Synergy in the heart: RV systolic function plays a key role in optimizing LV performance during exercise.

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Running title: RV during Exercise

Author contributions
B.R. and R.R conceived the study. B.R., M.N.F.V. and P.D. collected and analyzed the data. D.N. conceived the methods for the modeling experiments. D.N. and L.A. completed the numerical tests for the modeling experiments. R.R. K.P. and A.F. contributed to patient recruitment and supervision of the experiments. R.R. and D.N. are part of the supervision of B.R. B.R., R.R. and D.N. wrote the paper with input from all authors.

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Abstract
The right ventricle (RV) is often overlooked in the evaluation of cardiac performance and treatment of left ventricular (LV) heart diseases. However, recent evidence suggests the RV may play an important role in maintaining systemic cardiac function and delivering stroke volume (SV). We used exercise cardiac magnetic resonance and biomechanical modeling to investigate the role of the RV in LV stroke volume regulation. We studied SV augmentation during exercise by pharmacologically inducing negative chronotropy (sHRi) in healthy volunteers and investigating training-induced SV augmentation in endurance athletes. SV augmentation during exercise after sHRi is achieved differently in the two ventricles. In the RV, the larger SV is driven by increasing contraction down to lower end-systolic volume (ESV; \( p < .001 \)). In the LV, SV augmentation is achieved through an increase in end-diastolic volume (EDV; \( p < .001 \)), avoiding contraction to a lower ESV. The same mechanism is underlies the enhanced SV response observed in athletes. Changes in atrial area during SV augmentation suggest that the improved LV EDV response is sustained by the larger RV contractions. Using our biomechanical model, we explain this behavior and show that the RV systolic function driven regulation of LV SV optimizes the energetic cost of LV contraction, and leads to minimization of the total costs of biventricular contraction. In conclusion, this work provides mechanistic understanding of the pivotal role of the RV in optimizing LV SV during exercise. It demonstrates why optimizing RV function needs to become a key part of therapeutic strategies in patients and training for athletes.

New & Noteworthy
The right ventricle appears to have an important impact on maintaining systemic cardiac function and delivering stroke volume. However, its exact role in supporting left ventricular function has so far been unclear. This study demonstrates a new mechanism of ventricular interaction that provides mechanistic understanding of the key importance of the right ventricle in driving cardiac performance.
Introduction

Traditionally, evaluation of cardiac function in clinical cardiology and physiology has focused on the left ventricle (LV), with the role of the right ventricle (RV) often neglected. However, advances in medical imaging have improved our ability to assess RV function and new evidence has emerged showing that the RV is not merely a sub-pulmonary pump, but plays an important, yet unclear, role in overall cardiac performance. In athletes, function of the RV, instead of LV, seems to limit maximal cardiac performance during high intensity exercise (7, 12, 22). In patients with heart failure, outcomes and treatment benefits are poorer if the RV is also effected (20, 27). While in patients with a single ventricle circulation, the absence of a sub-pulmonary pump results in profound exercise intolerance and pre-mature heart failure (19). While the importance of a biventricular pump in effective cardiac performance seems evident from these results, the exact role of the RV during exercise, and in particular its impact on LV function and cardiac output (CO) remains unclear (38).

Heart rate (HR) increases during exercise, leading to a dramatic fall in diastolic filling time. Despite this fall, the biventricular heart is able to maintain stroke volume (SV) up to near maximal exercise capacity (16, 31, 35), resulting in an approximately linear increase in CO with HR. Athletes are able to augment SV even further during exercise (25, 33).

The mechanism of SV preservation during exercise, i.e. SV regulation, is not well understood. Anatomical and mechanical differences between the LV and RV (13) and pronounced early RV remodeling with training (2) suggest distinct roles for the two ventricles in SV regulation. Characterizing SV regulation could provide mechanistic understanding of the role of the RV in exercise physiology of the biventricular heart.

In this work, we explore the cooperativity or codependency of RV and LV in SV regulation. We utilize a recently developed method to perform cardiac magnetic resonance imaging during supine bicycle ergometer exercise (exercise CMR) (21) to; 1) observe the physiological RV and LV ventricular volume responses during exercise in healthy volunteers, 2) observe the changes in RV and LV behavior after provoking an increase in SV during exercise by addition of pharmacologically induced negative chronotropy (indirect positive inotropy) and 3) compare the mechanism of SV augmentation during the negative chronotropic test to the physiological adaptions in cardiac exercise response in endurance trained athletes. Finally, we introduce a personalized, anatomically correct biventricular
biomechanical model of the heart in order to explain the observed experimental findings and obtain mechanistic understanding of their impact on cardiac performance.

Methods
We recruited 16 non-smoking healthy volunteers (<2 hours of exercise per week) and 10 endurance-trained athletes with at least >10 hours of training per week for more than 4 years. None of participants used prescription medication, multivitamins or other supplements. All subjects underwent cardiac magnetic resonance imaging (CMR) imaging during bicycle ergometer exercise under normal physiological conditions. The volunteer-group underwent a second, identical exercise CMR test after selective inhibition of the physiological HR response (sHRi) by administration of a single oral dose of 7.5 mg of ivabradine, a selective funny current inhibitor that reduces HR via sinus node inhibition without impacting inotropy or lusitropy (5, 24). See Figure 1 for the experimental set-up and flowchart of the study. This study and all the involved experiments was approved by our regional ethics committee for medical research (Bloomsbury, London, UK. Protocol no. 15/LO/522).

Data acquisition protocol
Exercise CMRs were performed using a supine MRI compatible exercise bicycle (Lode, The Netherlands) in a 1.5 Tesla MRI scanner (Ingenia, Philips, The Netherlands). During the exercise CMRs, long axis (LAX) and short axis (SAX) image stacks were acquired to quantify ventricular volumes at rest and during two increments of exercise (ExLevel1 and ExLevel2).

Imaging was performed using a validated exercise CMR protocol (21). In short, highly-accelerated cine imaging was performed without cardiac gating and during free breathing. 80-100 consecutive frames with a thickness of 8 millimeter were acquired over 14-15 slices in SAX orientation and 4-5 slices in LAX orientation. Imaging parameters were: field of view, 300x280 millimeter (approximately); matrix, 76x72; flip angle 50°; SENSE factor 3; repetition time 1.8 milliseconds; echo time 0.9 milliseconds; and reconstructed voxel size, 2.3x2.3 millimeter, slice thickness, 8 millimeter; temporal resolution ~30-35 milliseconds. To ensure accurate image planes during exercise, the interactive planning sequence, available on Philips CMR systems, was used to monitor and update acquisition planes at each stage of exercise.
We aimed to compare the cardiac response between volunteers and athletes at similar levels of tachycardia in order to evaluate the impact of similar filling and ejection times on cardiac behavior during exercise. To do so, we defined two levels of exercise prior to the test; ‘moderate exercise’ was defined as a HR between 105-110 beats per minute (bpm), and ‘sub-maximal’ was defined as a HR between 140-150 bpm. The workload (Wattage) corresponding to these levels was obtained for each individual from the results of a supine CPET that was performed one week prior to the exercise CMRs. Each exercise level was maintained for ~5 minutes: two minutes to attain a steady state and three minutes for image acquisition. All participants underwent a 10-minute warm-up and familiarization ride prior to the CPET and each exercise CMR to minimize training effects. At completion of the baseline exercise CMR, healthy volunteers received sHRi. After a three-hour break to allow for recovery and wait for the HR inhibiting effect, the healthy volunteers underwent the second exercise CMR. During this sHRi-test, exercise levels, cycle rotations per minute, room temperature, humidity, imaging and exercise time were kept identical to the baseline exercise CMR.

Data Analysis

Ventricular volumes were calculated from the SAX imaging stacks at end-expiration using dedicated exercise CMR analysis software (RightVol, KU Leuven, Belgium) (21). LAX images were used for cross-reference of the position of the ventricular valve planes. All volumes were indexed for body surface area. Atrial dimensions could be obtained from the acquired LAX stack using RightVol in end-expiration. Care was taken to select the appropriate 4-chamber views, using the SAX images as a reference. The analyst was blinded for test-stage (physiological or sHRi-test), but could not be blinded for group (volunteer or athlete) due to the characteristic differences in cardiac morphology (and cardiac volumes) between sedentary volunteers and athletes that are present in the images.

In addition, 4-chamber images selected for atrial analysis were cross-checked between the different exercise levels and, in healthy volunteers, between the two exercise-CMRs to ensure similar quantification planes and minimize potential errors due to motion of the heart through the image-plane. Based on these criteria, atrial analysis was possible in 12 healthy volunteers and 9 athletes.
**Definition of the biomechanical model**

To study the mechanical behavior of the biventricular heart, a biomechanical model was constructed based on previous works by the authors (3, 14). The model reference anatomy was personalized based on CMR data collected at end systole from one of the volunteers, a 30-year-old female. Technical details with regard to the model and its personalization can be found in the supplemental materials. We used the biventricular model to examine the influence of activation and work in the myocardium during sub-maximal exercise. The model was exposed to typical LV / RV exercise afterloads (LV systolic pressure was defined as 90% of the measured systolic brachial blood pressure obtained during sub-maximal exercise (142 mmHg), RV systolic pressure was estimated to be 40 mmHg (16)). Active tension was subsequently introduced into both heart chambers and the amount of active tension needed to overcome afterload was calculated at a range of different intraventricular volumes. From these calculations, we derived active tension curves for LV and RV, showing the active tension with respect to intraventricular volume. The area under the curve between a given EDV and ESV represent the total cost of active contraction to generate SV in the ventricle.

**Statistics**

Data were analyzed using IBM SPSS statistics (version 22, Chicago, IL, USA). Descriptive data for continuous variables are presented in the text as means ± standard deviation. Discrete variables are presented as frequencies and percentages. For the physiological test, two-way repeated measures analysis of variance (ANOVA) was used to compare the absolute change (mL/m²) in atrial and ventricular volumes from rest between LV and RV in the healthy volunteers, with exercise intensity as a within-subject effect and atrium or ventricle (LV/RV) as a between-subject effect. The difference in ventricular volume responses between baseline and shRHi-test in healthy volunteers was compared using a two-way repeated measures ANOVA, with exercise intensity and test-type (baseline vs. shRHi) as within-subject effects, and are reported as percentage change. The difference in exercise response between athletes and the baseline test in healthy volunteers was compared using two-way repeated measures ANOVA with exercise intensity as within-subject effect and group (volunteer/athlete) as between-subject effect, and is reported as the absolute change from rest in mL/m². When appropriate, post-hoc paired or unpaired samples T-tests were performed at the individual
exercise levels. Bonferroni correction for multiple comparisons was performed and a $p$-value <0.05 after correction was considered statistically significant.

**Results**

Characteristics of the recruited subjects are displayed in Table 1. All recruited subjects were Caucasian. Athletes had an average training intensity of 17±4 hours/week over the last four years. Quantitative results of all exercise CMR tests are shown in Table 2.

**Exercise response in volunteers**

In the healthy volunteers, SV increased from rest to moderate exercise in both ventricles and was subsequently maintained during sub-maximal exercise (mean increase from rest to moderate exercise: +3.7±2 mL/m$^2$, $p<$.01), see Figure 2. As shown in Figures 3A, EDV fell in both LV and RV. However, this fall was larger in the RV compared to the LV (interaction $p<$.001), with a nearly twice as large drop of RV EDV from rest to sub-maximal exercise (RV -18±5 mL/m$^2$ vs. LV -10±5 mL/m$^2$, $p<$.001). To overcome the larger drop in EDV, the RV contracted down to a lower ESV than the LV (interaction $p=0.001$), with a total change of ESV from rest – sub-maximal exercise of -21±6 mL/m$^2$ and -13±5 mL/m$^2$ for RV and LV respectively ($p<$.001, see Figure 3B).

**SV augmentation during sHRi**

The results of the sHRi-test are shown in Figure 4A and B.

Exercise HR decreased between the physiological and sHRi-test (mean effect: -7.5±1.5%, $p<$.001) and forced an increase in SV (mean effect: +7.8±2.6%, $p<$.001), see Figure 2. In the RV, the increase in SV during the sHRi-test was obtained primarily by contraction down to a lower RV ESV (mean effect: -10.5±4%, $p<$.001), while the RV EDV response did not change between the two tests (mean effect: +1.3±1.4%, $p=0.07$). SV augmentation in the LV stemmed principally from an increase in LV EDV (mean effect +5.6±1.4%, $p<$.001), while the LV ESV response exhibited no change (mean effect: 0.5±3.1%, $p=0.76$). Even during moderate exercise, when the LV still exhibited the ability to decrease ESV (as evidenced by the lower ESV at sub-maximal in the baseline test), the additional increase in SV seen with sHRi was driven by an increased LV EDV and not a decrease in ESV.
SV augmentation in athletes

SV augmentation during exercise was larger in the athletes compared to the volunteers (interaction $p<.001$, see Figure 2), leading to a higher CO (interaction $p<.001$). The mechanism underlying improved SV augmentation in athletes, compared to healthy volunteers during the physiological test, is shown in Figure 4C and D. In the RV, the larger SV was driven by increased contraction to a lower ESV (interaction $p=0.01$), while there was no increase in RV EDV (interaction $p=0.79$). In the LV, the SV increase was achieved through an improved EDV response (interaction $p<.001$), whereas the ESV change was not different between the two groups (interaction $p=0.32$).

Atrial response during exercise

Left atrial (LA) area responses during exercise are shown in Supplemental Figures 1 and 2. In the healthy volunteer group, maximal LA area ($\text{LA}_{\text{max}}$, e.g. the area at atrial end-diastole, just before ventricular filling) was preserved during the physiological test, while maximal right atrial ($\text{RA}_{\text{max}}$) area decreased (interaction $p<.001$). During the sHRi-test, $\text{LA}_{\text{max}}$ increased in comparison to the physiological test (mean effect: $+7\pm2\%$, $p<.001$). There was no significant change in minimal LA area ($\text{LA}_{\text{min}}$ mean effect: $+0\pm2\%$, $p=0.87$). In the group of athletes, $\text{LA}_{\text{max}}$ was increased during exercise compared to the healthy volunteer group (interaction $p=0.001$), while $\text{LA}_{\text{min}}$ response from rest was not significantly different (interaction $p=0.11$).

Model results

Figure 5A shows the active tension curve of the LV during sub-maximal exercise. As can be appreciated from the figure, active tension in the LV is high at large ventricular volumes and decreases with falling volumes, following Laplace’s law. At very low volumes, the cost of activation increases steeply as internal shear deformation of the LV myocardium becomes mechanically limiting. To optimize the total cost of LV contraction, the LV should therefore ideally contract no further than an ESV close to the minimal LV active tension. The results of our individualized model show that LV ESV indeed operates in this small range during exercise (between the moderate and sub-maximal markers in Figure 5A). While minimizing costs of contraction in this way, the LV restricts its ESV reserve. A further decrease in LV
ESV would lead to an exponential increase in active fiber stress (see ‘decrease in ESV’ marker in Figure 5A), and therefore total cost of contraction of the LV. As a consequence, efficient further SV augmentation during exercise is better achieved by increases in LV EDV, driven via extra RV contraction (illustrated by the ‘increase in EDV’ marker in Figure 5A).

In the RV, the costs of contraction are significantly lower than in the LV (see Figure 5B), reflecting the relatively low afterload of the RV. Active tension in the RV is also less influenced by ventricular volume. As a result, the RV is able to operate at larger cardiac volumes, and thus maintain a larger ESV reserve without significantly impacting the costs of contraction. This can be appreciated by the observed larger range between the moderate and sub-maximal ESV in Figure 5B, seen alongside a larger fall in EDV. This experiment shows that increasing biventricular SV by 10% during exercise using a further decrease in RV ESV (‘decrease in ESV’ marker, Figure 5B) to improve LV EDV (‘increase EDV’ marker, Figure 5A) is less expensive than a utilizing a further decrease in LV ESV (‘decrease ESV’ marker, Figure 5A).

Discussion

In this study, we explored the cooperativity between LV and RV in SV regulation during exercise. We utilized exercise CMR imaging to interrogate cardiac volume responses during exercise and combined this with a negative chronotropic stimulus and natural adaption in trained athletes to investigate the individual roles of the two ventricles in SV augmentation.

SV augmentation

The results of the physiological exercise test in healthy volunteers show that the RV and LV operate differently during exercise. RV filling deteriorates more compared to that of the LV with increasing HR (see Figure 3). As a consequence, the RV needs to contract down to a lower ESV to drive similar SV. This observation reflects the different preload conditions of the LV and RV in the biventricular circulation. RV preload is governed by systemic venous return, which in turn is largely determined by factors outside the heart (such as the muscle pump and arterial and venous tone). Although venous return is enhanced during physiological exercise, RV preload increases only marginally up to sub-maximal supine exercise (28, 39). In contrast, LV preload is actively augmented during exercise, as the increased RV systolic contraction leads to a higher pulmonary artery pressure and blood flow that is transmitted
through the pulmonary circulation to the LA (16, 23). Taking into account the results of our baseline test in healthy volunteers, this difference in preload dynamics in the heart seems to support a better preservation of LV filling during exercise, despite the inherent lower compliance of the more muscular LV (30).

We gained further insight into mechanisms underlying SV regulation in the two ventricles, using the sHRi-test. During exercise, CO is tightly regulated by oxygen demand (26). Therefore, the negative chronotropy in the sHRi-test naturally drove an increased inotropic response (indirect positive inotropy) to augment SV and maintain CO. This allowed us to interrogate how the two ventricles regulate SV during exercise. The sHRi-test shows that the mechanism of SV augmentation in different in the two ventricles (See Figure 4A). In the RV, SV augmentation was reached by contracting to a lower ESV. In contrast, the LV relied on increased EDV to provide the additional SV.

In endurance athletes, training is known to cause a natural adaptation of the heart that allows it to drive larger increases SV during exercise compared to normal individuals (25, 33). As athletes have larger hearts compared to volunteers, we compared the relative changes from rest between athletes and the volunteers. Our results show that the natural adaption of the SV response in athletes acted via a similar mechanism as observed in the sHRi-test. Again, the larger SV in the RV was mainly achieved by contractions to a lower ESV, while in the LV the augmented SV was achieved by increasing EDV. These outcomes echo earlier studies that showed an enhanced LV EDV response in endurance-trained individuals during exercise (25, 33). More importantly, the similar mechanisms in sHRi and natural SV adaption suggest the observed RV-LV differences are fundamental in SV regulation.

RV push or LV pull?

The increased LV filling during SV augmentation observed in our experiments could originate from an improved active LV relaxation (‘LV pull’), an increased support of LV filling through the RV systolic ejection (‘RV push’), increased LA contraction or some combination of these. By examining changes in atrial behavior during exercise we aimed to determine which of these factors dominated the observed behavior. We were unable to measure total atrial volumes during the exercise CMRs. However, we were able to quantify changes in atrial maximal and minimal areas from the acquired long axis image-stacks.
We show that with SV augmentation in the sHRi-test and in athletes, LA\textsubscript{max} was larger in comparison to the baseline test, while there was no significant difference in LA\textsubscript{min} response. These results suggest that the main change driving improved LV filling in our experiments is a factor outside the left heart, most likely extra supply from the RV. If the LV pull or atrial contraction dominated the changes, it would lead to a decrease in LA\textsubscript{max}.

Single plane atrial areas are not direct surrogates for atrial volume changes. However, our observations during the physiological test are in keeping with a previous studies quantifying atrial areas and volumes during exercise (10, 34). They are also consistent with invasive studies that have shown that mean LA pressures increase compared to mean RA pressures during supine exercise in healthy volunteers and more so in athletes (28, 39). Previous studies have additionally showed that LV relaxation, while augmented in athletes (4), is not the limiting factor determining EDV and SV during exercise (35). Altogether, we therefore conclude it is plausible that the RV push is the dominant factor improving LV filling in our exercise experiments.

### Advantage of biventricular SV regulation

A core question arising from our experiments is: What drives the heart to maintain or improve LV SV by relying on increased RV contraction to support LV filling during exercise, instead of further LV systolic contraction to lower LV ESV? We used a highly detailed, personalised 3-dimensional biomechanical model of the biventricular heart (See Figure 5C) to explore the benefit of this mechanism. From the model, we estimated the costs of activation – the sum of active stresses between EDV and ESV – for each ventricle. This way, changes in the energetic cost for increased SV (through some combination of increasing EDV and decreasing ESV) could be explored.

Our modelling results show that the LV operates to optimize the cost of contraction during exercise by maintaining an ESV just below minimal point in the active tension curve. However, this behaviour limits ESV reserve, and contracting to an ESV beyond the optimal point increases the cost of contraction exponentially. As a result, LV is dependent on filling to augment SV during exercise. This is in keeping with previous observations of LV behaviour, which showed that LV ESV, after an initial decrease, plateaus long before peak exercise (31, 35). We further show that the RV ESV reserve (e.g. the point from the working ESV to where costs increase exponentially) is larger compared to the LV during exercise.
This is likely the result of its geometry, allowing it to contract into the LV septal wall, as well as the lower afterload in the RV. As a result, the RV is able to contract to lower ESV. In combination with the lower RV afterload, these results imply that the heart optimizes the total contractile costs of the two ventricles by utilizing RV systolic contractions to drive diastolic filling of the LV during SV augmentation.

Implications

Appreciation of ventricular interdependence has so far largely focused on mechanical inter-ventricular interaction through the septum (9). We demonstrated that ventricular cooperation through RV driven LV stroke volume regulation presents another core functional interaction pivotal to cardiac performance. Effectively, the RV acts as the hearts’ equivalent of the supercharger in a combustion engine, optimizing performance of the systemic pump during exercise. These findings can explain the importance of RV function in the prognosis of patients with LV heart failure (20, 27). They could also justify why treatments for LV heart failure, such as cardiac resynchronization therapy, are shown to be ineffective in patients with RV dysfunction (37). Patients with congenital heart disease and a single-ventricle circulation experience a progressive decline in cardiac function from early adult life (32). This decline may also be explained by our work, as the lack of a sub-pulmonary ventricle to optimize LV contractions is likely to increase strain on the single-ventricle. Similarly, dysfunction of the RV in patients with pulmonary hypertension and its negative impact on LV filling (8, 17) – and therefore impaired RV supported optimization of LV function – could help clarify the somber prognosis in these patients. Finally, exploitation of RV systolic function to maintain optimal LV performance could explain the adverse effects of high intensity exercise on the RV in competitive athletes, such as the transient RV injury observed in early recovery after exercise to maximal exhaustion (7) and adverse RV-remodeling and its RV associated ventricular arrhythmias (15).

Optimizing RV function is often overlooked as a clinical or training strategy. The current study provides mechanistic understanding of the importance of the RV. Based on this, training the RV to optimize cardiovascular fitness and athletic performance, targeting RV health as a therapeutic strategy in cardiac dysfunction and finding alternative sub-pulmonary pumps for patients with congenital heart disease with a single-ventricle circulation become important goals to pursue. Indeed, recently developed RV targeted treatments, such as RV
assist devices (1), RV resynchronization therapy (18), or, in the case of a single ventricle
circulation, implantation of pre-pulmonary impellors (11), have shown promising results in
pre-clinical studies.

Limitations

Our study has some major limitations. Firstly, we did not measure invasive ventricular
pressures in this study. Based on the ventricular and atrial volume changes observed in our
different experiments we suggest the RV push is main driver of the observed changes in LV
EDV, but we cannot totally exclude a minor role of improved LV relaxation or a change in
pulmonary pressures between the baseline and sHRi test. Changes in behavior of the
pulmonary circulation between the two tests in healthy volunteers are unlikely. Pulmonary
pressures and pulmonary capillary wedge pressures are highly correlated with CO (29),
which remained unchanged. Furthermore, maximal pulmonary vasodilatation is reached early
during exercise (16, 29), making significant further changes improbable. Secondly, we could
not randomize the order of the tests (baseline or sHRi) in healthy volunteers due to the long
effect of sHRi (T_{1/2} = 12 hours). We used extensive familiarization and training trials prior to
each test. However, a bias due to training cannot totally be excluded. Thirdly, selective HR-
inhibition itself could result in changes in ventricular behavior observed during exercise. The
decrease in HR results in a longer diastole and therefore will have impacted LV and RV
EDV. Indeed, we observed a trend towards a larger RV EDV, in which preload is largely
independent of the heart’s actions. A similar effect can thus be expected in the LV. However,
extrapolated from the effect of the RV, and taking into account the large compliance in the
LV, this increased filling time cannot explain the magnitude of change in LV EDV observed
during our experiments. Lastly, CMR measurements, including the ones obtained using our
exercise CMR protocol, have a 5-10% variability for single measurements (21). We
compared the response trends over multiple measurements in this study (at rest, moderate and
high exercise) between and within individuals. This repeated measurements design reduces
the impact of single measurement variability with regard to the observed trend. Several
previous studies have used this exercise CMR technique and shown that trends of the
magnitude described in our paper can be reliably assessed (6, 25, 34, 36).
Conclusion

We demonstrate a fundamental mechanism of functional ventricular interaction in the heart: the synergy between RV and LV function in SV regulation during exercise-stress, in which RV systolic ejection plays a pivotal role in efficient LV function and CO generation. The RV must therefore not be ignored in assessment and treatment of patients with cardiac diseases and optimization of training in competitive athletes.
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Supplemental Methods

https://doi.org/10.6084/m9.figshare.12122739.v1

https://figshare.com/s/f97b356a61ccf4a5d5fa

Downloaded from journals.physiology.org/journal/ajpheart at Kings Col London Jrnl Sec (082.169.056.183) on August 11, 2020.
Figure 1. Exercise CMR setup and flowchart of Exercise CMR experiments. A: Supine bicycle ergometer in a wide bore 1.5T MRI scanner. B: Study Flowchart.
Figure 2. Change in Stroke Volume (SV) from rest during the baseline (blue) and selective heart rate (HR)-inhibited tests (red) in healthy volunteers (n=16), and the baseline test in athletes (green, n=10). Data points are the mean±standard error SV at the corresponding exercise levels. An asterisk denotes a statistically significant difference in total SV response over all exercise stages using two-way repeated measures ANOVA ($p<.01$ after Bonferroni correction). A dagger and double-dagger denote a significant difference at the corresponding exercise level for the heart rate (HR)-inhibited test and athletes, with respect to the baseline test in healthy volunteers using paired and unpaired T-testing, respectively ($p<.01$ after Bonferroni correction).
Figure 3. A: Change in end-diastolic volume (EDV) and B: change in end-systolic volume (ESV) from rest in the right ventricle (RV; solid blue line) and left ventricle (LV; dotted blue line) during physiological exercise in healthy volunteers (n=16). Data points are the mean±standard error EDV and ESV measured at the corresponding exercise level. An asterisk denotes a statistically significant different response (total response over all exercise stages) between the two ventricles using two-way repeated measures ANOVA ($p<.01$ after Bonferroni correction). A dagger denotes statistically significant difference in volume change from rest between the two ventricles at the corresponding exercise level using unpaired T-testing ($p<.01$ after Bonferroni correction).
Figure 4. Biventricular responses during stoke volume augmentation. Right and left ventricular volume changes from rest during the exercise CMRs. Blue lines represent the end-diastolic volume (EDV) and end-systolic volume (ESV) responses during the baseline-test in healthy volunteers (n=16). Data points are expressed as mean±standard error of EDV and ESV measured at the corresponding exercise level. Blue boxes illustrate stroke volume (SV). The red lines in A and B represent the ventricular responses during the selective heart rate inhibited (sHRi) test. The red boxes show the difference in SV from the baseline test. The green lines in C and D represent the ventricular responses from rest in athletes (n=10) and the green boxes show the difference in SV augmentation in the athletes relative to the baseline test in healthy volunteers. The grey dotted lines represent the resting volumes. An asterisk denotes a statistically significant difference between the baseline and sHRi-test in healthy volunteers in A and B, and between athletes and healthy volunteers in C and D using two-way repeated measures ANOVA (p<.01 after Bonferroni correction). A dagger denotes a statistically significant difference at the corresponding exercise level using paired (A and B) and unpaired (C and D) T-testing (p<.01 after Bonferroni correction).
Figure 5. Biventricular costs of contraction during stroke volume regulation. A: left ventricular (LV) and B: right ventricular (RV) active tension curves obtained from the personalized biomechanical model. The grey areas represent the ventricular volumes measured at sub-maximal exercise. The white dotted line represents the ESV at moderate exercise. The grey dotted lines and markers represent the different available strategies for a further 10% increase in stroke volume in LV and RV. C: Illustration of the personalized biventricular biomechanical model with a color map illustrating active tension in the myocardium during contraction.
Table 1. Baseline characteristics of subjects

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<th>Healthy Volunteers (n=16)</th>
<th>Athletes (n=10)</th>
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</tr>
<tr>
<td>Hours of exercise/week</td>
<td>0.5±0.6</td>
<td>16±4</td>
<td>&lt;.001*</td>
</tr>
</tbody>
</table>

Hours of exercise/week is the average over the last 4 years. Cm denotes centimeters, kg; kilograms, m; meter. The data is expressed as mean±standard deviation. An asterisk denotes a statistical significant difference between the groups (p<.05) using unpaired T-testing.
Table 2: Changes in heart rate, cardiac output and cardiac volumes during exercise.

<table>
<thead>
<tr>
<th></th>
<th>Healthy Volunteers: Physiological exercise</th>
<th>Physiological exercise</th>
<th>Athletics Physiological exercise</th>
<th>Physiological exercise</th>
<th>Physiological exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Change from rest to:</td>
<td>Rest</td>
<td>Change from rest to:</td>
<td>Rest</td>
</tr>
<tr>
<td>Exercise Load (Watts)</td>
<td>0</td>
<td>+65±5</td>
<td>+121±5</td>
<td>0</td>
<td>+80±5</td>
</tr>
<tr>
<td>Heart Rate (beats per minute)</td>
<td>67±10</td>
<td>+46±5</td>
<td>+91±8</td>
<td>65±10</td>
<td>+40±4†</td>
</tr>
<tr>
<td>Cardiac Output (L/min/m²)</td>
<td>3.4±0.6</td>
<td>+2.9±0.5</td>
<td>+4.8±0.7</td>
<td>3.3±0.6</td>
<td>+3.1±0.5</td>
</tr>
<tr>
<td>Left Ventricle</td>
<td>End Diastolic Volume (mL/m²)</td>
<td>83±11</td>
<td>+64</td>
<td>+1015</td>
<td>82±10</td>
</tr>
<tr>
<td></td>
<td>End Systolic Volume (mL/m²)</td>
<td>31±7</td>
<td>+8±4</td>
<td>+13±5</td>
<td>31±6</td>
</tr>
<tr>
<td>Stroke Volume (mL/m²)</td>
<td>52±6</td>
<td>+42±2</td>
<td>+3±2</td>
<td>51±6</td>
<td>+11±3†</td>
</tr>
<tr>
<td>Ejection Fraction (%)</td>
<td>62±4</td>
<td>+8±4</td>
<td>+13±4</td>
<td>62±4</td>
<td>+11±4</td>
</tr>
<tr>
<td>Right Ventricle</td>
<td>End Diastolic Volume (mL/m²)</td>
<td>96±14</td>
<td>+11±6</td>
<td>+18±5</td>
<td>95±13</td>
</tr>
<tr>
<td></td>
<td>End Systolic Volume (mL/m²)</td>
<td>42±10</td>
<td>+14±5</td>
<td>+21±6</td>
<td>42±8</td>
</tr>
<tr>
<td>Stroke Volume (mL/m²)</td>
<td>52±6</td>
<td>+42±2</td>
<td>+3±2</td>
<td>51±6</td>
<td>+10±3†</td>
</tr>
<tr>
<td>Ejection Fraction (%)</td>
<td>56±5</td>
<td>+11±4</td>
<td>+17±4</td>
<td>55±4</td>
<td>+18±3†</td>
</tr>
</tbody>
</table>

The data is expressed as mean±standard deviation. P-values displayed were obtained using two-way repeated measures ANOVA. An asterisks denotes a statistical significant difference (p<.05 after Bonferroni correction) in exercise response between the respective experiments. A dagger denotes a statistical significant difference (p<.05 after Bonferroni correction) at the corresponding exercise level from the physiological test in healthy volunteers (n=16), using a paired T-test for the heart-rate (HR)-inhibited test and an unpaired T-test for the athletes (n=10).
Change in SV during exercise

Physiological test
HR-inhibited test
Athletes

Change in SV (mL/m²)

Rest
Moderate
Sub-maximal

0
5
10
15
20

† † † *

*
Table I. Baseline characteristics of subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy Volunteers (n=16)</th>
<th>Athletes (n=10)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27±5</td>
<td>26±5</td>
<td>0.54</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>9 (52)</td>
<td>7 (58)</td>
<td>0.17</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>176±11</td>
<td>180±9</td>
<td>0.29</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72±11</td>
<td>69±10</td>
<td>0.44</td>
</tr>
<tr>
<td>Body Surface Area (m²)</td>
<td>1.88±0.20</td>
<td>1.87±0.16</td>
<td>0.93</td>
</tr>
<tr>
<td>Hours of exercise/week</td>
<td>0.5±0.6</td>
<td>16±4</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Hours of exercise/week is the average over the last 4 years. Cm denotes centimeters, kg; kilograms, m; meter. The data is expressed as mean±standard deviation. An asterisk denotes a statistical significant difference between the groups (p<.05) using unpaired T-testing.
Table 2: Changes in heart rate, cardiac output and cardiac volumes during exercise.

<table>
<thead>
<tr>
<th></th>
<th>Healthy Volunteers (n=16):</th>
<th>HR-inhibited exercise</th>
<th>Athletes (n=10):</th>
<th>Physiological exercise</th>
<th>Change from rest to:</th>
<th>P-value of the mean effect between physiological vs. HR-inhibited test in healthy volunteers</th>
<th>P-value of the interaction between physiological exercise tests of healthy volunteers and athletes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Physiological exercise</td>
<td>HR-inhibited exercise</td>
<td>Physiological exercise</td>
<td>Physiological exercise</td>
<td></td>
<td></td>
<td></td>
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<tr>
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</tr>
<tr>
<td></td>
<td>Rest</td>
<td>Rest</td>
<td>Rest</td>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise Load (Watts)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+65±5</td>
<td>+121±5</td>
<td>n/a</td>
</tr>
<tr>
<td>Heart Rate (beats per minute)</td>
<td>67±10</td>
<td>+46±5</td>
<td>+81±8</td>
<td>65±10</td>
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</tr>
<tr>
<td>Cardiac Output (L/min/m²)</td>
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<td>+3.1±0.5</td>
<td>+4.9±0.7</td>
<td>3.5±0.7</td>
</tr>
<tr>
<td>Left Ventricle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End Diastolic Volume (mL/m²)</td>
<td>83±11</td>
<td>-4±4</td>
<td>-10±5</td>
<td>82±10</td>
<td>+3±4†</td>
<td>-1±4†</td>
<td>103±14†</td>
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<tr>
<td>End Systolic Volume (mL/m²)</td>
<td>31±7</td>
<td>-8±4</td>
<td>-13±5</td>
<td>31±6</td>
<td>-8±4</td>
<td>-12±4</td>
<td>39±9</td>
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<td>-18±5</td>
<td>93±13</td>
<td>-8±5</td>
<td>-15±5</td>
<td>122±13†</td>
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<td>End Systolic Volume (mL/m²)</td>
<td>42±10</td>
<td>-14±5</td>
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<td>42±8</td>
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<td>55±4</td>
<td>+18±3†</td>
<td>+25±4†</td>
<td>53±5</td>
</tr>
</tbody>
</table>

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