<sub>diast</sub>: area under the curve during diastole.
Figure 1

A. Warm-up
6 x 10% 1RM
6 x 20% 1RM
2 min rest

Exercise at 30% of 1RM
1 x double leg press 2 min rest

10 min rest

Exercise at 60% of 1RM
1 x double leg press 2 min rest

Echocardiography, HR and blood pressure.
Figure 2. Example of circumferential strain rate (SR) curves. The graphs show the group average circumferential SR curves (n=9) at the LV base (top) and apex (bottom) during the 30% (left) and 60% (right) resistance exercise trial. For the purpose of clarity, error bars have been omitted.
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**Figure 4.** Regional peak strain rate (SR). Peak SR was significantly different at the base and apex of the LV. Moreover, the pattern of responses differed between regions as evidenced by significant interaction effects, suggesting that the overall HR cannot be strictly related to peak SR. Note that the absolute longitudinal SR was almost identical to basal circumferential SR, indicating that this parameter is unsuitable for the detection of regional LV function as it markedly underestimates the contribution of the apex. *: significant interaction between base and apex; †: significant difference between pre, during and post; Number of symbols reflects p<0.05, p<0.01 and p<0.001.
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Figure 6a

![Graphs showing correlation between LV Base, LV Apex, and Average LV longitudinal function with systolic duration.](image)
Figure 6. Associations between the area under the curve (AUC) for strain rate (SR) and
A) systolic and B) diastolic duration. Similar to the relationships with peak SR and HR, associations between SR AUC were mostly weak. Note that diastolic longitudinal SR and diastolic duration were negatively associated. $AUC_{sys}$: area under the curve during systole; $AUC_{dias}$: area under the curve during diastole.