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Effects of selective heart rate reduction with ivabradine on LV function and central hemodynamics in patients with chronic coronary syndrome

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ABSTRACT

Objectives: We assessed left ventricular (LV) function and central hemodynamic effects in patients with a heart rate (HR) at rest of ≥70 beats per minute (bpm) and chronic coronary syndrome (CCS) after long-term treatment with ivabradine compared to placebo by cardiac magnetic resonance (CMR) imaging.
Methods and results: In a randomized, double-blinded, prospective cross-over design, 23 patients (18 male, 5 female) were treated with ivabradine (7.5 mg bid) or placebo for 6 months. CMR imaging was performed at baseline and after 6 and 12 months to determine LV functional parameters.

Mean resting HR on treatment with ivabradine was 58 ± 8.2 bpm and 70.2 ± 8.3 bpm during placebo ($p < 0.0001$).There was no difference in systolic LV ejection fraction (ivabradine 57.4 ± 11.2% vs placebo 53.0 ± 10.9%, $p = 0.18$), indexed end-diastolic (EDVi) or end-systolic volumes (ESVi). Indexed stroke volume (SVi) (ml/m^2) remained unchanged after treatment with ivabradine. Volume time curve parameters reflecting systolic LV function (peak ejection rate and time) were unaffected by ivabradine, while both peak filling rate (PFR) and PFR/EDV were significantly increased. Mean aortic velocity (cm/s) was significantly reduced during treatment with ivabradine (ivabradine 6.7 ± 2.7 vs placebo 9.0 ± 3.4, $p = 0.01$). Aortic flow parameters were correlated to parameters of vascular stiffness. The strongest correlation was revealed for mean aortic velocity with aortic distensibility (AD) ($r = -0.86$ [−0.90 to −0.85], $p < 0.0001$).
Conclusion: Long-term reduction of HR with ivabradine in patients with CCS improved diastolic function and reduced mean aortic flow velocity.

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1. Introduction

Resting heart rate (RHR) impacts outcome in patients with various cardiovascular diseases [1,2] and affects cardiovascular function and physiology [3]. Elevated RHR interferes at all stages of the cardiovascular disease continuum, initiating from endothelial dysfunction and continuing via atherosclerotic lesion formation and plaque rupture to end-stage cardiovascular disease [4–7]. In a previous study we characterized vascular effects of heart rate reduction (HRR) with the If channel inhibitor ivabradine in patients with chronic coronary syndrome [8]. We showed that selective HRR reduced arterial stiffness and restored brachial flow

Abbreviations: ACS, acute coronary syndrome; AD, aortic distensibility; bpm, beats per minute; CAD, coronary artery disease; CCS, chronic coronary syndrome; cf, carotid-femoral; CMR, cardiac magnetic resonance; CV, cardiovascular; EDV, end-diastolic; EF, ejection fraction; ESC, European Society of Cardiology; ESV, end-systolic; FMD, flow mediated dilation; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; HRR, heart rate reduction; LV, left ventricular; MRI, magnetic resonance imaging; PET, peak ejection time; PER, peak ejection rate; PFR, peak filling rate; PFT, peak filling time; PWV, pulse wave velocity; RHR, resting heart rate; SV, stroke volume; VTC, volume-time curve.

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mediated dilation (FMD) and thereby characterized heart rate (HR) as a key determinant of vascular function. Moreover, ivabradine increased central aortic blood pressure.

Cardiac magnetic resonance (CMR) imaging is increasingly applied for non-invasive assessment of left ventricular (LV) function and hemodynamics [9]. In addition, LV volume-time curves (VTC) are used as a complement to evaluate continuous volume changes of the LV [10,11]. Its parameters include peak ejection rate (PER), peak ejection time (PET), peak filling rate (PFR), peak filling time from end-systole (PFT), peak ejection rate normalized to end-diastolic volume (PER/EDV) and peak filling rate normalized to EDV (PFR/EDV) [12]. Among these, PER, PET and PER/EDV are indices of systolic function whereas PFR, PFT and PFR/EDV characterize diastolic function [11]. In chronic heart failure, HRR with ivabradine modulates cardiac pre- and afterload, increases stroke volume and diastolic perfusion time [13,14]. Whether HRR mediates similar effects in patients with CCS without heart failure is not known. Therefore, as an extension of our previous study (Hohneck et al. [8]), we investigated LV function and central hemodynamic effects by CMR in our cohort of patients with CCS after 6 months of treatment with ivabradine compared to a 6-month treatment period with placebo.

2. Methods

2.1. Study population

23 patients with CCS who underwent coronary angiography at the Saarland University Medical Centre were enrolled in a placebo-controlled, double-blind, cross-over study as reported previously [8]. Patients were randomly allocated to treatment with placebo or ivabradine (7.5 mg bid; Servier, Neuilly-sur-Seine, France) over 6 months with a following cross-over to the alternative treatment arm. Analyses were carried out as pooled analysis, regardless of whether the patients received ivabradine or placebo in the first treatment period or after cross-over. The main inclusion criteria were coronary artery disease (CAD) detected by coronary angiography and a resting HR of at least 70 bpm. Other inclusion and exclusion criteria and a full study protocol have been reported previously [8]. The study complies with the declaration of Helsinki and has been approved by the local ethics committee (ID Nr 240/11; ClinicalTrials.gov Identifier: NCT 01768585, Eudra CT Number: 2012–001989-15). Written informed consent was obtained from all patients and data were analyzed anonymously. Data protection was in accordance to the EU Data Protection Directive.

2.2. CMR imaging

CMR imaging was performed on a 1.5 Tesla scanner (Magnetom Aera; Siemens Healthineers, Erlangen, Germany), using a phased-array body surface coil and ECG synchronization. For assessment of LV volume and function parameters ECG-gated cine SSFP sequences in short axis, 2-chamber view and 4-chamber view orientation were acquired retrospectively (TR/TE = 50.6/1.2 ms, FA = 70°, FOV = 30 × 30 cm, matrix = 192 × 192, slice thickness = 6 mm, 25 frames). Data acquisition was obtained during end-inspiratory breath holding. A total number of 8–12 slices in short axis orientation was acquired in every subject from the level of the mitral valve to the level of the apex. Flow measurements of the ascending aorta were performed acquiring velocity encoded phase-contrast sequences with retrospective ECG-gating (TR/TE = 42.8/3.1 ms, FA = 20°, FOV = 30 × 30 cm, matrix = 192 × 192, slice thickness = 6 mm, 20 frames) perpendicular to the ascending aorta at the level of the right pulmonary artery [15].

2.3. Imaging analysis

CMR data were transferred to an external workstation and were analyzed by two blinded experienced radiologists (PF and JS) using dedicated image evaluation software (Syngo.via (VA30A), Siemens Healthineers, Erlangen, Germany). Global LV function and the VTC were analyzed by semi-automated segmentation of the endocardial and epicardial borders of the LV myocardium from the image slices between the mitral valve and the apex at end-diastole and at end-systole; additionally, papillary muscles were carefully assigned to the cardiac lumen. LV function parameters (including end-diastolic (ED) volumes, end-systolic (ES) volumes, stroke volume (SV), EF, cardiac output (CO) and myocardial mass) as well as VTC parameters (PER, PET, PFR, PFT, PER/EDV and PFR/EDV) were obtained automatically.

Phase contrast images were analyzed to generate a velocity time integral of the aortic flow curve providing the following parameters: medium and maximum flow (ml/s), time to maximum flow, forward flow volume, backward flow volume, regurgitant fraction, mean and maximum velocity (cm/s) and pressure gradient (mmHg). For that purpose, a region-of-interest (ROI) was placed within the lumen of the ascending aorta sparing the vessel wall to avoid misregistration of voxel outside of the vessel lumen. The ROI was transferred to every frame of the phase-contrast sequence acquisition.

2.4. Parameters of vascular stiffness

Both aortic distensibility (AD) and pulse wave velocity (PWV) have been previously assessed by CMR imaging and by applanation tonometry as reported [8].

2.5. Statistical analysis

All data are presented as mean ± standard deviation (SD) or frequency (percentage). Continuous variables were compared using a two-tailed Student's *t*-test for parametric and Mann–Whitney *U* test for non-parametric variables. Categorical variables were compared with the χ^2 test. All results were considered statistically significant when $p < 0.05$. Univariate regression analysis was performed to correlate aortic flow parameters to parameters of vascular stiffness (AD, PWV and FMD).

Analyses were performed with Statistical 1 Package for Social Sciences (SPSS for Windows 23.0, Chicago, IL, USA) and GraphPad Prism 8.0 (Graphpad Software, Inc., California, USA). All analyses are of exploratory nature.

3. Results

23 patients (18 male, 5 female) were included in this analysis, as complete CMR data sets were only available in 88.5% (23 of 26 patients). Baseline characteristics of the study cohort (n = 23) are displayed in Table 1. Mean age at time of study inclusion was 62.4 ± 9.8 years. 61% had a history of nicotine consumption or were active smokers. Angina pectoris related symptoms were graded according to the classification of the Canadian Cardiovascular Society. One third suffered from angina severity I° and the remaining two thirds of angina severity II°. 78% received guideline conforming concomitant treatment with betablockers, while 6 patients had contraindications (e.g. bronchial asthma, asymptomatic peripheral arterial occlusive disease). 96% were treated with ACE inhibitors/ ARB and platelet aggregation inhibitors/anticoagulants. The majority was treated with a statin (91%) and 13% of the study population had an additional antianginal therapy with nitrates.

Table 1
Baseline characteristics of the study cohort (n = 23).

n = 23	Baseline
Age (years)	62.4 ± 9.8
Sex (male/ female)	(18/5)
Smoking history, n (%)	14 (60.9)
BMI, kg/m^2	29.4 ± 4.6
Angina severity I°, n (%)	8 (34.8)
Angina severity II°, n (%)	15 (65.2)
Concomitant treatment, n (%)	
Betablocker	18 (78.3)
ACE inhibitor/ ARB	22 (95.7)
Calcium channel blocker	4 (17.4)
Diuretics	15 (65.2)
Platelet inhibition/ anticoagulants	22 (95.7)
Statin	21 (91.3)
Nitrate	3 (13.0)

Data are presented as the mean value ± standard deviation or number (%) of subjects. ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; BMI: body mass index; BP: blood pressure; bpm: beats per minute.

Baseline HR were 78.0 ± 8.9 bpm for the treatment group receiving ivabradine first and 76.4 ± 8.0 bpm for the group receiving placebo first, within the cross-over design before each treatment phase. In both groups HR was significantly reduced during treatment with ivabradine (to 58.4 ± 10.4 bpm in the ivabradine first group and to 59.1 ± 6.2 bpm in the placebo first group; p < 0.0001 vs baseline for both).

In the pooled analysis, the mean RHR was 58.8 ± 8.2 bpm during treatment with ivabradine and 70.2 ± 8.3 bpm during treatment with placebo (p < 0.0001 ivabradine vs placebo). There were no differences in systolic or diastolic blood pressure (Table 2).

3.1. Systolic and diastolic LV function

CMR imaging was performed at three time points (baseline, 6 months, 12 months) in all study participants. All results are reported as pooled analysis, regardless of whether patients received ivabradine or placebo first or after cross-over. LV assessment was performed on conventional CINE-CMR and by VTC. There was no difference in LVEF (%) (ivabradine 57.4 ± 11.2 vs placebo 53.0 ± 10.9, p = 0.18), ESVi and EDVi. SVi (ml/m^2) was increased by 13.7% (ivabradine 40.6 ± 9.6 vs placebo 35.7 ± 8.8, p = 0.08). VTC parameters reflecting systolic LV function (peak ejection rate (PER), peak ejection time (PET)) were unaffected by ivabradine, while both peak filling rate (PFR) and PFR/EDV were significantly increased (PFR/EDV (s^{-1}) ivabradine 2.4 ± 0.4 vs placebo 2.1 ± 0.4, p = 0.03). Peak filling time (PFT) (ms) was slightly longer during treatment with ivabradine, but without reaching statistical significance (ivabradine 841 ± 225 vs placebo 810 ± 211, p = 0.64). In contrast, time to PFR (ms) was shortened during treatment with ivabradine (ivabradine 294 ± 86 vs placebo 344 ± 76, p = 0.04) (Table 3).

3.2. Aortic flow parameters

Medium and maximum aortic flow was not affected by treatment with ivabradine. There was a moderate increase in forward flow volume (15.7%) ((ml) ivabradine 69.7 ± 22.2 vs placebo 60.2 ± 17.0, p = 0.11), and a significant increase of backward flow volume ((ml) ivabradine 9.8 ± 5.8 vs 5.3 ± 4.2, p < 0.01). Aortic pressure gradient remained unaffected. Mean aortic flow velocity (cm/s) was significantly reduced during treatment with ivabradine (ivabradine 6.7 ± 2.7 vs placebo 9.0 ± 3.4, p = 0.01) (Fig. 1). Complete results are shown **in** Table 4**.**

Aortic flow parameters were subsequently investigated in depth and correlated to parameters of vascular stiffness (Table 4). AD was inversely correlated to both aortic flow and mean flow velocity, whereby mean velocity showed the strongest inverse correlation to AD (r = -0.86 (95%CI −0.91 to −0.78), p < 0.0001). A positive correlation between AD and regurgitant fraction could also be identified (r = 0.69 (95%CI 0.55 to 0.80), p < 0.0001). PWV was inversely correlated to aortic flow and mean velocity. FMD) as surrogate of endothelial function showed no significant correlation to aortic flow parameters. Medium aortic flow and mean aortic flow velocity in correlation to AD and PWV are displayed in Fig. 2.

4. Discussion

The present study investigated the effects of a long-term treatment with ivabradine on systolic and diastolic function and aortic blood flow in patients with CCS. Chronic HRR improved diastolic function and reduced aortic flow velocity. Moreover, aortic flow and flow velocity show an inverse correlation to indices of arterial stiffness (AD and PWV).

In animal heart-failure models, long-term treatment with ivabradine improved LV function and increased SV [16]. This effect can be attributed to a prolongation of diastolic time which improves LV filling and thus increases SV by the Frank-Starling mechanism. An echocardiographic substudy of the SHIFT trial showed that HRR with ivabradine increased SV by 15% after 8 months of treatment in patients with systolic heart failure [17]. In our cohort of patients with CCS we documented a nominal, though not significant increase in SV by 13.7%. This may probably be attributed to the "healthier" patient population with normal systolic EF at baseline, whose problem is mainly impairment of diastolic function. Particularly, however, the limited number of patients may have contributed here.

Treatment with ivabradine increases the duration of diastole and thereby contributes to a prolongation of coronary perfusion [18,19]. In animal models of heart failure with preserved EF (HFpEF), HRR with ivabradine reduced vascular stiffness and thereby improved diastolic function [20]. VTC obtained from conventional cine-CMR serves as a metric that can be used to evaluate continuous volume changes in the LV. Previous studies have indicated that PFR is reduced and PFT is increased in CAD patients [21]. Here, we apply this method to explore the effects of selective HRR on LV filling patterns which has not been described before so

Table 2
Vital parameters at baseline and during treatment with placebo or ivabradine.

Vital parameters	Baseline	Placebo	Ivabradine	p-value Placebo vs Ivabradine
Heart rate, bpm	79.7 ± 7.2	70.2 ± 8.3	58.8 ± 8.2	**< 0.0001**
Systolic BP, mmHg	137.9 ± 18.4	141.5 ± 17.8	144.4 ± 22.1	0.49
Diastolic BP, mmHg	80.1 ± 11.5	82.2 ± 10.7	79.4 ± 11.6	0.22

Data are presented as the mean value ± standard deviation. Values for ivabradine and placebo are given as pooled analysis, regardless of whether patients received ivabradine or placebo first or after cross-over. BP, blood pressure; bpm, beats per minute.

Table 3
CMR characteristics including LV function and aortic flow parameters.

n = 23	Baseline	Placebo	Iva	p-value Placebo vs Iva
LV function				
LV-EF (%)	55.6 ± 9.9	53.0 ± 10.9	57.4 ± 11.2	0.18
LV-EDVi (ml/m^2)	68.3 ± 20.8	69.5 ± 20.6	72.6 ± 20.5	0.61
LV-ESVi (ml/m^2)	31.9 ± 17.4	33.8 ± 16.9	32.0 ± 15.9	0.72
LV-SVi (ml/m^2)	36.4 ± 6.2	35.7 ± 8.8	40.6 ± 9.6	0.08
LV-CI (ml/min/m^2)	2.5 ± 0.5	2.2 ± 0.6	2.4 ± 0.5	0.16
LV-EDMi (g/m^2)	69.6 ± 19.4	63.4 ± 12.4	66.2 ± 12.3	0.45
PER (ml/s/m^2)	−189.1 ± 33.5	−182.0 ± 36.4	−201.0 ± 28.2	0.06
PFR (ml/s/m^2)	151.4 ± 40.8	144.1 ± 43.9	169.5 ± 36.7	**0.04**
PET (ms)	135.8 ± 16.5	132.0 ± 21.9	124.3 ± 19.9	0.29
PFT (ms)	714.9 ± 214.4	810.3 ± 211.1	840.8 ± 225.3	0.64
Time to PFR (ml/s)	305.1 ± 87.2	343.7 ± 75.7	294.2 ± 85.6	**0.04**
PER/EDV (s^{-1})	−2.9 ± 0.6	−2.7 ± 0.5	−2.9 ± 0.6	0.32
PFR/EDV (s^{-1})	2.3 ± 0.5	2.1 ± 0.4	2.4 ± 0.4	**0.03**
Aortic flow parameters				
Medium flow (ml/s)	63.5 ± 15.4	63.7 ± 20.0	57.4 ± 20.6	0.30
Medium flow/ BSA (l/min/m^2)	1.8 ± 0.4	1.8 ± 0.5	1.6 ± 0.5	0.17
Max. flow (ml/s)	343.0 ± 55.2	354.2 ± 66.3	365.2 ± 88.0	0.63
Time to max. flow (ms)	136.8 ± 25.1	144.3 ± 86.3	159.7 ± 173.8	0.71
Forward flow volume (ml)	61.9 ± 13.9	60.2 ± 17.0	69.7 ± 22.2	0.11
Backward flow volume (ml)	6.3 ± 5.0	5.3 ± 4.2	9.8 ± 5.8	**< 0.01**
Regurgitant fraction (%)	11.7 ± 11.4	10.1 ± 8.9	15.1 ± 10.5	0.09
Netto forward flow volume (ml)	55.6 ± 15.4	54.9 ± 18.4	59.8 ± 21.2	0.40
Mean velocity (cm/s)	8.0 ± 2.5	9.0 ± 3.4	6.7 ± 2.7	**0.01**
Max. velocity (cm/s)	99.9 ± 25.7	119.0 ± 42.7	114.0 ± 47.3	0.71
Pressure gradient (mmHg)	4.2 ± 2.2	5.5 ± 3.1	4.8 ± 2.6	0.39

Data are presented as the mean value ± standard deviation or number (%) of subjects. Volumes are indexed (i) to body surface area (BSA). Bold values mark statistical significance.
CI: cardiac index; CMR: cardiac magnetic resonance; EDM: end-diastolic mass; EDV: end-diastolic volume; ESV: end-systolic volume; EF: ejection fraction; LV: left ventricular; max.: maximum; PER: peak ejection rate; PET: peak ejection time; PFR: peak filling rate; PFT: peak filling time; SV: stroke volume

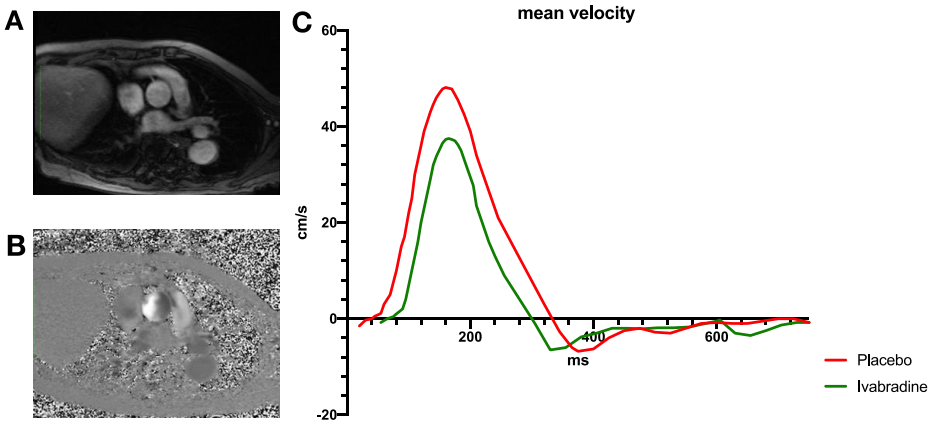

Fig. 1. Mean aortic flow velocity. Aortic flow analyses were performed by phase contrast imaging at the level of the truncus pulmonalis. Exemplary sections of A) magnitude and B) velocity encoded images are shown on the left side. On the right side (C), automatically derived aortic flow curves of one patient during treatment with placebo (red) and treatment with ivabradine (green) are displayed integrated into a single graphic for better comparison. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

far. In our cohort PFR was increased and the time to PFR decreased by ivabradine, indicating a significant improvement in relaxation and thus a better filling during diastole. This direct improvement of ventricular-arterial coupling was previously demonstrated in a subgroup of the SHIFT cohort [13]. Thus, with regard to the available data from mechanistic studies, the relationship between HR and diastolic function appears to be clear. However, translation of those findings into a clinical context is challenging. In EDIFY, a randomized controlled trial assessing whether HRR improves outcomes in patients with HFpEF, ivabradine showed no effect on functional and echocardiographic outcomes [22]. In our cohort baseline indices of diastolic function were impaired, corresponding to a diastolic dysfunction I° compared to standard CMR values, as expected in hypertensive patients [21].

Biological and vascular aging is closely connected to stiffening of the large arteries and aortic stiffness can be viewed as subclinical evidence of target organ damage [23,24]. One of the earliest determinants of vascular aging in healthy individuals is the loss of the phasic distensibility of the ascending aorta [25], which defines LV afterload as it acts as a reservoir that buffers the pulsatile force from left ventricular contraction. A decay of distensibility of the ascending aorta as seen with cardiovascular risk factors or age leads to an increased pulsatile load on the left ventricle and impairs coupling between the heart and the aorta [26]. In heart failure with reduced EF (HFrEF) selective HRR with ivabradine augments arterial compliance and thereby unloads the LV and improves ventricular-arterial coupling [13]. As described previously, HRR with ivabradine restores AD and reduces

Table 4
Correlation of aortic flow parameters to arterial stiffness a) aortic distensibility and b) pulse wave velocity.

	a) Aortic distensibility		b) Pulse wave velocity	
	p-value	r (95%CI)	p-value	r (95%CI)
Medium flow (ml/s)	**<0.0001**	−0.68 (−0.79 to −0.53)	**0.0006**	−0.42 (−0.61 to −0.20)
Medium flow/ BSA (l/min/m^2)	**<0.0001**	−0.71 (−0.81 to −0.57)	**0.0006**	−0.42 (−0.61 to −0.19)
Max. flow (ml/s)	**0.005**	−0.33 (−0.53 to −0.10)	**0.003**	−0.37 (−0.57 to −0.13)
Time to max. flow (ms)	**0.048**	0.24 (0.01 to 0.45)	0.10	–
Forward flow volume (ml)	**0.02**	−0.29 (−0.49 to −0.05)	**0.002**	−0.39 (−0.58 to −0.15)
Backward flow volume (ml)	**<0.0001**	0.61 (0.44 to 0.74)	0.26	–
Regurgitant fraction (%)	**<0.0001**	0.69 (0.55 to 0.80)	**0.03**	0.28 (0.03 to 0.50)
Netto forward flow volume (ml)	**<0.0001**	−0.46 (−0.63 to −0.25)	**0.001**	−0.40 (−0.59 to −0.17)
Mean velocity (cm/s)	**<0.0001**	−0.86 (−0.91 to −0.78)	**0.03**	−0.27 (−0.48 to −0.02)
Max. velocity (cm/s)	0.23	–	0.57	–
Pressure gradient (mmHg)	0.10	–	0.94	r (95%CI)

Bold values mark statistical significance. 95% confidence intervals are given for Spearman's Rho (r). BSA, body surface area; CI, confidence interval; max., maximum.

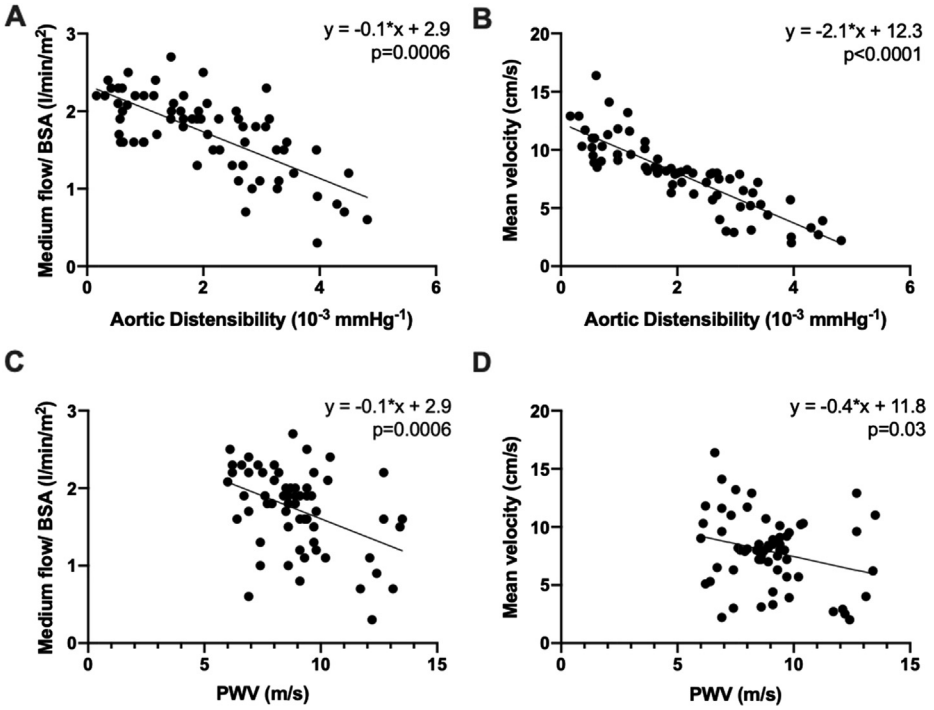

Fig. 2. Aortic flow parameters in correlation to aortic distensibility and pulse wave velocity. Scatter plots for A) medium flow and aortic distensibility, B) mean velocity and aortic distensibility C) medium flow and pulse wave velocity and D) mean velocity and pulse wave velocity. Both mean velocity and medium flow are inversely correlated with aortic distensibility and pulse wave velocity, with even higher correlation of aortic distensibility. BSA; body surface area; PWV; pulse wave velocity.

carotid-femoral PWV (cfPWV) in patients with CAD [8]. Whereas cfPWV serves as an average and surrogate of overall arterial stiffness, direct assessment of PWV in the ascending aorta by MRI more precisely defines instantaneous velocity and thereby visco-elastic and functional properties of the central arteries [5]. Assessment of aortic PWV using MRI–derived flow waves is well validated by comparisons with invasive intra-aortic pressure assessment [27] and was successfully applied to determine aortic stiffness in several large cross sectional cohorts [28]. Therefore, we characterized flow velocity in the ascending aorta by MRI. A central finding that significantly expands our previous data is that mean aortic flow velocity is reduced by HRR. By adding MRI based characterization of aortic flow, we are able to provide a broad and comprehensive assessment of aortic function (strain, distensibility and PWV). Heart rate affects vascular integrity and plays a central role as a mediator of maladaptive mechanic stress leading to increased aortic stiffness. In keeping with our previous data selective HRR with ivabradine reduces stiffness as it reduces aortic PVW, which can be considered as a central protective mechanism of selective HRR.

In parallel to a reduction of mean aortic flow velocity aortic backward flow volume increases. This effect supports the concept of HR as a determinant of flow propagation and wave reflection as shown by a magnitude of clinical and experimental investigations [29]. However, whereas the inverse association between HR and central aortic hemodynamics (e.g. central aortic pressure, pulse pressure) is well characterized, the relationship between HR and backward flow volumes is not. Though an increase in backward flow may result from an increase in stroke volume as seen under low resting HR conditions induced by inhibitors of If-channels [30,31]. To further promote our hypothesis of a close connection between HR and aortic properties, aortic flow-parameters were investigated in depth and correlated to indices of aortic compliance that were validated before. A strong inverse correlation between mean flow velocity and medium flow and AD as well as cfPVW could be detected which unequivocally underpins the consistency of a multimodal approach to characterize central aortic hemodynamics.

There are several limitations of our study, most notably the limited size of patients may have prevented clearer effects especially

with regard to LV stroke volume. Meanwhile, 3-dimensional time-resolved phase-contrast CMR (4D flow) is emerging as a promising tool, which is also able to quantify wall shear stress and to provide direct measurements of pulse wave propagation and thus determination of aortic pulse wave velocity. This technique is of interest and should be performed in further studies.

5. Conclusion

Long-term reduction of heart rate with ivabradine in patients with CCS improved diastolic function and reduced mean aortic flow velocity. AD and PWV, as surrogate parameters for arterial stiffness were inversely correlated to aortic flow and flow velocity. In this regard reversibility of aortic stiffness by selective HRR is encouraging and should be investigated in a broad range of vascular patients in further long-term studies.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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