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

3 'Longitudinal' strain rate markedly underestimates apical contribution

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34   **NEW FINDINGS**

35

36   ***What is the central question of this study?***

37   Regulation of cardiac function is typically achieved by changes in heart rate (HR) and

38   cardiac shortening velocity (strain rate, SR), but their interdependence *in vivo* remains poorly

39   understood.

40   ***What is the main finding and its importance?***

41   Using resistance exercise to physiologically increase heart rate and arterial resistance in

42   humans, and measuring regional cardiac SR (at the base and apex), we found that HR and

43   SR were not strictly coupled because SR at the base and apex responded differently,

44   despite the same HR. Importantly, our data show that the region-averaged 'longitudinal' SR,

45   which is currently popular in the clinical setting, markedly underestimated the contribution of

46   the apex.

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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 (r^2: 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.*,

113   2014). Consequently, previous studies measuring HR and longitudinal SR may not have

114   captured the contribution of the LV apex. Showing differences in regional SR at the base *vs.*

115   apex would provide strong evidence that the overall HR cannot be strictly coupled with *in vivo*

116   SR because regional differences in shortening and lengthening velocities would occur within

117   the same heart beat independently of the frequency of contractions. Taken together, it is clear

118   that presently the physiological *in vivo* interdependence of SR and HR is still poorly understood

119   because extrapolation of patient data and inference from pharmacological and/or

120   electrophysiological pacing interventions does not permit a confident conclusion on whether

121   *in vivo* SR is related (or not related) to HR in humans. At present this theory is lacking empirical

122   evidence obtained from healthy individuals undergoing physiological stress, which would

123   respect the integrative nature of cardiovascular regulation beyond artificial isolated

124   stimulation. In fact, some existing data are suggestive of the hypothesis that HR and SR may

125   not be coupled *in vivo.* For example, Sengupta *et al.* (2006) demonstrated that different

126   regions of the left ventricle (LV) are activated for different periods of time. These different

127   activation times could be indicative of region-dependent SR to ensure an overall well-

128   coordinated contraction of the whole LV muscle. A comprehensive investigation into the *in*

129   *vivo* interdependence of SR and HR in healthy humans will advance our current understanding

130   of fundamental cardiac function and may help to revisit the role of regional cardiac function in

131   various conditions and populations.

132   An important aspect to consider when evaluating the *in vivo* interdependence between

133   HR and SR are false associations caused by confounding factors, such as a concomitant

134   decrease in peripheral resistance. SR has been shown to be reduced when afterload is

135   increased and consequently an increase in SR is expected when afterload is reduced (Burns

136   *et al.*, 2010). This means that any condition that raises HR but that is concomitantly also

137   associated with a reduction in afterload or peripheral arterial resistance may result in

138   enhanced SR that is potentially falsely associated with HR. Thus, a physiological stimulus that

139   acutely raises HR but that does not concomitantly reduce peripheral vascular resistance may

140   help to improve our understanding of HR and SR coupling. One such stimulus is resistance

141 exercise, which is known to acutely increase systemic vascular resistance and transiently

142 disassociate HR and blood pressure immediately following physical effort (Rezk *et al.*, 2006),

143 making it a suitable model to verify the coupling between HR and SR *in vivo*. Accordingly, the

144 aim of this study was to examine the integrated physiological response of HR, SR, blood

145 pressure and vascular resistance before, during and immediately following resistance

146 exercise.

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148   **Methods**

149 ***Ethical approval and study population.*** Following ethical approval from the Cardiff

150 Metropolitan University School of Sport ethics committee, twelve healthy, non-smoking males

151 provided verbal and written informed consent to take part in the study. Two volunteers did not

152 complete the trial because of poor echocardiographic windows at baseline. Due to insufficient

153 quality of echocardiographic images in another volunteer, the final study group consisted of

154 nine participants (Age: 20±1 years; height: 178±6 cm; weight: 82.2±15.8 kg; 1 repetition

155 maximum (1RM): 313±81 kg). This study conforms to the standards set by the latest revision

156 of the *Declaration of Helsinki* and procedures used were in agreement with institutional

157 guidelines.

158 ***Experimental protocol.*** Participants attended the laboratory twice; for initial testing of their

159 maximal leg strength as reflected by their one repetition maximum, 1RM, (ref) during double

160 leg press exercise and on the experimental day for the assessment of SR, HR, blood pressure

161 and arterial resistance. All exercise was performed on a commercially available leg press

162 machine (Linear Leg Press, Life Fitness, Cambridgeshire, UK). During visit one, participants'

163 one repetition maximum (1RM) for the 45° inclined double-leg press exercise was determined

164 according to the guidelines set by the National Strength and Conditioning Association

165 (Baechle *et al.*, 2008). Following a warm-up set with a light resistance that allowed 5-10

166 repetitions, participants were given a two min rest period. The first attempt was performed

167 using a load equal to ~50% of the participant's estimated 10 RM, allowing 3-5 repetitions. After

168 3-5 min the load was increased to be somewhat more difficult, based on the ease with which

169 the previous trial was performed. This process continued by increasing or decreasing the load

170 until the participants could perform only one complete repetition with proper exercise

171 technique. Between four and six trials were typically required for determining each participant's

172 1RM. Participant position was noted and repeated during the experimental condition described

173 as follows.

174 On the experimental day, participants were weighed and then asked to sit down on the leg

175 press machine. In this position, a 3-lead ECG was attached and recorded within the ultrasound

176 (Vividq, GE Medical Systems Israel LTD, Israel) and a continuous blood pressure monitor

177 (FinometerPRO, Finapres Medical Systems FMS, Arnheim, Netherlands) was used to capture

178 the change in blood pressure over time (Schutte *et al.*, 2003). Participants were then asked to

179 raise their legs and place their feet onto the weight-bearing platform of the leg press machine

180 to perform a brief warm-up that consisted of six repetitions at 10 and 20% of 1RM to familiarise

181 participants with the postural position. Following the warm-up participants rested for two

182 minutes. Then, participants performed one double leg extension. Exercise was performed with

183 an assistant releasing the weight, the participant receiving it and performing a near complete

184 leg extension followed by an immediate, consistent leg flexion to a 90 degree knee angle.

185 There, participants were asked to hold the weight isometrically for 3-5 seconds before

186 participants were released of the weight. Participants' feet remained raised on the leg press

187 platform for post-exercise assessment until 12 seconds following exercise, after which every

188 participant was asked to put their feet on the ground and rest for 2 minutes. 90 seconds into

189 this recovery period, participants were asked to raise their legs again and put their feet on the

190 double leg press platform in preparation for the next double leg press exercise. Because only

191 one echocardiographic image can be acquired per double leg press exercise and this

192 investigation was part of a bigger study, participants performed a total of ten leg extensions,

193 interspersed with 2 minutes of recovery. Following ten repetitions, participants rested for ten

194 minutes with their feet on the ground. Thereafter, the same previous exercise performed at

195 30% 1RM was repeated at 60% 1RM (see figure 1 for a schematic of the protocol).

196

197 ***Data collection and analysis.***

198 ***Blood pressure.*** Blood pressure was measured using photoplethysmography

199 (FinometerPRO, Finapres Medical Systems FMS, Arnheim, Netherlands) on the middle finger

200 of the right hand, with the right arm rested on a cushioned box positioned next to the

201 participant. Blood pressure was recorded throughout the entire experiment (PowerLab,

202 ADInstruments, Oxford, UK). To align the beat-by-beat blood pressure waveforms with cardiac

203 SR measurements, an assistant added markers into the blood pressure recording software

204 (LabChart 7 Pro v7.2, ADInstruments, Oxford, UK) upon instruction from the cardiac

205 sonographer, who simultaneously recorded three consecutive cardiac cycles as outlined in

206 detail below. The three blood pressure waveforms preceding the marker in the data capture

207 were then analysed for peak systolic blood pressure and results were averaged.

208 ***Echocardiography***. One specialist cardiac sonographer acquired all images with a phased-

209 array probe (M4S, GE Medical Systems Israel LTD, Israel) on a commercially available

210 ultrasound system (Vividq, GE Medical Systems Israel LTD, Israel). For the purpose of this

211 study, three out of ten recorded images were relevant; the apical 4-chamber view and the

212 parasternal short-axis view at the LV base and the parasternal short-axis view at the apex.

213 The LV base was defined as the short-axis window that showed the mitral valve leaflets in

214 early diastole. The LV apex was obtained by moving the transducer along the long-axis of the

215 LV as close to the true apex as possible, ensuring that the lumen remained circular across the

216 entire cardiac cycle and avoiding obliteration of the lumen at the end of systole. LV base and

217 apex short-axis images were recorded during successive leg press repetitions. For each

218 image, five consecutive cardiac cycles were recorded during gentle end-expiration. For all

219 three of the echocardiographic windows, the same image was recorded immediately before,

220 during and 7 seconds following each leg press repetition, resulting in a total of 18 images per

221 participant (3 x base, 3x apex, 3x longitudinal, each at 30% and 60% of 1RM, respectively,

222   totalling 54 cardiac cycles per participant). Echocardiographic images were analysed in

223   accordance with current guidelines (Gorcsan & Tanaka, 2011) using a commercially available

224   computer platform (EchoPAC, GE Medical Systems, Version 112). Stroke volume was

225   calculated from the difference between the end-diastolic and end-systolic areas in apical 4-

226   chamber views as previously described (Lang *et al.*, 2006). Flow propagation velocity, a

227   surrogate of intra-ventricular pressure gradients and LV suction (Carrick-Ranson *et al.*, 2013)

228   was measured from colour M-mode images of the LV chamber (Garcia *et al.*, 2000). SR data

229   were obtained by tracing the endocardial border of the LV. The region of interest width was

230   then adjusted to cover the entire myocardium, excluding valves and trabeculations. Raw

231   speckle tracking data of longitudinal, circumferential and radial SR were saved and imported

232   into custom software (2D Strain Analysis Tool, Version 1.0beta14, Stuttgart, Germany). The

233   software applied a cubic spline algorithm to interpolate the raw speckle tracking data to 600

234   data points in systole and diastole, respectively. All SR data in this manuscript are based on

235   interpolated results and are reported as either peak SR in systole and diastole, respectively,

236   or the systolic and diastolic areas under the curve (see Figure 1). AUC was calculated because

237   associations between SR and HR relate peak values (=SR) with a metric of duration (HR),

238   whereas AUC of SR and HR cover the same time periods. All SR data represent the average

239   SR for six (longitudinal and base) and four (apex) myocardial segments, except for some

240   exclusions when speckles could not be tracked in less than 5% of the cases (Cerqueira *et al.*,

241   2002). If a segment was excluded in one condition, it was removed for all conditions for this

242   individual, to maintain within-subject comparability.

243   ***Systolic arterial resistance.*** In order to determine the resistance the heart was facing during

244   the contraction phase, systolic arterial resistance were estimated as peak systolic blood

245   pressure (mmHg) divided by stroke volume (ml).

246   ***Statistical analyses.*** All data are reported as means ± SD unless otherwise stated. Two-way

247   analysis of variance (ANOVA) was used to determine main effects for time (pre, during and

248   post exercise), exercise intensity (30% *vs.* 60% of 1RM) and the interaction between these.

249   Data that showed significant main effects ($p < 0.05$) were analysed *post hoc* with the Bonferroni

250   test. Relationships were determined using linear regression analysis. Statistical analyses were

251   performed with GraphPad Prism (GraphPad Prism for Windows, Version 5.0.1, San Diego,

252   California, USA).

253

254   **Results**

255   Within each of the two exercise trials, HR, cardiac output, systolic blood pressure, diastolic

256   blood pressure and systolic arterial resistance increased during exercise (p<0.0001, Figure

257   2). HR and cardiac output remained elevated following exercise while systolic blood pressure,

258   diastolic blood pressure and systolic arterial resistance declined back to baseline levels.

259   Stroke volume declined during resistance exercise but increased back to baseline levels

260   immediately after (ANOVA main effects P<0.002). Flow propagation velocity was mildly

261   reduced during resistance exercise, although this change did not reach statistical significance

262   (30%: baseline 103±33 cm/s, exercise 82±16 cm/s, recovery 92±43 cm/s, respectively; 60%:

263   baseline 95±28 cm/s, exercise 84±22 cm/s, recovery 88±32 cm/s, respectively ANOVA

264   p=0.11). Peak circumferential, radial and longitudinal SR changed significantly over time

265   across the three conditions (ANOVA main effects p<0.0001, p<0.0001 and p<0.0042,

266   respectively). Importantly, there were significant interaction effects between the peak SR

267   responses at the LV base compared with the LV apex (Figure 3). Accordingly, relationships

268   between peak systolic circumferential and radial SR and HR were mostly weak and non-

269   significant, except for peak radial SR at the base during the 30% trial (r^2: 0.24, p=0.01, Figure

270   4). Even longitudinal SR, which represents a global average over six myocardial segments

271   from base to apex, only explained between 35 and 42% of the variance of HR. With the

272   exception of peak radial SR during the 30% trial (r^2: 0.30, p=0.005), there were no significant

273   relationships between SR and stroke volume (P>0.05). To check the possibility that by

274   choosing peak SR we may have underestimated the influence of the pattern of SR across the

275   entire cardiac cycle, we also determined the area under the curves (AUC) for systolic and

276   diastolic SR and examined their relationships with systolic and diastolic duration, respectively.

277   However, these associations were even weaker, as illustrated in Figure 5. Similarly, peak SR

278   and areas under the curve for SR were weakly associated with blood pressure or arterial

279   resistance (Figure 6). There were no differences between the responses at 30% and 60% of

280   1RM (all main effects for exercise intensity $p>0.05$). With the exception of radial SR at the

281   base during the 30% trial (r^2: 0.30, $p<0.05$), SV also did not correlate with SR ($p>0.05$).

282

283   **Discussion**

284   The aim of this study was to verify the common assumption that the *in vivo* shortening and

285   lengthening velocity of human cardiac tissue is closely related to the prevailing HR. Our

286   measurements of systolic and diastolic strain rate (SR) – *in vivo* indicators of cardiac

287   shortening and lengthening velocity – show that there can be substantial regional variation in

288   the SR response to acute stress and that consequently the *in vivo* SR is not coupled with HR.

289   These data indicate a more complex regional adjustment of the *in vivo* contractile state of the

290   human heart than previously thought and suggest that SR is not simply related to chronotropic

291   state. Future studies should examine the exact cause for the regional disparities in SR as

292   these may be important for the general understanding of normal human cardiac function and

293   may help in the diagnosis of malfunction.

294

295   ***Potential mechanisms for regional SR differences***

296   It is well known that the shortening velocity of the human heart is influenced by several

297   fundamental determinants of cardiac function including inotropic and chronotropic state, as

298   well as preload and afterload (Sonnenblick, 1962; Colan *et al.*, 1984). The key finding of this

299   study was that *in vivo* SR differed between the LV base and apex and that SR in these two

300   regions responded differently to an acute rise in HR. Consequently, the composite

301   measurement of longitudinal SR, although showing good correlations with HR in some

302   instances in this study, cannot be a true reflection of regional SR. The observation that SR is

303   regionally different agrees with several fundamental cardiac principles. In the following

304   paragraph, three potential mechanisms for the regional disparities in LV SR will be discussed:

305   1) Differential electrical activation times, 2) the shape of the left ventricle and the associated

306   tension on the wall, and 3) intra-ventricular pressure gradients.

307   ***Electrical activation times****.* The contraction of the human heart is initiated and controlled by

308   an intrinsic pacemaker that typically originates in the sinoatrial node and then spreads across

309   the entire heart in a well-described sequence. In the healthy human heart this electrical

310   propagation is translated into mechanical work, characterised by sequential contraction of all

311   cardiomyocytes during each heart beat (Bers, 2002). The overall frequency of contraction is

312   also controlled by the sinoatrial node, and by circulating sympathetic and parasympathetic

313   hormones. However, owing to the variable cardiac chamber sizes and the different distances

314   that each sinoatrial signal needs to ultimately cover across each chamber, different regions of

315   the heart are electrically activated at different time points within one cardiac cycle (Sengupta

316   *et al.*, 2006). Recently, Sengupta *et al.*(2006) showed that the LV apex is activated for longer

317   during systole. Our data agree with this finding by showing a consistently greater

318   circumferential SR at the apex compared with the base. These regional differences also

319   explain why longitudinal SR was only moderately associated with HR, because the basal and

320   apical segments will have contributed disproportionally to the average longitudinal SR. As

321   such, the authors believe that longitudinal SR represents an artificial value not in agreement

322   with the natural LV shortening velocity, mostly by underestimating the contribution of the LV

323   apex as evidenced by its low absolute values shown in figure 3. This is further supported by

324   the observation that despite a within-subject design, longitudinal SR explain at most 42% of

325   the variance of HR, which the authors consider too weak to reflect a true coupling between

326   these parameters. Instead, the present results suggest that the longer activation time at the

327   apex enables the development of a greater rate of shortening at the apex, which is in

328   agreement with previous data highlighting regional differences in LV function (Stöhr *et al.*,

329   2012; Weiner & Baggish, 2012; Stöhr *et al.*, 2014). Whether regional cardiac activation times

330   change when HR increases is not known to the authors of this article. However, because SR

331   did not change to the same magnitude at the base and apex in the present study, the present

332   data provide evidence for at least one physiological condition during which SR and HR are not

333 coupled. It could be postulated that regional activation times during the present study changed

334 disproportionally at the LV base and apex when HR increased. Future research may seek to

335 determine whether changes in the regional activation pattern underpin regional changes in SR

336 during stress.

337 ***Shape of the left ventricle and regional wall tension.*** In addition to the previously discussed

338 regional differences in duration of cardiomyocyte activation, the shape of the LV may also

339 explain why SR in the present study differed between the LV base and apex. The tension of

340 the LV wall and the associated tension of myofibres is dependent on the shape (the curvature)

341 of the wall and the internal and transmural pressures (Choi *et al.*, 2010). Although one of the

342 main reasons for the regulation of LV wall thickness is to minimise LV wall stress and equalise

343 wall stress evenly from the endocardium to the epicardium (Vendelin *et al.*, 2002), some

344 differences may still persist as reflected by the non-uniform wall thickness of the LV. Typically,

345 the LV myocardium is thinner at the LV apex compared with the base (Dong *et al.*, 1994; Lee

346 *et al.*, 2013). These regional differences are likely caused by a different tension on the wall of

347 the LV base compared with the LV apex. Since wall tension and shortening velocity are related

348 (Brutsaert *et al.*, 1971) and the role of end-systolic wall stress in circumferential shortening

349 velocity has been highlighted (Colan *et al.*, 1984), the present observation that SR differs

350 between the LV base and apex may be explained by differences in LV shape and wall tension

351 along the long-axis of the human LV. It is likely that acute LV shape changes caused by altered

352 preload and afterload during resistance exercise explain some of the differential adjustment

353 of SR at the LV base and apex. Future studies may wish to investigate this more in-depth, as

354 shape changes occur in many difference physiological and pathological conditions.

355 ***Intra-ventricular pressure gradients.*** Intra-ventricular pressure gradients exist in the human

356 LV (Popovic *et al.*, 2006). These pressure differences have been mostly associated with

357 diastolic LV function and have been suggested to create a suction effect that aids LV filling.

358 Similarly, intra-ventricular pressure gradients are present during ventricular ejection (Yotti *et*

359 *al.*, 2005). Resistance exercise is known to cause large increases in arterial blood pressure

360 (Haykowsky *et al.*, 2001), which was confirmed by the large rise in systolic blood pressure

361   during sub-maximal effort in the present study. Such changes in arterial pressure are likely to

362   also impact on ventricular pressures and the intra-ventricular pressure gradient during

363   ejection. While we did not measure intra-ventricular pressure gradients during ejection in the

364   present study, our analysis of diastolic flow propagation velocity, which has been associated

365   with intra-ventricular pressure gradients and LV suction (Carrick-Ranson *et al.*, 2013),

366   revealed no difference across the six exercise conditions. This is in agreement with diastolic

367   SR data which were consistent throughout the experiment (Figure 6b). In contrast, the

368   significant interaction effect between SR at the base and apex suggests that ejection pressure

369   gradients may have changed. We and others have previously highlighted the importance of

370   regional LV differences and the implications for ejection of blood at rest (Eriksson *et al.*, 2011)

371   and for LV function during exercise (Stöhr *et al.*, 2014). A change in the ejection pressure

372   gradient and SR during resistance exercise, similar to that seen in aortic stenosis (Bauer *et*

373   *al.*, 2004), would cause different wall tension on the LV base compared with the apex and

374   hence differently impact regional cardiac shortening velocity (Colan *et al.*, 1984). The

375   following paragraph will discuss this and the other findings in relation to the potential clinical

376   significance.

377

378   ***Clinical significance***

379   When technological advances first enabled the easy assessment of SR with tissue Doppler

380   and then speckle tracking ultrasound, there was hope that this new parameter would provide

381   a regional index of myocardial contractile state (Edvardsen *et al.*, 2002; Greenberg *et al.*,

382   2002) and provide superior prediction of patient outcome (Bjork Ingul *et al.*, 2007). More

383   recently, the influence of cardiac preload and afterload on SR has been shown (Burns *et al.*,

384   2010; Weiner *et al.*, 2012). Together with the assumption that SR is dependent on the

385   prevailing HR, these data have somewhat reduced the interest in assessing SR as an

386   independent marker of cardiac function. By showing that SR is independent of HR, the present

387   study advances our current understanding of regional cardiac contractile function in healthy

388   individuals and suggests that SR may indeed be a sensitive local measurement of cardiac

389   contractile state. In particular the contractile function of the LV apex is highlighted by the

390   present study, which would be missed by exclusive examination of the global 'longitudinal SR'.

391   These findings suggest that a more focused assessment of regional SR in patient populations

392   may be beneficial, with the ultimate aim to generate normal reference ranges. As such, the

393   authors believe that the present findings extend beyond conditions with enhanced afterload.

394   Rather, the results show that the shortening behaviour of the LV is highly region-dependent,

395   irrespective of HR. This could have multiple implications for the clinical setting, where many

396   cardiac diseases such as myocardial infarctions, myocarditis and even some forms of

397   asymmetric cardiomyopathies are characterised by a local impairment in cardiac function. For

398   some, if not many, cardiac diseases the local evaluation of contractile behaviour measured

399   from SR may provide an indication of the disease progression and thus inform treatment plans.

400   Finally, the present data suggest that assessing regional myocardial contractile state by using

401   pharmacological stimulation with chronotropic agents may not be as successful at detecting

402   regional contractile function compared with using a physiological stress such as exercise or

403   isometric handgrip testing, which can be employed in humans (Doucende *et al.*, 2010; Stöhr

404   *et al.*, 2011; Stöhr *et al.*, 2012; Weiner *et al.*, 2012).

405

406   **Conclusions**

407   By using resistance exercise as a model to examine whether *in vivo* HR and SR are closely

408   related, the present study reveals that the *in vivo* shortening and lengthening velocity of the

409   healthy human heart is not strictly coupled with HR. SR in different regions across the LV can

410   respond differentially to an integrated physiological stimulus, suggesting that region-specific

411   SR may be important in the regulation of cardiac function during acute stress. The findings

412   highlight the independent role of SR in cardiac regulation and may therefore lead to a 'revival'

413   of SR as a valuable (patho)physiological marker of regional contractile function.

414

415 **Additional information**

416 ***Competing interests***

417 None of the authors have any competing interests to report.

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420

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422 ***Author contributions***

423 All data collection was performed in the physiology laboratory of the Cardiff School of Sport,

424 Cardiff Metropolitan University, Cardiff, United Kingdom.

425 E.J.S. conceived the research and wrote the manuscript. All authors contributed to the design

426 of the experiment and pilot work, data collection, data analysis, interpretation of the data as

427 well as the critical revision of the manuscript for its intellectual content. All authors have

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595   **Figure legends**

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597   **Figure 1. Schematic of the experimental protocol.** Following a warm-up, blood pressure

598   and echocardiographic images were taken before, during and immediately after double leg

599   press exercise at 30% (A) and 60% (B) of maximal strength (1RM).

600

601   **Figure 2. Example of circumferential strain rate (SR) curves.** The graphs show the group

602   average circumferential SR curves (n=9) at the LV base (*top*) and apex (*bottom*) during the

603   30% (*left*) and 60% (*right*) resistance exercise trial. For the purpose of clarity, error bars have

604   been omitted.

605

606   **Figure 3. Heart rate (HR), systolic blood pressure (BP) and systolic arterial resistance**

607   **before, during and immediately after resistance exercise.** HR, systolic BP and systolic

608   arterial resistance increased markedly during exercise compared with rest. Following exercise,

609   HR remained elevated at exercise levels while systolic BP declined back to baseline. *Note:*

610   HR increased during resistance exercise solely due to a reduction in diastolic duration, which

611   suggests that HR cannot be associated with systolic SR. There were no significant differences

612   between exercise at 30% and 60% of 1 repetition maximum (1RM). *: $p < 0.05$; ***: $p < 0.001$.

613

614   **Figure 4. Regional peak strain rate (SR).** Peak SR was significantly different at the base

615   and apex of the LV. Moreover, the pattern of responses differed between regions as evidenced

616   by significant interaction effects, suggesting that the overall HR cannot be strictly related to

617   peak SR. Note that the absolute longitudinal SR was almost identical to basal circumferential

618   SR, indicating that this parameter is unsuitable for the detection of regional LV function as it

619   markedly underestimates the contribution of the apex. *: significant interaction between base

620   and apex; †: significant difference between pre, during and post; Number of symbols reflects

621    $p < 0.05$, $p < 0.01$ and $p < 0.001$.

622

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_{sys}: area under the curve during systole; AUC_{diast}: area under the curve during diastole.

659   **Figure 1**

↓: Echocardiography, HR and blood pressure.

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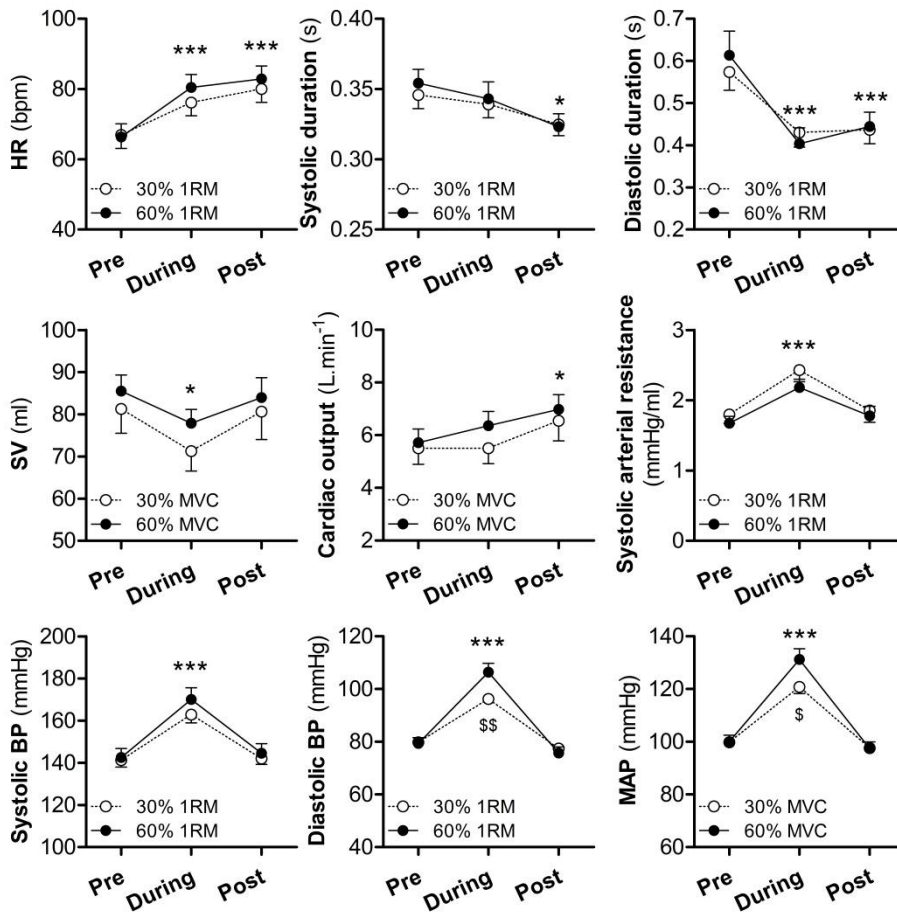664
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670   **Figure 2**
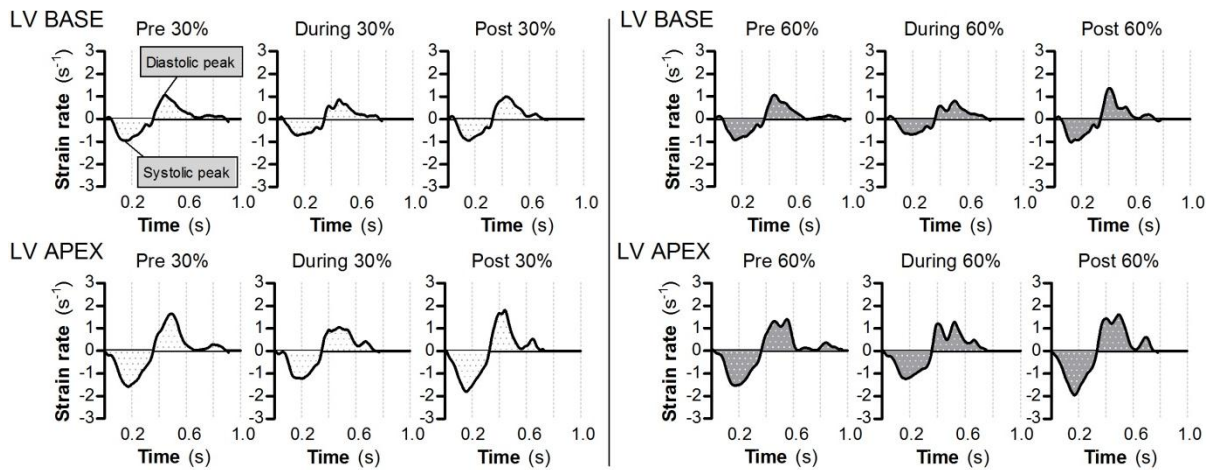
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676   30% (*left*) and 60% (*right*) resistance exercise trial. For the purpose of clarity, error bars have

677   been omitted.

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680 **Figure 3**

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684 **Figure 3. Heart rate (HR), systolic blood pressure (BP) and systolic arterial resistance**

685 **before, during and immediately after resistance exercise.** HR, systolic BP and systolic

686 arterial resistance increased markedly during exercise compared with rest. Following exercise,

687 HR remained elevated at exercise levels while systolic BP declined back to baseline. *Note:*

688 HR increased during resistance exercise solely due to a reduction in diastolic duration, which

689 suggests that HR cannot be associated with systolic SR. * and ***: $p < 0.05$ and $p < 0.001$,

690 respectively, compared with baseline; $ and $$: $p < 0.05$ and $p < 0.01$, respectively, for

691 comparison between the same condition during the 30% and 60% trials.

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693   **Figure 4**
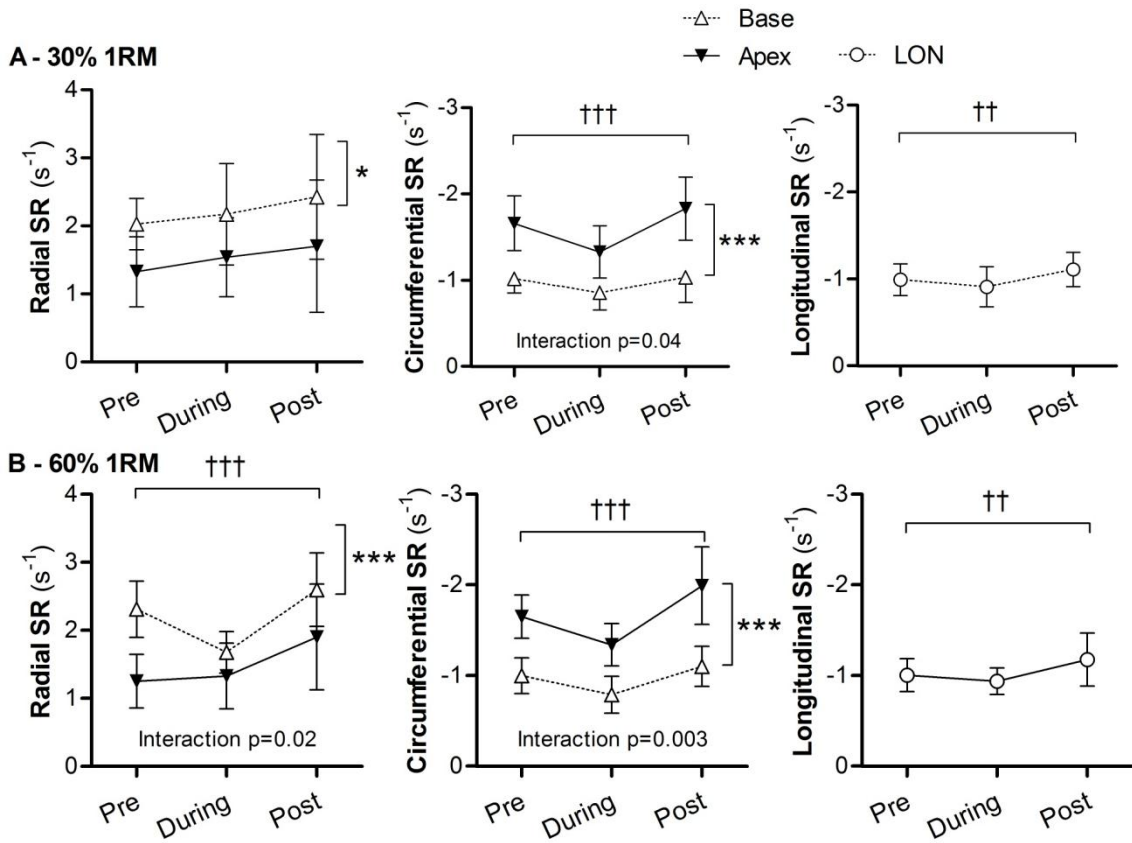
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707   **Figure 5**
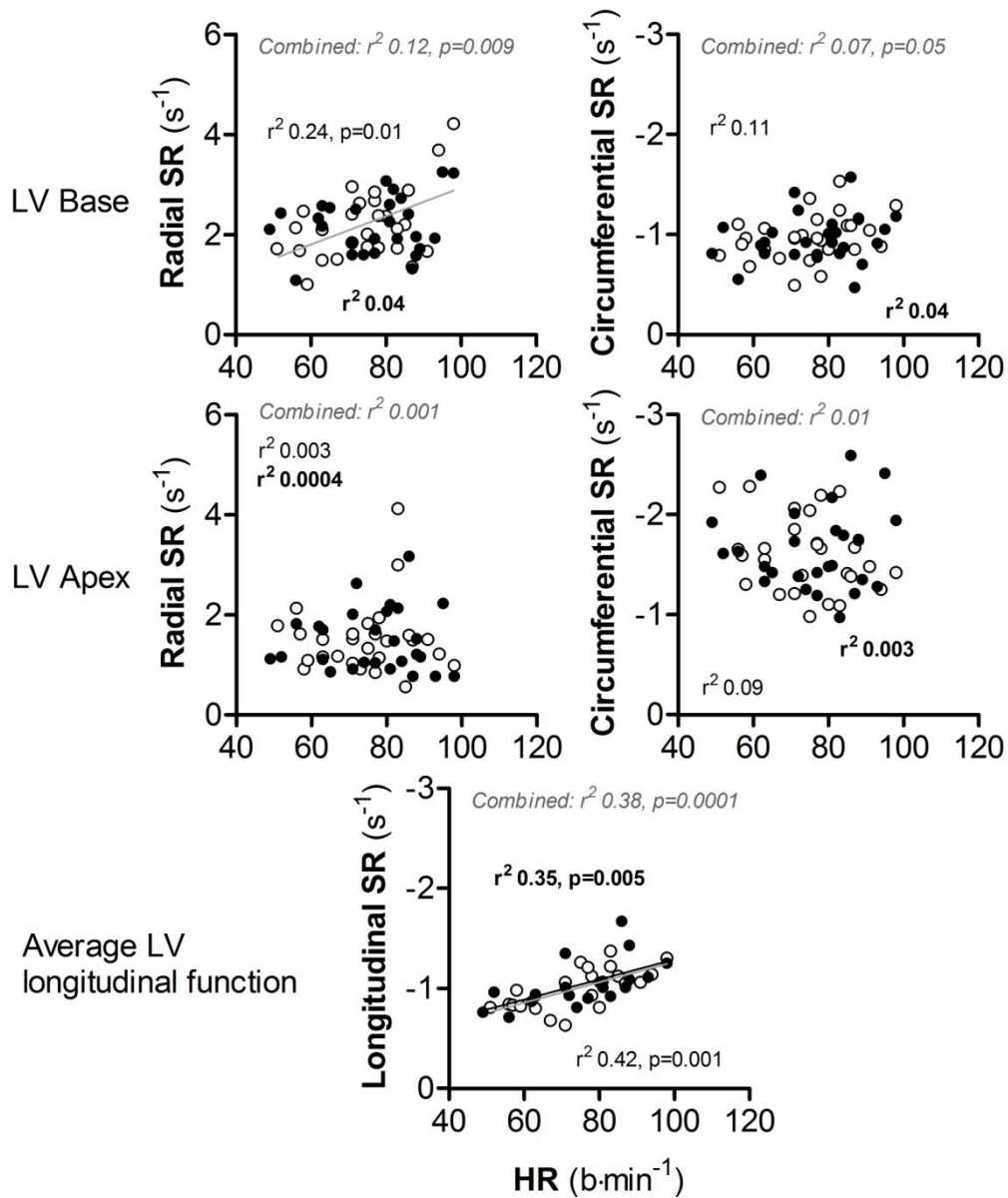
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713   observed between peak longitudinal SR (an average longitudinal parameter that includes

714   basal, apical and other segments) and HR, although SR only explained 35 - 42% of the
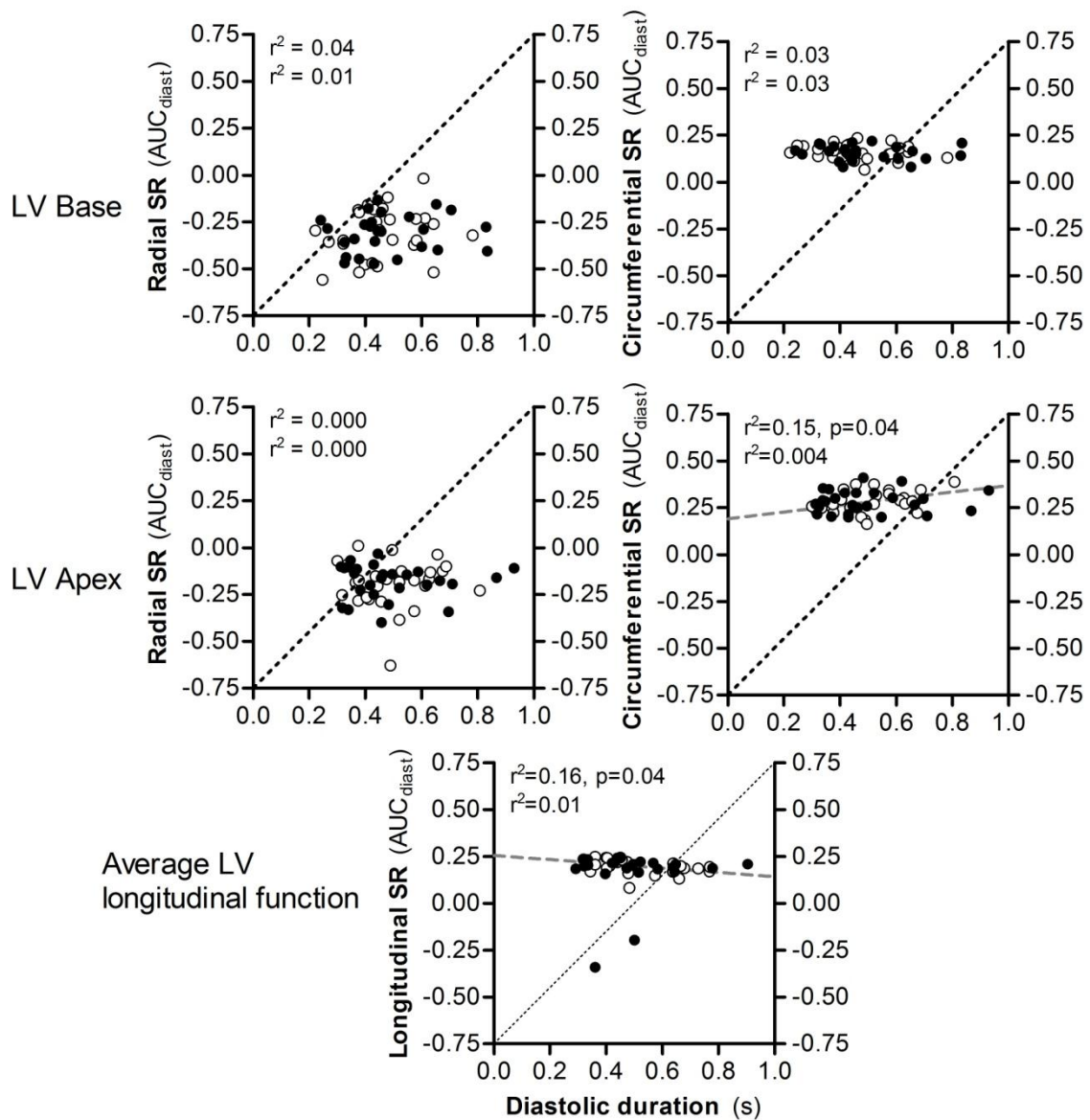
715   variance of HR.

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717   **Figure 6a**
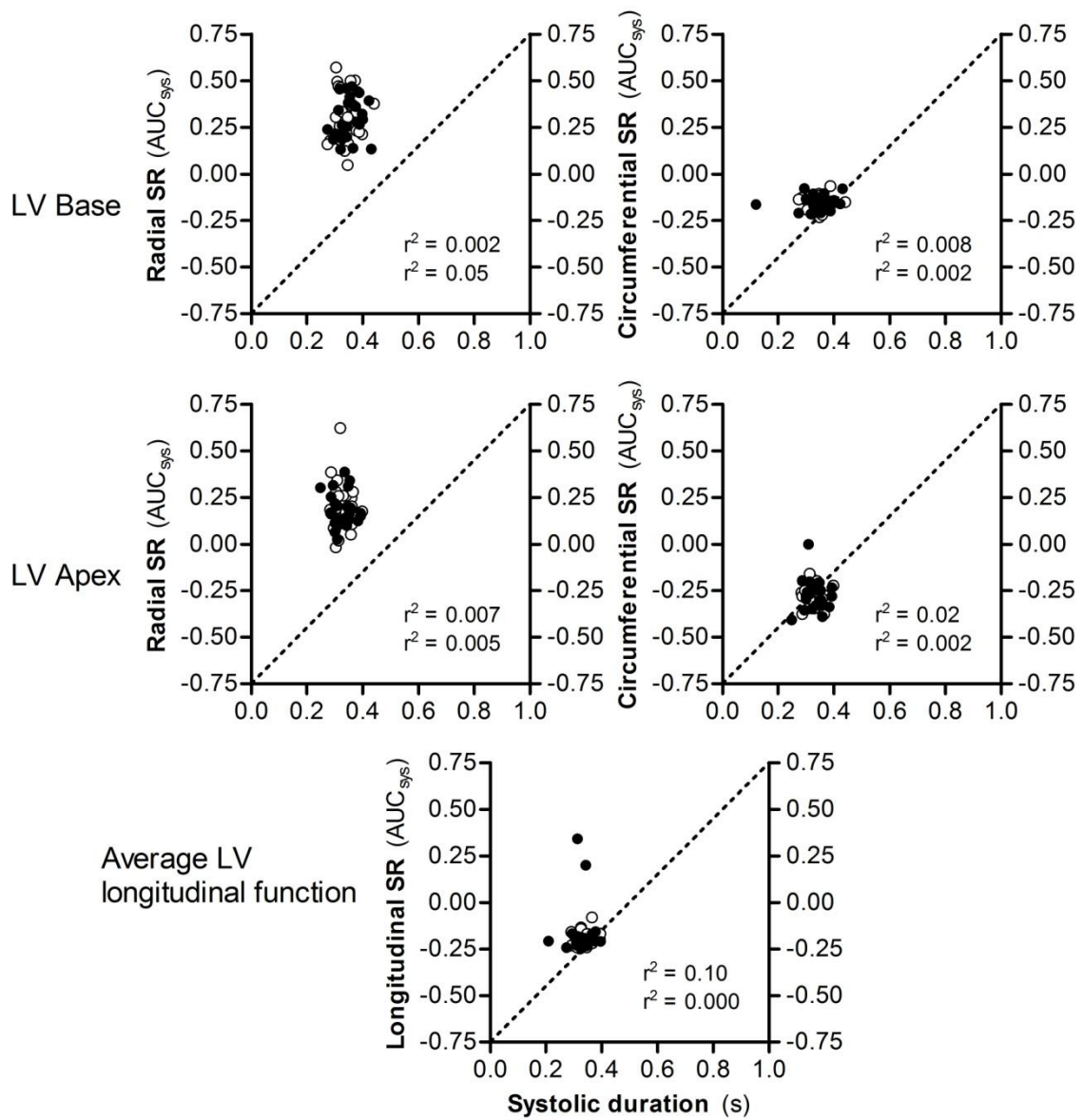
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720   **Figure 6b**

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723   **Figure 6. Associations between the area under the curve (AUC) for strain rate (SR) and**

724   **A) systolic and B) diastolic duration.** Similar to the relationships with peak SR and HR,

725   associations between SR AUC were mostly weak. Note that diastolic longitudinal SR and

726   diastolic duration were negatively associated. AUC_{sys}: area under the curve during systole;

727   AUC_{diast}: area under the curve during diastole.

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