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

Anna Lena Hohneck a,*, Peter Fries b, Jonas Stroeder b, Günther Schneider b, Stephan Henrik Schirmer c, Jan-Christian Reil d, Michael Böhm e, Ulrich Laufs f, Florian Custodis c,g

a First Department of Medicine, University Medical Centre Mannheim (UMM), Faculty of Medicine Mannheim, University of Heidelberg and DZHK (German Centre for Cardiovascular Research) Partner Site Heidelberg/Mannheim, Mannheim, Germany
b Clinic for Diagnostic and Interventional Radiology, Saarland University Medical Center, Saarland University, Homburg/Saar, Germany
c School of Medicine, University Hospital Schleswig-Holstein Location Lübeck, Lübeck, Germany
d Department of Internal Medicine III, Saarland University Medical Center, Saarland University, Homburg/Saar, Germany
e Clinic and Polyclinic for Cardiology, Leipzig University, Leipzig, Germany
f Clinic for Diagnostic and Interventional Radiology, Saarland University Medical Center, Saarland University, Homburg/Saar, Germany
g Department of Internal Medicine II, Klinikum Saarbrücken, Saarbrücken, Germany

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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/m2) 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.
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 x 30 cm, matrix = 192 x 192, slice thickness = 6 mm, 24 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 = 42.8/1.3 ms, FA = 20°; FOV = 30 x 30 cm, matrix = 192 x 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 χ² 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 beta-blockers, 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.
Vital parameters at baseline and during treatment with placebo or ivabradine.

| Vital parameters | Baseline | Placebo | Ivabradine | p-value  \\
|------------------|----------|---------|------------|----------|
| 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 ± 11.3 | 62.2 ± 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.
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].

#### Table 3

|               | n = 23 | Baseline | Placebo | Iva |
|---------------|--------|----------|---------|-----|
| **LV function** |        |          |         |     |
| LV-EF (%)     | 55.6 ± 9.9 | 53.0 ± 10.9 | 57.4 ± 11.2 | 0.18 |
| LV-EDV (ml/m²) | 68.3 ± 20.8 | 69.5 ± 20.6 | 72.6 ± 20.5 | 0.61 |
| LV-ESV (ml/m²) | 31.9 ± 17.4 | 33.8 ± 19.6 | 32.0 ± 15.9 | 0.72 |
| LV-SV (ml/m²)  | 36.4 ± 6.2  | 35.7 ± 8.8  | 40.6 ± 9.6  | 0.08 |
| LV-CI (ml/min/m²) | 2.5 ± 0.5  | 2.2 ± 0.6  | 2.4 ± 0.5  | 0.16 |
| LV-EDV(t (g/m²)) | 69.6 ± 19.4 | 63.4 ± 12.4 | 66.2 ± 12.3 | 0.45 |
| PER (ml/s/m²)  | −189.1 ± 33.5 | −182.0 ± 36.4 | −201.0 ± 28.2 | 0.06 |
| PFR (ml/s/m²)  | 151.4 ± 40.8 | 144.1 ± 43.9 | 109.5 ± 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 (ms) | 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/m²) | 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

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
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 PWV, 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 cfPWV 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 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 cfPWV could be detected which unequivocally underpins the consistency of a multimodal approach to characterize central aortic hemodynamics.

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| Table 4 Correlation of aortic flow parameters to arterial stiffness a) aortic distensibility and b) pulse wave velocity. |
|---------------------------------------------------------------|
| **a) Aortic distensibility**                                    |
| **p-value** | **r (95%CI)** |
| Medium flow (ml/s)   | <0.0001     | -0.68 (–0.79 to –0.53) |
| Medium flow/ BSA (l/min/m²)        | <0.0001   | -0.71 (–0.81 to –0.57) |
| Max. flow (ml/s)     | 0.005       | -0.33 (–0.53 to –0.10) |
| Time to max. flow (ms) | 0.048     | 0.24 (0.01 to 0.45)    |
| Forward flow volume (ml)    | 0.02      | -0.29 (–0.49 to –0.05) |
| Backward flow volume (ml)   | <0.0001    | 0.61 (0.44 to 0.74)    |
| Regurgitant fraction (%)    | <0.0001    | 0.69 (0.55 to 0.80)    |
| Netto forward flow volume (ml) | <0.0001  | -0.46 (–0.63 to –0.25) |
| Mean velocity (cm/s)      | <0.0001    | -0.86 (–0.91 to –0.78) |
| Max. velocity (cm/s)      | 0.23       | –                        |
| Pressure gradient (mmHg)      | 0.10      | –                        |
| **b) Pulse wave velocity**                                    |
| **p-value** | **r (95%CI)** |
| Pressure gradient (mmHg)      | 0.003      | -0.37 (–0.57 to –0.13) |
| Backward flow volume (ml)    | 0.002      | -0.39 (–0.58 to –0.15) |
| Mean velocity (cm/s)        | 0.023      | –                        |
| Max. velocity (cm/s)        | 0.57       | –                        |
| Netto forward flow volume (ml) | 0.001    | -0.40 (–0.59 to –0.17) |
| **p-value** | **r (95%CI)** |
| Medium flow (ml/s)   | 0.0006     | -0.42 (–0.61 to –0.20)  |
| Medium flow/ BSA (l/min/m²)    | 0.0006     | -0.42 (–0.61 to –0.19)  |
| Max. flow (ml/s)     | 0.003      | -0.37 (–0.57 to –0.13)  |
| Time to max. flow (ms) | 0.10      | –                        |
| Forward flow volume (ml)    | 0.26      | –                        |
| Backward flow volume (ml)   | 0.03       | –                        |
| Regurgitant fraction (%)    | 0.28 (0.03 to 0.50) |
| Netto forward flow volume (ml) | 0.001    | -0.40 (–0.59 to –0.17) |
| Mean velocity (cm/s)      | 0.03       | -0.27 (–0.48 to –0.02)  |
| Max. velocity (cm/s)     | 0.57       | –                        |

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