Usefulness of Individual Shear Rate Therapy, New Treatment Option for Patients With Symptomatic Coronary Artery Disease

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The aim of this study was to elucidate if patients with coronary artery disease (CAD), who fail to respond to revascularization procedures, can improve from individual shear rate therapy (ISRT). The ISRT is an adaptation of the external counterpulsation with lower individual treatment pressures based on Doppler-ultrasound measurements during counterpulsation. In contrast to the external counterpulsation therapy, the ISRT is based on the detection of the individual intra-arterial shear rate. Here we report about the first clinical trial of 31 patients with CAD who were enrolled for 30 sessions of ISRT. To determine the therapeutic effect of ISRT we measured the exercise capacity, the arterial stiffness, the aortic wave reflection, and the 24-hour blood pressure before and after 30 treatment sessions. After 6 weeks of accomplished ISRT the walking distance during the 6-minute walking test extended by 78 m ($p = 0.007$). The total exercise duration in the exercise stress electrocardiogram increased by 84 seconds ($p = 0.012$) but not the stress intensity ($p = 0.086$). The pulse wave velocity decreased by 1.2 m/s ($p = 0.004$) and demonstrated a decrease in arterial stiffness. Pulse wave analysis results demonstrated a progressive decrease in central blood pressure by 12 mmHg ($p = 0.008$), in pulse pressure by 9 mmHg ($p = 0.005$), and in augmentation pressure by 5.3 mmHg ($p = 0.004$). The 24-hour blood pressure decreased systolic by 15 mmHg ($p < 0.001$) and diastolic by 8 mmHg ($p = 0.033$). The patients also benefited subjectively followed by New York Heart Association and Canadian Cardiovascular Society classifications. In conclusion, the ISRT is an effective treatment for patients with CAD to improve cardiac fitness, arterial stiffness, and to reduce blood pressure. **(Am J Cardiol 2018;121:416–422)**

Around 20% to 30% of patients with coronary artery disease (CAD) fail to respond to revascularization procedures and still experience angina pectoris and dyspnea despite optimal medical therapy.[1–3] An alternative treatment strategy for these patients is necessary. The external counterpulsation (ECP) or enhanced external counterpulsation (EECP) is a noninvasive therapeutic option that promotes the formation of coronary collateral growth. Therefore, it leads to a better myocardial blood flow, but the applied treatment pressure is usually high (up to 250 or 300 mmHg[4–6]). Buschmann et al recently described individual shear rate therapy (ISRT), which is based on the individual detection of shear rates in each patient during counterpulsation and the basis for the calculation of optimal individual cuff pressures ranging from 160 to 220 mmHg.[7] So side effects may be drastically reduced, and acceptance of therapy is increased.[8] The aim of the study was to investigate whether ISRT could improve symptoms, such as angina pectoris or dyspnea, cardiac fitness, blood pressure (BP), arterial stiffness, as well as endothelial function in patients with CAD.

Methods

A total of 31 patients (24 men, 7 women; mean age 70.7 ± 9.7 years) with symptomatic CAD, who failed to respond to revascularization procedures by either percutaneous transluminal coronary angioplasty or coronary artery bypass grafting, were enrolled for ISRT. Included were patients who had angina pectoris (Canadian Cardiovascular Society I to III) and/or dyspnea (New York Heart Association I to III]) and who received coronary angiography in the last 12 months before starting the ISRT. All patients received optimal pharmacologic therapy during participation in this study and were instructed to keep this medication for the entire treatment period. Patients were excluded from the study if they met any of the following criteria: acute coronary syndrome, coronary artery bypass graft within the past 4 weeks, atrial fibrillation with ventricular rate >90 bpm, aortic valve insufficiency >II°, uncontrolled hypertension >180/100 mmHg, severe symptomatic peripheral vascular disease III/IV, active thrombophlebitis in lower limbs, pulmonary hypertension, and pregnancy.

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The ISRT is a noninvasive procedure, which is an adaption of the ECP. We used a commercial ECP system (Pu Shi Kang, Electronics, Zhejiang, China). Three pairs of pneumatic cuffs were wrapped around the calves, thighs, and hips. The inflation and deflation of the pneumatic cuffs were triggered by an electrocardiogram (ECG). The cuffs were inflated upon diastole and at the onset of systole they were deflated again. To determine the treatment pressure, we assessed the individual blood flow parameters for each patient in the common carotid artery with a high-definition ultrasound system (Philips, HD 11, Hamburg, Germany) on days 2, 12, and 22 of treatment. Signals were registered at 6 heart cycles, and the maximum systolic blood flow velocity and acceleration were calculated as described.[7] The Doppler-flow parameters were analyzed at different treatment pressure values which were 0 mmHg, 80 mmHg, 120 mmHg, 160 mmHg, 200 mmHg, and 220 mmHg. Each treatment pressure was maintained for 4 minutes. The Doppler-flow parameters were assessed within the third minute. The individually calculated treatment pressure varied from 160 mmHg to 220 mmHg. Each patient underwent ISRT for 30 sessions (6 weeks, 5 times per week) for 55 minutes.

To determine the therapeutic success, the following measurements were conducted at baseline and after 30 sessions of ISRT: 6-minute walking test (6MWT), exercise stress ECG, 24-hour blood pressure (24-h BP) measurement, pulse wave analysis (PWA), and pulse wave velocity (PWV).

The 6MWT was performed according to the standardization proposed by the American Thoracic Society.[9,10]

For the stress test we used a bicycle ergometer (custo med GmbH, Germany, Ottobrunn) and applied a standard protocol. Bicycle exercise stress tests were performed, starting at a workload of 50 W and increased by 25 W every second minute until exhaustion (e.g., dyspnea or angina pectoris). A 12-lead ECG was obtained at the beginning, monitored continuously, and recorded throughout the examination. Besides the stress intensity we also calculated the total exercise duration.

BP was determined by measuring the pulse transit time (PTT) using the SOMNOscreen plus system (SOMNOmedics, Randersacker, Germany). The ECG and the finger plethysmography curve were recorded simultaneously. PTT is defined as the time that a pulse wave needs to travel from the left ventricle to a certain site of the arterial system. The PTT depends on the wall stress of the blood vessels and correlates with the BP.[11] Data pairs for systolic and diastolic BP were obtained for each heartbeat of investigation.[12] To calculate the BP it is necessary to calibrate PTT to BP conventionally as described by Riva Rocci and Korotkow.[13] The 24-h BP measurements were divided into daytime and nighttime values according to individual waking and bedtimes.

The PWA is a noninvasive measurement to determine the central blood pressure (CBP). We use SphygmoCor XCEL (West Ryde, Australia), which measures initially the brachial systolic and diastolic pressures with a standard brachial cuff. The software (SpygmoCor) captures a brachial waveform, which is then analyzed to provide a central aortic waveform. From this analysis CBP measurements, such as central aortic systolic BP, central pulse pressure, augmentation pressure (AP), and augmentation index, are then calculated.

The aortic PWV is considered to be the gold standard for assessing aortic stiffness.[14–16] To conduct a carotid-femoral PWV measurement, a cuff is placed around the femoral artery of the patient to capture the femoral waveform, and a tonometer is used to capture the carotid waveform. The distance between the carotid and femoral arteries is measured, and the velocity is automatically determined by dividing the distance by the PTT. To get valid data, we followed the guidelines as described by an expert consensus.[14]

All patients were instructed to keep a diary during the 6 weeks of ISRT to document all episodes of angina pectoris and dyspnea.

An SPSS software package (SPSS Inc. v16.0, Chicago, Illinois) was used for the statistical analysis. The values are expressed as mean ± SD (standard deviation). The Mann-Whitney *U* test was used to test the differences between the 2 groups (baseline before ISRT and after 30 sessions of ISRT). Statistical significance was designated at $p \leq 0.05$.

Results

A total of 31 patients with symptomatic CAD (24 men, 7 women; 50 to 83 years), who failed to respond to revascularization procedures, were included in the study. All patients completed the entire ISRT treatment sessions. Their clinical baseline characteristics are listed in Table 1.

To determine the physical capacity, we performed a 6MWT and an exercise stress ECG at baseline and after 30 sessions of ISRT. After 6 weeks of accomplished ISRT, we could show significant increase in physical capacity: the walking distance during the 6MWT extended by 78 m ($p = 0.007$) (Figure 1) and the total exercise duration measured during the exercise stress ECG was prolonged by 84 seconds ($p = 0.012$) (Figure 2). The stress intensity increased by 14 W (Table 2 and Figure 2).

The 24-hour BP decreased systolic by 15 mmHg ($p < 0.001$) and diastolic by 8 mmHg ($p = 0.033$). We divided the BP into daytime and nighttime values according to individual waking and bedtimes. In daytime the BP decreased systolic by 17 mmHg ($p < 0.001$) and diastolic by 6 mmHg (p = n.s.); in nighttime the BP decreased systolic by 11 mmHg ($p = 0.012$) and diastolic by 4 mmHg (p = n.s.) (Table 2 and Figure 3).

The PWV and thereby the arterial stiffness were significantly decreased after 30 sessions of ISRT (−1.2 m/s; $p = 0.004$) (Figure 4). PWA results demonstrated that there was a progressive decrease in CBP by 12 mmHg ($p = 0.008$), in pulse pressure by 9 mmHg ($p = 0.005$), and in AP by 5.3 mmHg ($p = 0.004$) (Table 2 and Figure 5).

The patients described a strong improvement in their symptoms: 31/31 patients were feeling better and healthier. They described to have fewer episodes of angina pectoris and dyspnea after 30 sessions of ISRT. We compared data from Canadian Cardiovascular Society angina class and New York Heart Association dyspnea class before and after ISRT (Table 2 and Figure 6).

Discussion

Around 20% to 30% of patients with CAD fail to respond to revascularization procedures and still experience angina pectoris and dyspnea despite optimal medical therapy.[1–3] An alternative treatment strategy is therefore warranted. The aim

Table 1
Baseline characteristics of study patients with coronary artery disease

Variable	Values
Age (years)	70,7 ± 9,7
Men	24 (77.4%)
Body mass index (kg/m^2)	27.9 ± 5.2
Body mass index >30 kg/m^2	10 (32.3%)
Smoker	2 (6.5%)
Ex-Smoker	17 (54.8%)
Hypercholesterolemia†	22 (71.0%)
Hypertension*	31 (100%)
Number of coronary arteries narrowed	
1-Vessel	5 (16.1%)
2-Vessels	7 (22.6%)
3-Vessels	19 (61.3%)
Myocardial infarction	21 (67.7%)
Angina Pectoris, CCS Class	2.0 ± 0.9
Heart Failure, NYHA Class	2.3 ± 0.7
Atrial fibrillation	10 (32.3%)
Pacemaker	3 (9.7%)
Left ventricular ejection fraction < 55%	14 (47.2%)
Peripheral arterial disease	1 (3.2%)
Stroke	5 (17.1%)
Diabetes mellitus	11 (35.5%)
Renal insufficiency	6 (19.4%)
Chronic obstructive pulmonary disease	5 (17.1%)
Sleep apnea syndrome	15 (48.4%)
Medication	
Angiotensin-converting enzyme inhibitor	14 (47.2%)
Angiotensin-1 receptor antagonists	3 (9.7%)
Beta-blocker	26 (83.9%)
Aldosterone antagonists	2 (6.5%)
Calcium channel blocker	10 (32.3%)
Diuretics	14 (47.2%)
Statins	19 (61.3%)
Antianginal medication	12 (38.7%)

CCS = Canadian Cardiovascular Society; NYHA = New York Heart Association.

* Hypertension was defined as a previous diagnosis of hypertension and intake of antihypertensive medications.

† Hypercholesterolemia was defined as previous diagnosis of hypercholesterolemia, intake of lipid-lowering medications, low-density lipoprotein cholesterol levels > 160 mg/dl, high-density lipoprotein cholesterol levels < 40 mg/dl, or cholesterol levels > 200 mg/dl.

of this study was to investigate if ISRT is an effective therapeutic option for these patients. Before treatment with ISRT, all patients of this study received optimal invasive and noninvasive therapies; however, the therapeutic goal of being angina pectoris-free was not achieved. ISRT is an adaptation of ECP based on the increase in intra-arterial shear rate and fluid shear stress. Like ECP, the ISRT uses a series of 3 cuffs placed on the calves, thighs, and hips, which are triggered by an ECG. Upon diastole the cuffs are inflated, and at the onset of systole they are deflated again. The cuff inflation improves the diastolic blood flow significantly and leads to a profound increase in intra-arterial shear rate and fluid shear stress. In ECP, the applied treatment pressure is usually high—up to 250 or 300 mmHg.[4–6,17–20] In contrast to ECP, with ISRT we used considerably lower treatment pressures that were individually assessed for each patient, ranging from 160 to 220 mmHg. So it is possible to avoid unpleasant side effects, and this can lead to an increase in therapy acceptance. Our data show for the first time that 30 hours of ISRT lead to a significant improvement in cardiac fitness, reduction in BP, and improvement of arterial stiffness.

We demonstrated a significant increase by 78 m in the walking distance during the 6MWT, and in the ECG the total exercise duration was prolonged by 84 seconds. The stress intensity increased by 14 W, but this difference was not significant. The reason for terminating the exercise stress ECG in 29 out of 31 patients was a noncardiac cause but rather due to a lack of skeletal musculature training of the lower extremities. An improvement of physical strength cannot be expected by treatment with ISRT. After 30 sessions of ISRT, all patients were informed about the importance of physical exercise on a regular basis to keep up the improved state of vascularization. We recommended regular participation in heart-training groups. After 30 sessions of ISRT, physical activity was possible in 29 of the 31 patients because of the diminished symptoms.

To assess the effect of ISRT on BP, the levels of antihypertensive medication was held constant during the study period. Our data demonstrated a significant decrease in BP (systolic by 15 mmHg and diastolic by 8 mmHg). In previous reports there were different findings about the effect of ECP on BP. Campbell et al found a decrease in systolic BP by 6.4 mmHg but not in diastolic BP.[20] The study of May et al could not determine an effect of EECP on BP.[21] A possible explanation is that ISRT could be more effective than ECP. Common ECP lacks an evaluation that treats each patient individually. Buschmann et al[7] showed that a therapy pressure above 220 mmHg leads again to a deceleration, and this could inhibit the arteriogenesis.

Previous studies showed that CBPs are more strongly related to vascular disease than peripheral pressures.[22,23] Cheng et al determined a cut-off limit in CBP for normality.[24] CBP >130/90 mmHg was associated with a higher risk of future cardiovascular events. In our study group, the systolic CBP before ISRT was 134 mmHg and after 30 sessions of ISRT it was at the normal level at 122 mmHg. The central pulse pressure (CPP) is independently associated with adverse cardiovascular outcome. CPP >50 mmHg predicts adverse cardiovascular disease outcome and may serve as a target in intervention strategies. Values below 50 mmHg show a decrease of cardiovascular risk outcome.[22] The patients in our study showed a mean CPP of 54 mmHg before ISRT and after 30 therapy sessions a mean value of 45 mmHg. So we postulate that ISRT decreases the risk of cardiovascular outcome.

With incrementing endothelial dysfunction and arterial stiffness, the AP and the augmentation index rise as well.[16] In this study we showed a significant reduction in AP by 5.4 mmHg through ISRT. Therefore, it is to be concluded that ISRT improves endothelial function and arterial stiffness.

Recently the European Society of Cardiology guidelines for the management of arterial hypertension suggested the measurement of carotid-femoral PWV. This should be considered to be the gold standard for assessing arterial stiffness as a tool to evaluate the arterial system damage, vascular adaptation, and therapeutic efficacy.[15] It is recommended to use 10 m/s as a standard cut-off value for carotid-femoral PWV in the prediction of cardiovascular events.[14] In this study we could

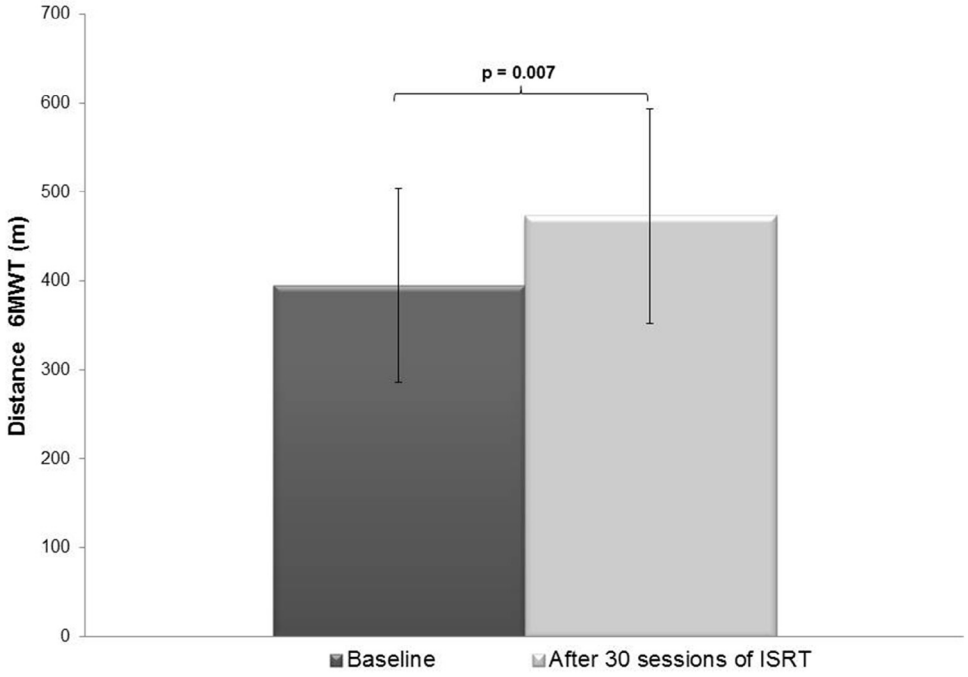

Figure 1. 6MWT distances before and after 30 sessions of ISRT. The average increase in distance walked was 78 m (19.7% increase). Data are given as mean ± SD. 6MWT = 6-minute walking test; ISRT = individual shear rate therapy.

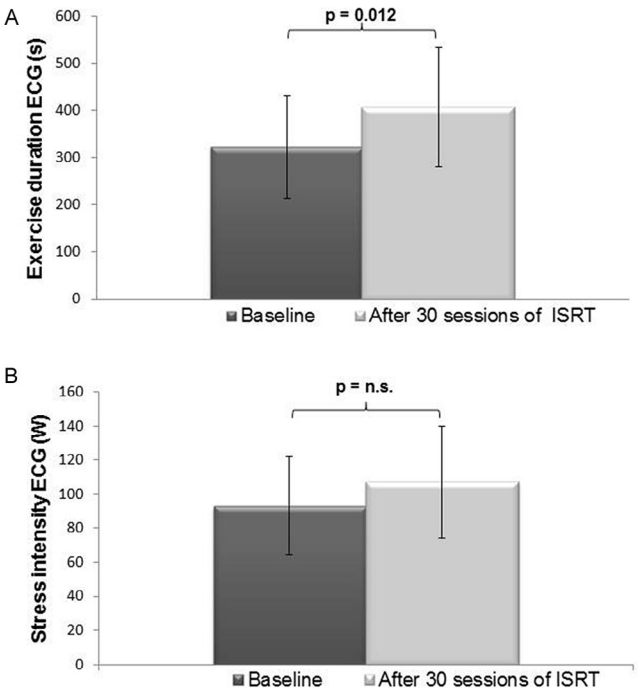

Figure 2. Exercise stress electrocardiogram before and after 30 sessions of ISRT. The exercise duration *(A)* increased by 84 seconds (26% increase) and the stress intensity *(B)* increased by 14 W, but this difference was not significant. Data are given as mean ± SD. ECG = electrocardiogram; ISRT = individual shear rate therapy.

Table 2
Functional parameters before and after 6 weeks (30 sessions) of ISRT

Parameter	Baseline	After ISRT	P-value
6-minute walking test (m)	395 ± 109	473 ± 106	0.007
Electrocardiogram, stress intensity (W)	93 ± 26	107 ± 29	n.s.
Electrocardiogram, exercise duration (s)	323 ± 99	407 ± 117	0.012
Blood pressure			
24-h systolic (mmHg)	134 ± 15	119 ± 10	< 0.001
24-h diastolic (mmHg)	75 ± 9	67 ± 9	0.033
Daytime systolic (mmHg)	138 ± 16	121 ± 10	< 0.001
Daytime diastolic (mmHg)	78 ± 9	72 ± 10	n.s.
Nighttime systolic (mmHg)	127 ± 17	116 ± 13	0.012
Nighttime diastolic (mmHg)	71 ± 9	67 ± 9	n.s.
Pulse wave velocity (m/s)	10.5 ± 1.3	9.3 ± 1.2	0.004
Central Blood pressure systolic (mmHg)	134 ± 16	122 ± 13	0.008
Central Pulse pressure (mmHg)	54 ± 11	45 ± 11	0.005
Augmentation pressure (mmHg)	19.1 ± 7.0	13.8 ± 6.1	0.004
Angina Pectoris, CCS class	2.0 ± 0,9	1.25 ± 0.4	0.002
Heart Failure, NYHA class	2.26 ± 0.7	1.35 ± 0.4	< 0.001

CCS = Canadian Cardiovascular Society; ISRT = individual shear rate therapy; n.s. = not significant; NYHA = New York Heart Association.

show that the PWV, and thereby the arterial stiffness, was significantly reduced after 30 sessions of ISRT. Before treatment with ISRT we measured the PWV value was above cutoff (10.5 m/s ± 1.3 m/s). After treatment the mean value was below the cutoff (9.3 m/s ± 1.2 m/s). It can therefore be concluded that the ISRT reduces the risk of future cardiovascular outcome. Casey et al[4] also showed a reduction of PWV in patients with chronic angina pectoris after 35 sessions of EECP but in contrast to our study, the applied treatment pressure was very high (300 mmHg).

In the current study we analyzed the effect of ISRT in 31 patients with CAD. Although the patient number is small, we

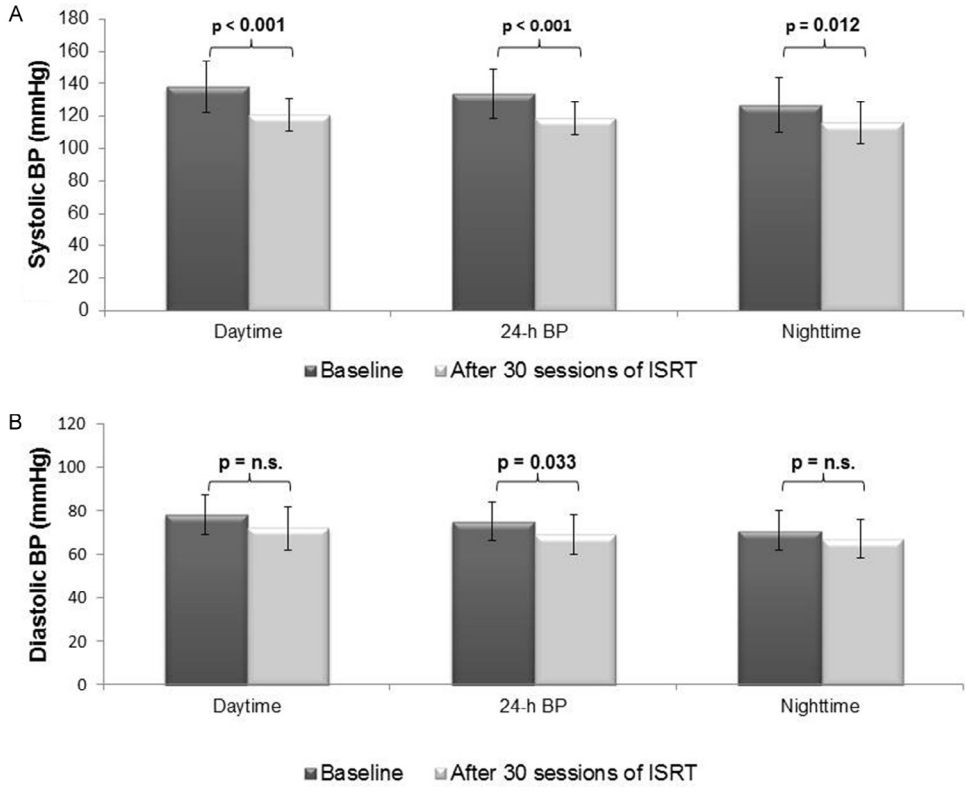

Figure 3. 24-Hour blood pressure (24-h BP) before and after 30 sessions of ISRT. Long-term ISRT reduced the systolic *(A)* and diastolic *(B)* 24-h BP. BP was determined by measuring the pulse transit time using the SOMNOscreen plus system (SOMNOmedics, Randersacker, Germany). The 24-h BPmeasurements were divided into daytime and nighttime values, according to individual waking and bedtimes. Data are given as mean ± SD. BP = blood pressure; ISRT = individual shear rate therapy.

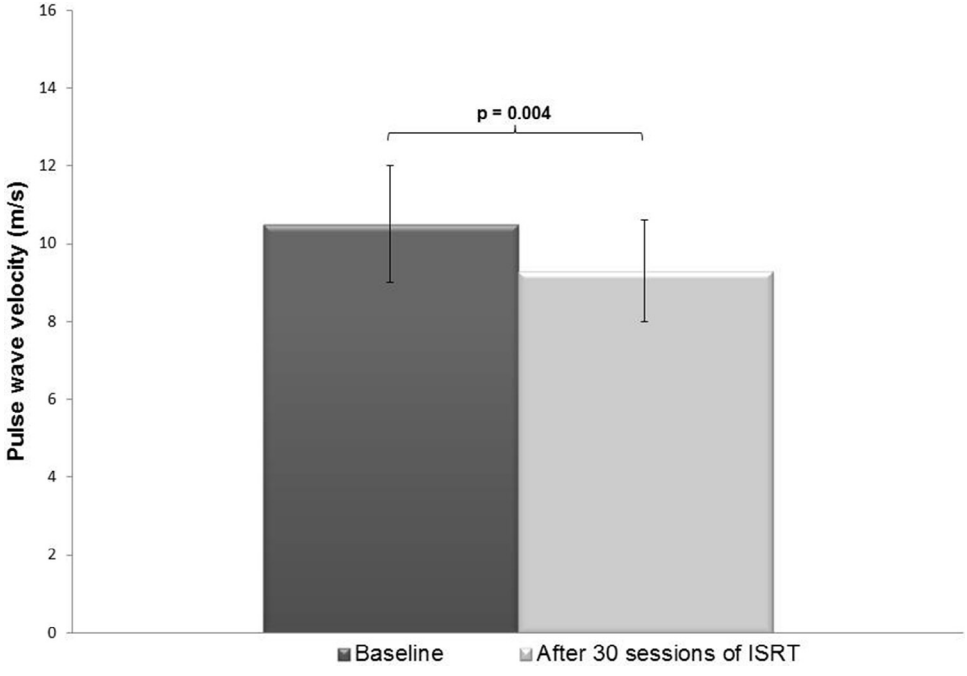

Figure 4. Pulse wave velocity before and after 30 sessions of ISRT; the average reduction in pulse wave velocity was 1.2 m/s. Data are given as mean ± SD. ISRT = individual shear rate therapy.

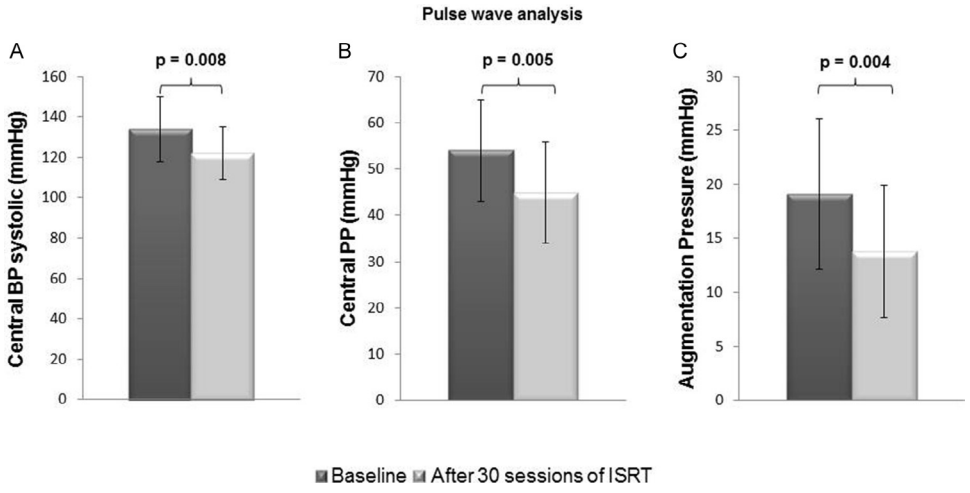

Figure 5. Pulse wave analysis before and after 30 sessions of ISRT. The average reduction in central blood pressure was 12 mmHg *(A)*, in central pulse pressure 9 mmHg *(B)*, and in augmentation pressure 5.3 mmHg *(C)*. Data are given as mean ± SD. BP = blood pressure; ISRT = individual shear rate therapy; PP = pulse pressure.

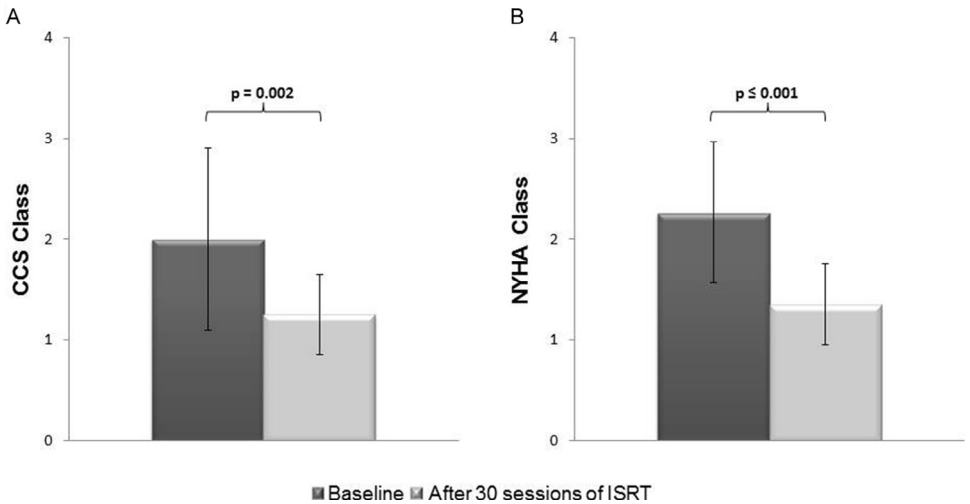

Figure 6. Episodes of angina pectoris and dyspnea before and after 30 sessions of ISRT. Long-term ISRT of patients with CAD reduced the episodes of angina pectoris and dyspnea. Data are given as mean ± SD. CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; ISRT = individual shear rate therapy; NYHA = New York Heart Association.

demonstrated a significant improvement in cardiac fitness, reduction in BP, and improvement of arterial stiffness. However, due to the small number of patients, conclusions are to be drawn with care.

Disclosures

The authors have no conflicts of interest to disclose.

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