

Original Research

Isometric Handgrip Exercise During Cardiovascular Magnetic Resonance Imaging: Set-up and Cardiovascular Effects

Florian von Knobelsdorff-Brenkenhoff, MD,^{1,2*} Matthias A. Dieringer, MSc,^{1,2}
Katharina Fuchs, Dipl-Phys,¹ Fabian Hezel, Dipl-Inf,¹ Thoralf Niendorf, PhD,^{1,3}
and Jeanette Schulz-Menger, MD^{1,2}

Purpose: To establish a suitable setup for combining isometric handgrip exercise with cardiovascular magnetic resonance (CMR) imaging and to assess cardiovascular effects.

Materials and Methods: Fifty-three healthy volunteers (31 males, mean age 45 ± 17 years) underwent handgrip exercise in a 3T scanner using a prototype handgrip system and a custom-made feedback system that displayed the force. Handgrip was sustained at 30% of the maximal contraction for 6–8 minutes. Heart rate, blood pressure (BP), and double product were determined sequentially. Stroke volume was quantified in a subgroup ($n = 21$) at rest and stress using phase contrast acquisitions.

Results: Heart rate increased significantly between rest and stress by $20 \pm 13\%$, systolic / diastolic / mean BP by $15 \pm 11\%$ / $20 \pm 18\%$ / $17 \pm 13\%$, double product by $37 \pm 21\%$, and cardiac output by $27 \pm 16\%$ (each $P < 0.001$). Stroke volume did not significantly increase ($3 \pm 9\%$; $P = 0.215$). Higher age was associated with reduced increase of stroke volume ($P = 0.022$) and cardiac output ($P < 0.001$). Overweight subjects showed less increases in heart rate ($P = 0.021$) and cardiac output ($P = 0.002$).

Conclusion: The handgrip exercise during CMR with the presented set-up leads to considerable hemodynamic changes in healthy volunteers.

Key Words: cardiac imaging; stress; isometric exercise; handgrip; hemodynamic

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STRESS TESTS are an effective way to discriminate normal from abnormal cardiovascular function by unmasking subtle pathologic responses that would have been undetectable at rest (1). Even though treadmill or bicycle electrocardiography (ECG) is the most frequently used stress test in cardiology, there is a trend to combine stressors with noninvasive imaging in order to improve the sensitivity and specificity of a stress test. With regard to cardiovascular magnetic resonance imaging (CMR) as the imaging tool, the common stressors are adenosine, dipyridamole, or dobutamine, and there is plenty of evidence that stress CMR has adequate diagnostic accuracy to detect myocardial ischemia (2–4). However, these tests primarily aim at detecting coronary artery stenosis, whereas, for instance, stress tests to assess diastolic function are rare. In addition, the mentioned tests cause pharmacological stress instead of provoking physical stress, which is supposed to have a diverse impact on the cardiovascular system and to more closely reflect everyday exercise. Hence, a CMR stress test with physical stressors might provide important complementary information to characterize cardiovascular diseases. Thereby, the combination of CMR imaging with bicycle exercise within the scanner may be limited by motion of the subject leading to inaccurate slice positioning, which is crucial for pre- and postexercise comparisons (5). Using treadmill/bicycle exercise outside the scanner room and moving the patient at peak stress into the scanner is more convenient from a practical perspective (6). However, the time period between peak stress and image acquisition may allow the subject's cardiovascular system to recover, hence stress-induced alterations may have already disappeared. Instead, a handgrip exercise appears to be an interesting alternative that combines physical exercise within the scanner and image acquisition at peak exercise. Motion artifacts are assumed to be less compared

¹Berlin Ultrahigh Field Facility (B.U.F.F.), Max-Delbrueck Center for Molecular Medicine, Berlin, Germany.

²Working Group on Cardiovascular Magnetic Resonance, Experimental and Clinical Research Center, a joint cooperation between the Charité Medical Faculty and the Max-Delbrueck Center for Molecular Medicine, HELIOS Klinikum Berlin Buch, Department of Cardiology and Nephrology, Berlin, Germany.

³Experimental and Clinical Research Center, a joint cooperation between the Charité Medical Faculty and the Max-Delbrueck Center for Molecular Medicine, Berlin, Germany.

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*Address reprint requests to: Florian v.K., Working Group on Cardiovascular Magnetic Resonance, Charité Medical University Berlin, Experimental and Clinical Research Center, Lindenberger Weg 80, 13125 Berlin, Germany. E-mail: florian.von-knobelsdorff@charite.de

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Table 1
Baseline Characteristics of the Total Study Cohort and of the Subgroup With Stroke Volume Measurements (Results as Mean ± 1 Standard Deviation)

Parameter	Total study cohort	Subgroup with stroke volume measurements
<i>n</i>	53	21
Age ± SD [years]	45 ± 17	50 ± 21
Males/females	31 / 22	12 / 9
Height [cm]	174 ± 9	173 ± 9
Weight [kg]	76 ± 14	73 ± 10
Body mass index [kg/m ²]	25 ± 4	24 ± 4
LV end-diastolic volume [mL]	144 ± 37	129 ± 26
LV end-diastolic volume index [mL/cm]	0.8 ± 0.1	0.7 ± 0.1
LV mass [g]	101 ± 28	95 ± 22
LV mass index [g/cm]	0.5 ± 0.1	0.5 ± 0.1
LV ejection fraction [%]	63 ± 5	64 ± 5

SD, standard deviation; LV, left ventricle.

to cycling. The hemodynamic effects of handgrip exercise have been previously analyzed in humans using invasive measurements (7–10). In general, they found marked increases in blood pressure, heart rate, cardiac index, left ventricular stroke work, and myocardial O₂ consumption. Also, the pattern of hemodynamic response to isometric exercise differed between healthy controls and patient groups (8,9,11,12). In combination with CMR, previous studies tested the feasibility of handgrip exercise during CMR (13), used handgrip exercise during magnetic resonance (MR) spectroscopy to assess cardiac metabolism (14), as well as during phase contrast acquisitions to assess coronary blood flow (15–17).

However, setting up a handgrip exercise unit requires adequate hardware and software as well as instructions, including which stress protocol to use and how to achieve the best performance. Thus, the aim of the present study was to establish a robust set-up for isometric handgrip exercise during CMR imaging and to evaluate the cardiovascular effects that can be expected in this setting.

MATERIALS AND METHODS

Study Cohort

Fifty-three healthy volunteers were enrolled in the study and underwent isometric handgrip exercise in

an MR scanner as outlined below. The status “healthy” was based on: 1) uneventful medical history; 2) absence of any symptoms indicating cardiovascular dysfunction; 3) normal ECG; and 4) normal cardiac dimensions and function on CMR cine imaging (18). All volunteers gave written informed consent to participate in the study and the institutional Ethics Committee approved the study. Table 1 depicts the baseline characteristics of the volunteers.

CMR Setting and Techniques

All CMR examinations were performed in a wide-bore (70 cm) 3T system (Magnetom Verio, Siemens Healthcare, Erlangen, Germany) using a 32-channel cardiac coil for signal reception, the integrated body coil for transmission, and ECG for cardiac gating. For volume-selective B₀ shimming, a field map was used based on the double-echo gradient echo. For each subject first- and second-order shims were calculated to reduce the frequency shift across a rectangular region around the heart. The CMR protocol comprised the following techniques (Fig. 1).

All Subjects

Steady-state free-precession (SSFP) cine images were acquired during repeated breath-holds in standard long axes (four-, three-, and two-chamber views) and in a stack of short axes covering the whole left ventricle (LV) from base to apex (no interslice gap). Imaging parameters were: repetition time (TR) 3.1 msec, echo time (TE) 1.3 msec, flip angle (FA) 45°, voxel size 1.8 × 1.4 × 6 mm³, receiver bandwidth 704 Hz/Px, generalized autocalibrating partially parallel acquisition (GRAPPA) acceleration factor 2, 30 calculated cardiac phases, approximate breath-hold length 12 seconds. These images served for the visual assessment of any wall motion abnormalities and for the quantification of LV parameters at rest. The quantification comprised LV end-diastolic volume (LVEDV), LVEDV indexed by height (LVEDVI), LV end-systolic volume (LVESV), LVESV indexed by height (LVESVI), LV mass (LVM), LV mass indexed by height (LVMI), and LV ejection fraction (LV-EF). SSFP cine images were acquired only once at baseline and not repeatedly during the handgrip exercise.

Subgroup of 21 Volunteers (Randomly Selected)

Breath-held, through-plane phase contrast measurements were acquired at the aortic sinotubular level to

Figure 1. Schematic of the examination protocol. Cardiac function was assessed once at baseline. Heart rate and blood pressure (in all subjects) and stroke volume (in a subgroup) were obtained at rest, at peak stress, and during recovery. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

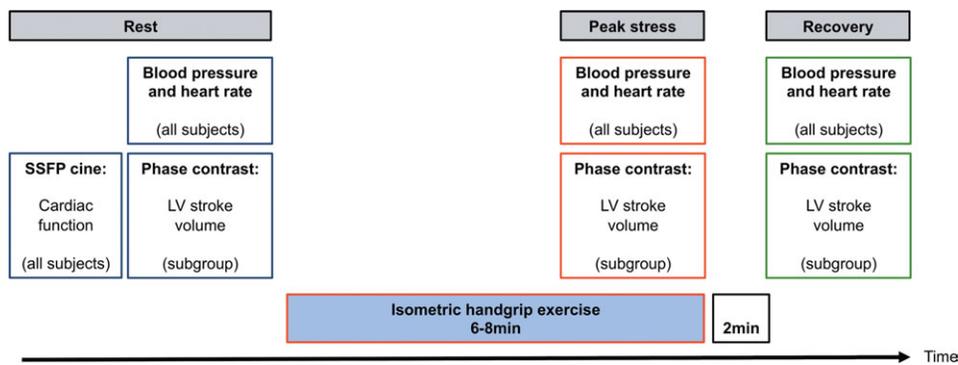




Figure 2. The system used for isometric exercise (Sensory-Motor Systems Lab) consisted of the handgrip (shown in this image), a plastic fiber cable, an electronic switchbox, and corresponding software. The force was registered by an optical measurement principle integrated into the plastic handgrip. This facilitated squeezing of the handgrip with negligible subject movement.

assess left ventricular stroke volume. Imaging parameters were: TR 9.5 msec, TE 1.98 msec, FA 25°, voxel size $1.7 \times 1.1 \times 5.5 \text{ mm}^3$, receiver bandwidth 554

Hz/Px, GRAPPA acceleration factor 2, 20 calculated cardiac phases, velocity encoding typically 150 cm/sec, approximate breath-hold length 16 seconds. These phase contrast measurements were obtained both at baseline and at stress during sustained handgrip exercise.

The CMR data were analyzed using CMR⁴² (Circle Cardiovascular Imaging, Calgary, Canada).

Handgrip Technique and Protocol

For isometric exercise we used a CMR-compatible prototype of a handgrip system (Sensory-Motor Systems Lab, Zurich, Switzerland), which consists of a handle, an electronic switchbox, and corresponding software (Fig. 2) and has previously been used for functional MRI (19). The force was registered by an optical measurement principle integrated into the plastic handgrip. This facilitated squeezing of the handgrip with negligible subject movement. The force limit was 600N and the handgrip was set to measure isometric grip force with a sampling frequency of 30 Hz. The handgrip was connected with the electronic box via plastic fibers. The fiber cable length from the handgrip to the electronic box was 15 m. The electronic box was located outside the scanner room and the cable was led through the wave-guide. The serial output of the switchbox was connected via a USB-converter to a personal computer in the control room. Specific software (MRI force monitor, Sensory-Motor Systems Lab) continuously displayed the handgrip force on a graph in real time (Fig. 3).

To provide information about the actual force to the subject in the MR scanner we developed a feedback-system: Using the posterior part of a head coil as the platform, we installed a mirror system on a plastic

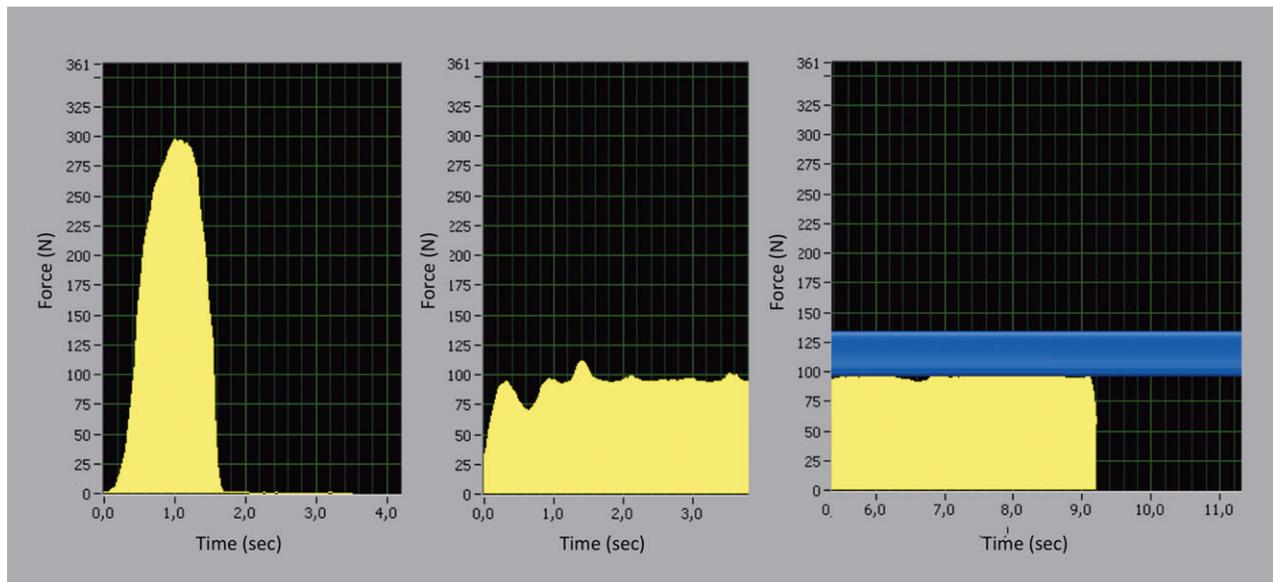


Figure 3. Monitoring software (MRI force monitor, Sensory-Motor Systems Lab) continuously displayed the handgrip force on a screen: Left: In the beginning, the maximum voluntary contraction of the dominant forearm muscles is registered. Middle: During isometric exercise, a constant force on the handgrip at 30% of the maximum was required. Right: The individual target force was marked on the screen by adding an electronic tag to facilitate the volunteer to constantly sustain the required force.

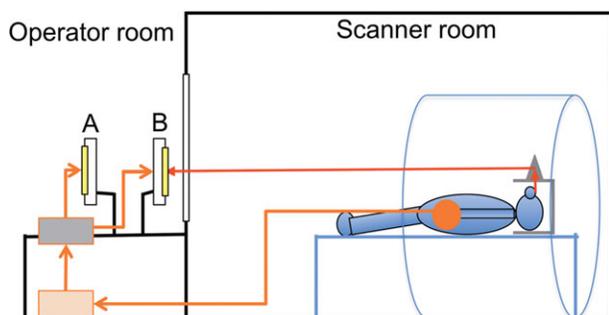


Figure 4. Feedback system to provide information about the actual force to the volunteer in the MR scanner: If the volunteer squeezes the handgrip (orange circle), the force is registered by an optical measurement principle and transferred via fiber cable (orange arrow) to the switchbox (orange rectangle) in the operator room. The switchbox is connected to a PC (gray rectangle) that runs specific software to display the actual handgrip force. This PC is connected to screen A that displays the actual force to the operators and screen B that is oriented to the scanner. In the scanner, a mirror system is installed above the volunteer's eyes (gray triangle) using the posterior part of a head coil as the platform (gray lines) that enables the volunteer to look outside the scanner (red arrow). By this, the volunteer sees the screen within the control room that continuously displays the actual force. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

frame above the volunteer's eyes enabling the volunteer to look outside the scanner in the direction of his/her legs. By this, the volunteer was able to see a wide screen display within the control room (distance between mirror and screen ~ 5 m). This screen was connected to the computer that runs the "MRI force monitor" software and continuously displayed the actual force to the volunteer (Fig. 4). The operators marked the individual target force on the screen by adding an electronic tag to facilitate the volunteer's ability to sustain a constant force (Fig. 3). In case that myopia or obesity impeded the volunteer's view of the screen, the operators guided the volunteer orally using the intercommunication function of the MR system.

Based on published data for isometric exercise, we established the following protocol (8,9,14,16): At first, each volunteer was asked to squeeze the handgrip using her/his dominant hand at the maximal force he/she could develop for an instant. This measurement was taken as an estimate of the maximum voluntary contraction of the forearm muscles. Each volunteer was then asked to sustain their grasp on the handgrip at 30% of maximum force for a period of at least 6 minutes and if tolerable for 8 minutes. The test was prematurely terminated if the hand became intolerably fatigued.

Cardiovascular Monitoring

The heart rate was assessed using ECG monitoring. The average heart rate during the phase contrast acquisition was noted. Systolic and diastolic blood pressure were measured by a semiautomatic arm cuff sphygmomanometer at the nondominant arm (Fig. 1). The double product or rate-pressure product (heart rate \times systolic blood pressure in mmHg/min) was calculated as an in-

dicator of myocardial oxygen consumption and cardiac work (20). Furthermore, we calculated its change from rest to maximal exercise, the so-called double product reserve, which has been shown to have prognostic value in patients with coronary artery disease (21). Measurements were performed in all volunteers at rest, at peak stress, and 2 minutes after terminating the handgrip exercise. In the subgroup, stroke volume as assessed by CMR in conjunction with heart rate was used to calculate cardiac output (L/min) and (referred to body surface area) cardiac index (L/min/m²).

Statistical Analysis

Statistical analysis was performed using SPSS 20.0 (IBM, Armonk, NY) and results presented using Prism 5.0b (GraphPad Software, San Diego, CA). A Kolmogorov-Smirnov-test was applied to examine normal data distribution. Data are expressed as mean value ± 1 standard deviation. Paired Student's *t*-tests were used to compare baseline and stress measurements. Student's unpaired *t*-tests were used to compare the proportionate changes from rest to stress between groups. Correlations were assessed using the Pearson product-moment approach. A stepwise multiple linear regression analyses examined the coherency between baseline characteristics and stress parameters. Statistical significance was defined as $P < 0.05$.

RESULTS

Procedural Information From Handgrip Exercise

All 53 enrolled volunteers performed isometric handgrip exercises within the MR scanner using the described setting. In $n = 8$, the screen-based feedback system was not usable due to myopia or obesity, so oral instruction was used. Average maximum voluntary force was $259\text{N} \pm 92\text{N}$ (range 110–450N). Men exhibited higher values than women ($314 \pm 72\text{N}$ vs. $180 \pm 53\text{N}$; $P < 0.001$), whereas age and body mass index (BMI) did not influence the average maximum voluntary force ($P = 0.198$ and $P = 0.396$). Mean squeeze duration was 6.6 ± 1.3 minutes (range 3–8 min). In 21/27/1/2 and 2 volunteers, exercise was terminated after 8/6/5/4 and 3 minutes due to muscular weakness of the forearm. Older participants exhibited shorter squeeze duration ($P = 0.015$), whereas squeeze duration was independent of sex ($P = 0.899$), BMI ($P = 0.750$), and maximum voluntary force ($P = 0.571$). All volunteers tolerated the exercise well and the muscular strain relieved promptly after finishing squeezing. No adverse events occurred. Heart rate and blood pressure results were available for every measurement. All CMR flow measurements provided diagnostic image quality without motion artifacts during exercise.

Cardiovascular Effects of Isometric Handgrip Exercise

Table 2 shows the mean results for heart rate, systolic / diastolic / mean blood pressure, double product, stroke volume, cardiac output, and cardiac index at rest and at peak stress. All hemodynamic parameters

Table 2
Cardiovascular Effects of Isometric Handgrip Exercise (Results as Mean \pm 1 Standard Deviation)

Parameter	Total study cohort			Subgroup with stroke volume measurements		
	Rest	Stress	<i>P</i> -value	Rest	Stress	<i>P</i> -value
Heart rate [min ⁻¹]	68 \pm 12	81 \pm 13	<0.001	70 \pm 12	88 \pm 12	<0.001
Systolic blood pressure [mmHg]	126 \pm 14	144 \pm 18	<0.001	125 \pm 17	149 \pm 21	<0.001
Diastolic blood pressure [mmHg]	70 \pm 10	83 \pm 13	<0.001	68 \pm 13	84 \pm 14	<0.001
Mean blood pressure [mmHg]	88 \pm 10	103 \pm 13	<0.001	87 \pm 13	105 \pm 14	<0.001
Double product [mmHg/min]	8530 \pm 2173	11522 \pm 2674	<0.001	8824 \pm 2660	12880 \pm 3139	<0.001
Stroke volume [mL]	—	—	—	78 \pm 12	80 \pm 13	0.215
Cardiac output [L/min]	—	—	—	5.4 \pm 0.8	6.9 \pm 1.1	<0.001
Cardiac index [L/min/m ²]	—	—	—	2.9 \pm 0.5	3.7 \pm 0.7	<0.001

except stroke volume showed on average a significant stress-induced increase. The mean double product reserve was 2992 \pm 1544 mmHg/min, ranging from 777 mmHg/min to 8676 mmHg/min. The changes between rest and stress expressed as percentage of the baseline value are illustrated in Fig. 5. On an individual basis, heart rate, double product, and cardiac output/index increased between rest and stress in all subjects, and systolic / diastolic / mean blood pressure increased in all but 2/6/2 subjects. Stroke volume mildly increased in 12 subjects, remained constant in two, and decreased in seven subjects (Fig. 6). After terminating the isometric exercise, the hemodynamic changes returned to the baseline level within 2 minutes in all subjects of the subgroup.

Factors With Potential Influence on the Hemodynamic Response to Handgrip Exercise

These factors were tested in a stepwise multiple linear regression model. Factors and results are summarized in Table 3.

Age

Age was a significant influencing factor for percentage increase of stroke volume ($P = 0.022$), cardiac output

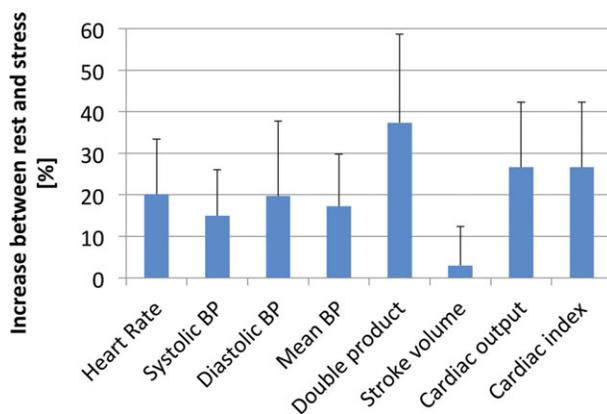


Figure 5. Percentage change between rest and stress of the measured hemodynamic parameters (BP = blood pressure). To provide a context: With bicycle/treadmill exercise performed to maximum exertion, heart rate increases 1.5–2-fold, systolic blood pressure by about 50%, and double product 2.5-fold (21,25). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

($P < 0.001$), and cardiac index ($P < 0.001$). Higher age resulted in lower stroke volume ($r = -0.66$; $P = 0.001$) and lower cardiac output/index (each $r = -0.79$, $P < 0.001$). All seven individuals with decreasing stroke volume were ≥ 65 years.

Sex

We did not observe significant differences between men and women regarding the hemodynamic response to stress.

BMI

The multiple regression analysis did not find a correlation between BMI and hemodynamic response to stress. When separating the sample into overweight subjects (BMI > 25.0 kg/m²; $n = 23$) and subjects with BMI in the normal range (18.5–24.9 kg/m²; $n = 30$), those who were overweight exhibited less proportionate increase of heart rate ($P = 0.021$), cardiac output ($P = 0.002$), and cardiac index ($P = 0.002$).

Force and Squeeze Duration

Higher maximum voluntary force resulted in a more extensive increase of mean blood pressure during stress ($P = 0.007$). In subjects with shorter squeeze duration, the systolic blood pressure increase was more pronounced ($P = 0.002$).

Resting Blood Pressure

There was a significant association between resting systolic blood pressure and proportionate increase of heart rate ($P = 0.001$), systolic blood pressure ($P = 0.029$), double product ($P < 0.001$), cardiac output ($P = 0.003$), and cardiac index ($P = 0.003$). Thereby, resting systolic blood pressure correlated negatively with the proportionate increase of heart rate ($r = -0.43$; $P = 0.02$), systolic blood pressure ($r = -0.29$; $P = 0.051$), double product ($r = 0.50$; $P < 0.001$), and cardiac output/index ($r = -0.77$; $P < 0.001$).

Resting Stroke Volume and Resting Cardiac Index

Resting stroke volume was linked with proportionate increase of diastolic blood pressure ($P = 0.010$). Thereby, the higher the baseline stroke volume, the higher the increase of diastolic blood pressure ($r = 0.71$; $P < 0.001$). There was an association of baseline cardiac index and stress-induced increase of double

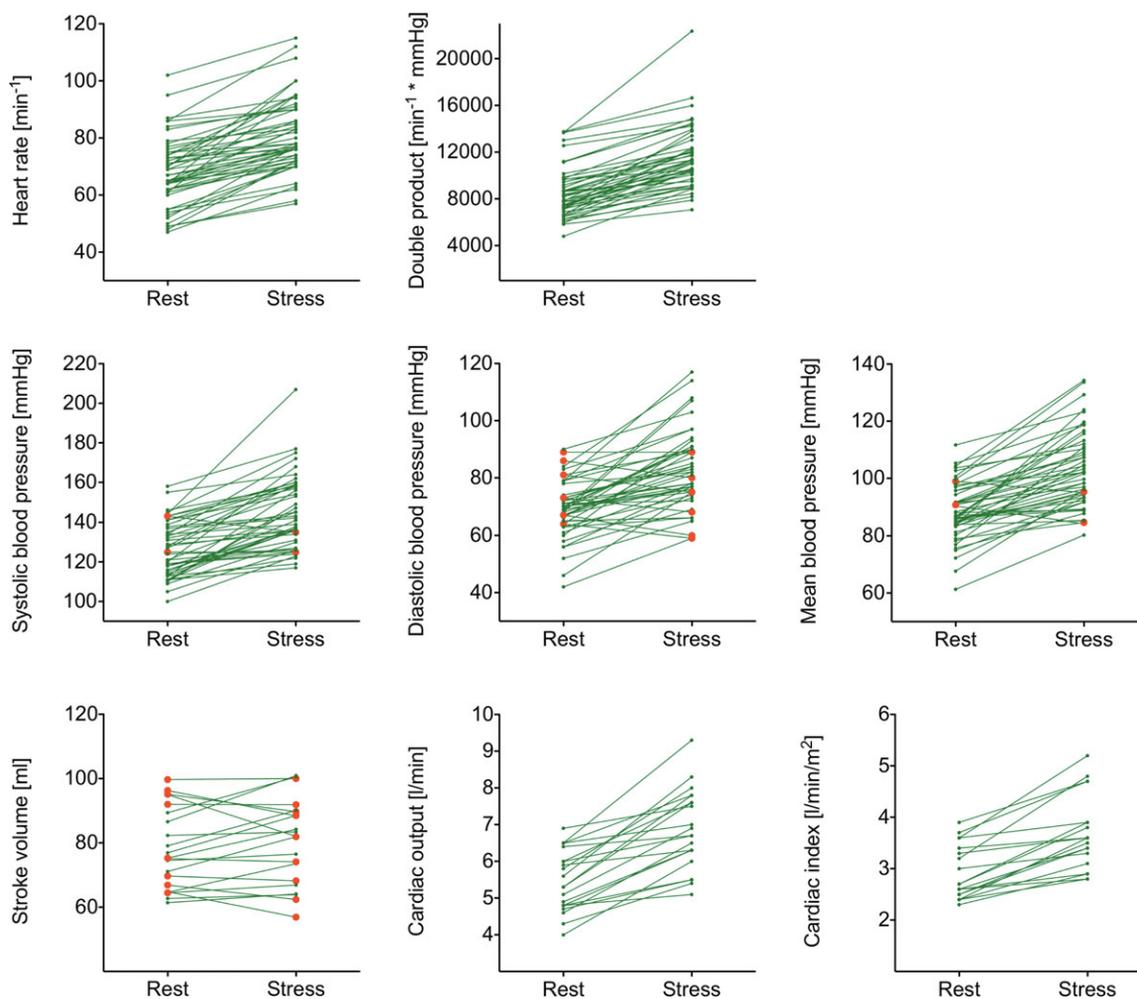


Figure 6. Individual changes between rest and peak exercise for heart rate, blood pressure, double product, stroke volume, cardiac output, and cardiac index. The red dots mark those individuals in whom stress did not induce an increase of the specific hemodynamic parameter. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 3
Stepwise Multiple Linear Regression Analysis of Factors With Potential Influence on the Proportionate Hemodynamic Changes Between Rest and Stress (Gray Shaded Cells Highlight Significant Results With $P < 0.05$)

Parameter	Heart rate	Systolic BP	Diastolic BP	Mean BP	Double product	Stroke volume	Cardiac output	Cardiac index
Sex	0.743	0.127	0.708	0.432	0.828	0.304	0.649	0.649
Age	0.176	0.821	0.314	0.317	0.718	0.022	<0.001	<0.001
BMI	0.175	0.905	0.518	0.300	0.543	0.793	0.286	0.286
Max. force	0.846	0.160	0.218	0.007	0.431	0.435	0.216	0.216
Squeeze duration	0.592	0.002	0.162	0.086	0.114	0.834	0.272	0.272
LV-EDV	0.823	0.212	0.425	0.878	0.504	0.851	0.237	0.237
LV-EDV-I	0.530	0.251	0.229	0.646	0.369	0.668	0.292	0.292
LV-Mass	0.280	0.328	0.159	0.652	0.566	0.212	0.960	0.960
LV-Mass-I	0.387	0.375	0.072	0.443	0.622	0.237	0.884	0.884
LV-EF	0.829	0.492	0.459	0.389	0.354	0.886	0.367	0.367
Resting heart rate	0.475	0.221	0.807	0.441	0.491	0.364	0.723	0.723
Resting systolic BP	0.001	0.029	0.196	0.107	<0.001	0.578	0.003	0.003
Resting diastolic BP	0.342	0.564	0.086	0.100	0.828	0.071	0.062	0.062
Resting mean BP	0.344	0.562	0.094	0.077	0.827	0.154	0.063	0.063
Resting double product	0.719	0.105	0.639	0.251	0.290	0.491	0.702	0.702
Resting stroke volume	0.279	0.774	0.010	0.340	0.586	0.103	0.575	0.575
Resting cardiac output	0.526	0.136	0.809	0.900	0.952	0.532	0.230	0.230
Resting cardiac index	0.089	0.192	0.846	0.644	0.041	0.290	0.515	0.515

product ($P = 0.041$). Correlation analysis demonstrated a nonsignificant negative correlation ($r = -0.16$; $P = 0.534$).

Cardiac Function/Dimension

LVEDV, LVEDV-I, LV mass, LVMI, and LV-EF did not significantly influence the hemodynamic changes between rest and stress in healthy volunteers.

DISCUSSION

The present study established and elaborately describes a suitable setting to perform isometric handgrip exercise in a CMR unit. Furthermore, it confirms the hemodynamic effects that have been described previously using invasive measurements.

Isometric handgrip exercise has the potential to offer an interesting approach to perform physiological stress examinations during CMR imaging. To be used in a clinical and research setting and to achieve accurate and reproducible results, a practical and robust setting is mandatory. We describe a setting that combines a prototype handgrip system with a custom-made feedback system that can easily be recreated. The present experiences demonstrated that this system technically worked adequately in all studied volunteers. We did not observe any motion artifacts during CMR imaging, which we attribute to the lack of any physical body movement using the proposed handgrip. Oral instruction using the intercommunication function of the CMR scanner worked adequately in subjects where obesity or myopia impeded the view to the feedback screen. Nevertheless, the visual feedback approach achieved a more constantly sustained handgrip and was more operator-friendly, as the technician simultaneously had to perform the CMR scans. Poor subject cooperation leading to uninterpretable results or interactions between breath-holding and squeezing were not observed, which we attributed to the continuous visual or audio feedback. In summary, the present report describes a contemporary CMR-compatible handgrip exercise and feedback system that may be implemented by those who intend to set up a handgrip test at their CMR unit. However, it remains to be shown in future studies whether this set-up also works in sick and older patients, who, for instance, might develop difficulties to coordinate breath-holding and handgrip squeezing synchronously.

Isometric exercise associated with sustained handgrip exercise is associated with a strong somato-sympathic reflex that results in increased activity of plasma catecholamines and cardiac work (10,22,23). The present study confirms previous reports that used invasive measurements for hemodynamic monitoring and demonstrated that handgrip exercise causes a substantial stress to the left ventricle (8,9,11). In accordance with these studies, we observed increases of heart rate, blood pressure, double product, cardiac output, and cardiac index in almost all subjects. For example, Fisher et al (11) reported an average increase of heart rate by 20%,

which is identical to our study. Similarly, Hays et al (16) reported an increase of heart rate by 16%. Systolic, diastolic, and mean blood pressure increased in our series by $15 \pm 11\%$, $20 \pm 18\%$, and $17 \pm 13\%$, which is in the range of published results, eg, by Hays et al (16) and Fisher et al (11), who reported an increase of mean blood pressure by 13% and 23%, respectively. Other previous studies reported even slightly higher increases of mean blood pressure, which may be attributed to differences of the handgrip protocol and the studied subjects as well as invasive vs. noninvasive blood pressure measurements (9,24). In our studies the cardiac index increased relatively by $27 \pm 16\%$ and absolutely by 0.8 ± 0.5 L/min/m², which is similar to the rise by 0.8 L/min/m² as reported by Helfant et al (9) in healthy individuals. Contrary to this, Fisher et al described an increase of cardiac index by only 18%. The difference to our results can be explained by differences in the study cohort, as Fisher et al also included patients with cardiac disease. These patients are known to be less capable to increase cardiac index during stress compared to healthy individuals (9). Increases in cardiac output and cardiac index in our series were mainly attributable to increases of heart rate, whereas absolute stroke volume increased only slightly in 12 subjects, remained constant in two, and even decreased in seven subjects. This stability of stroke volume in healthy subjects is in accordance with previous reports, eg, by Fisher et al (11), who reported a nonsignificant increase from 69 mL to 79 mL, by Taylor et al (24), who reported even a minimal decrease in young men and no change in older men, as well as by Helfant et al (9), who also observed a nonsignificant decrease of stroke volume index during handgrip exercise in healthy individuals. Finally, double product increased in our series by $37 \pm 21\%$, which falls between a 27% increase reported by Hays et al (16) and 54% by Gobel et al (20) increase achievable during bicycle exercise using a symptom-tolerated maximal exercise protocol.

Obviously, the hemodynamic changes achieved by isometric handgrip exercise did not reach the extent of bicycle/treadmill exercise tests performed to maximum exertion, where heart rates often increase 1.5–2-fold, systolic blood pressure by about 50%, and double product 2.5-fold (21,25). Therefore, isometric handgrip exercise in our opinion may not replace these stress tests. Rather, it has the potential to provide complementary information by uncovering disease-specific response patterns to isometric exercise. One possible application may be the assessment of patients with heart failure and preserved ejection fraction, in whom both diagnosis and characterization of the stage of diastolic disease are still suboptimal using current techniques (26). In addition, an attempt to analyze the occurrence of wall motion abnormalities during isometric handgrip exercise in patients with coronary artery disease would be of great interest in future studies. Technically, repeated SSFP cine acquisitions during stress should be feasible based on the present experiences with phase contrast images during stress.

The prevalence of diastolic dysfunction increases with age. In general, we observed that higher age was associated with less increase of stroke volume, cardiac output, and cardiac index. In particular, all seven subjects who exhibited a decrease of stroke volume between rest and stress were above the age of 65 years. This finding in “healthy” volunteers may be an indicator for age-dependent diastolic dysfunction and requires further studies. In discordance with a study by Taylor et al (24), who analyzed the circulatory regulation during sustained isometric exercise in young (mean age 26 years) and older (mean age 66 years) men, we did not identify an association of age and heart rate response, which may be attributable to differences in sample characteristics.

We identified an interesting link that ties BMI with hemodynamic response to isometric exercise: Subjects with BMI >25.0 kg/m², which is recognized as the threshold between normal weight and overweight (27), revealed a less intense increase of heart rate, cardiac output, and cardiac index between rest and stress. Hence, even though these subjects were classified as “healthy” based on the mentioned inclusion criteria, the response pattern to stress may be an indicator for subclinical impaired autonomic and/or cardiovascular function (28). Similarly, an association of baseline systolic blood pressure and subsequent hemodynamic response to isometric exercise was seen. Thereby, higher resting systolic blood pressure resulted in lower increase of heart rate, systolic blood pressure, double product, cardiac output, and index, respectively. This response pattern in volunteers may also reflect early stages of cardiovascular disease and dysfunction and should be confirmed in patients with known systemic hypertension in future.

We found that those subjects with shorter squeeze duration exhibited a larger increase of systolic blood pressure. Furthermore, the majority of subjects terminated squeezing after 6 minutes or even less. We anticipate that patients, in contrast to healthy subjects, will have even more problems sustaining the handgrip pressure for more than 6 minutes. Based on these considerations, we will apply a target squeeze duration of maximum 6 minutes in future patient studies.

Furthermore, we observed that the hemodynamic changes provoked by isometric exercise disappeared within 2 minutes after releasing the handgrip force. This prompt recovery confirms previous reports, which described even faster returns to control values (8,10). Even though the stress mechanisms of handgrip exercise and bicycle/treadmill exercise are different (10), the fast hemodynamic recovery observed here underscores potential limitations of stress tests outside the MR scanner before subsequently performing the imaging inside the MR scanner (6). Furthermore, the attenuation of cardiovascular changes when handgrip exercise is paused possibly restricts the approach to switch between arms if one arm suffers from muscular exhaustion, as sometimes proposed in the literature (14). Therefore, we preferred to terminate the handgrip test in case the volunteer suffered from muscular exhaustion of the dominant arm.

Another argument against switching the handheld between arms is that this maneuver potentially leads to movements of the volunteer, which might negatively influence slice positioning.

Finally, we did not observe any arrhythmogenic effect of handgrip exercise, which has been reported in the past (29). Nevertheless, in particular when applying this stress test to patients with cardiac diseases, careful monitoring and preparation for emergencies is mandatory.

In conclusion, the present study provides a detailed description of how isometric handgrip exercise can be performed successfully during CMR imaging by combining a prototype handgrip system with a custom-made feedback system that can easily be recreated. Using this set-up in combination with the proposed stress protocol, distinct hemodynamic changes are achievable that resemble previous experiences based on invasive measurements.

Limitations

Previous studies demonstrated moderate reproducibility regarding the pressure response to isometric handgrip exercise (30,31). In the present study, each subject was examined only once. Hence, repeated scans to assess the intraindividual reproducibility of the presented handgrip set-up are required in future studies.

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