

# Selective Heart Rate Reduction With Ivabradine Increases Central Blood Pressure in Stable Coronary Artery Disease

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**Abstract**—Heart rate (HR) lowering by  $\beta$ -blockade was shown to be beneficial after myocardial infarction. In contrast, HR lowering with ivabradine was found to confer no benefits in 2 prospective randomized trials in patients with coronary artery disease. We hypothesized that this inefficacy could be in part related to ivabradine's effect on central (aortic) pressure. Our study included 46 patients with chronic stable coronary artery disease who were randomly allocated to placebo (n=23) or ivabradine (n=23) in a single-blinded fashion for 6 months. Concomitant baseline medication was continued unchanged throughout the study except for  $\beta$ -blockers, which were stopped during the study period. Central blood pressure and stroke volume were measured directly by left heart catheterization at baseline and after 6 months. For the determination of resting HR at baseline and at follow-up, 24-hour ECG monitoring was performed. Patients on ivabradine showed an increase of 11 mmHg in central systolic pressure from  $129\pm 22$  mmHg to  $140\pm 26$  mmHg ( $P=0.02$ ) and in stroke volume by  $86\pm 21.8$  to  $107.2\pm 30.0$  mL ( $P=0.002$ ). In the placebo group, central systolic pressure and stroke volume remained unchanged. Estimates of myocardial oxygen consumption (HR $\times$ systolic pressure and time-tension index) remained unchanged with ivabradine. The decrease in HR from baseline to follow-up correlated with the concomitant increase in central systolic pressure ( $r=-0.41$ ,  $P=0.009$ ) and in stroke volume ( $r=-0.61$ ,  $P<0.001$ ). In conclusion, the decrease in HR with ivabradine was associated with an increase in central systolic pressure, which may have antagonized possible benefits of HR lowering in coronary artery disease patients.

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**Key Words:** central blood pressure ■ coronary artery disease ■ heart rate ■ ivabradine ■ stroke volume ■ ventricular-vascular mismatch

More than 25 years ago, Kjekshus<sup>1</sup> documented the importance of heart rate (HR) in determining  $\beta$ -blocker efficacy in acute and long-term myocardial infarction intervention trials: the greater the decrease in HR, the better were short- and long-term prognosis. HR lowering became the standard by which  $\beta$ -blocker efficacy was assessed in the post-myocardial infarction patient population.<sup>2</sup> Presumably, a decrease in the double product (HR $\times$ blood pressure [BP]) by  $\beta$ -blockade served to reduce myocardial workload, thereby acutely diminishing infarct size and, over the long term, preventing remodeling of the left ventricle.

Unexpectedly, in 2 recent landmark studies, HR lowering with a specific negative chronotropic drug, that is, ivabradine, conferred little if any benefits in patients with coronary artery disease (CAD).<sup>3,4</sup> At a first glance, the absence of an effect of ivabradine in CAD seems to be a conundrum.<sup>5</sup> However, as Ferrari and Fox have pointed out, the role of HR (and its reduction) may differ according to the pathophysiologic setting.<sup>3,4,6</sup> Of note, HR lowering with the same drug significantly improved hospitalization rates in heart failure with reduced

ejection fraction as shown in the Systolic Heart Failure  $I_f$  Trial (SHIFT) study by Swedberg et al.<sup>7</sup> These conflicting observations triggered the provocative question whether ivabradine was less effective in left ventricular systolic dysfunction of ischemic than of nonischemic origin.<sup>7,8</sup> A relevant aspect to consider in this context and that could at least in part explain these differing results is that HR has an important impact on central BP, particularly in hypertensive patients.<sup>9</sup> Indeed, the negative chronotropic effects of  $\beta$ -blockers (with the exception of the vasodilating ones) was shown to be associated with an elevated central BP.<sup>9-12</sup> Because ivabradine can be considered as a pure negative chronotropic agents without relevant effects on other BP regulating mechanisms, we wondered whether its relative inefficacy in CAD patients could also be related to increase of central (aortic) BP associated with HR lowering.

## Methods

Study design and patient characteristics have been previously described.<sup>13</sup> Briefly, this was a prospective study in 46 patients with

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chronic stable CAD who were randomly allocated to placebo (n=23) or ivabradine (n=23) given in a single-blinded fashion for the duration of 6 months. Inclusion criteria for the study were age >18 years and 1- to 3-vessel chronic stable CAD. In 48% (n=22) of the patients, a test of ischemia (bicycle stress testing) was performed, whereas in 52% (n=24) of patients, classical angina pectoris was present. Exclusion criteria were acute coronary syndrome, CAD treated best by surgical coronary bypass, resting HR <50/min without any treatment, sick sinus syndrome, sino-atrial block or more than second-degree atrioventricular block, atrial fibrillation, long-QT syndrome, cardiac pacemaker, severe hepatic or renal failure (creatinine clearance <15 mL/min), hypersensitivity against ivabradine, or adjuvants. The study protocol was approved by the ethics committee of the University of Bern, Switzerland. All included patients gave written informed consent to participate.

Baseline BP measurements (both brachial and central) were performed after tapering of  $\beta$ -blocker medications over 5 days before baseline measurements.

Brachial BP measurement was performed with a validated device (Omron 705-IT, Kyoto, Japan) before invasive assessment. Brachial mean BP was calculated as follows: diastolic BP+(0.4×pulse pressure).<sup>14</sup>

Patients underwent left heart catheterization and coronary angiography for diagnostic purposes from the right femoral artery approach. Aortic pressures were directly measured via a 6F coronary artery guiding catheter.

Damping coefficient ( $\beta$ ) and natural frequency ( $F_n$ ) were measured using the flash flush test. Briefly, 0.9% saline was flushed at high pressure (300 mmHg), and the undershoot and overshoot waves were registered.  $F_n$  (Hz) was measured by dividing the paper speed (mm/s) by the peak to peak distance (mm) of the 2 waves.  $\beta$  was derived using the amplitude ratio of the 2 waves (smaller wave divided by the higher wave).<sup>15</sup>

Central BP was measured using the HaemoSphere Systems (Philips, Best, the Netherlands), and mean arterial pressure calculated as running average (1 s) over a period of 10 heart beats by electric integration. Stroke volume was calculated by tracing the end-diastolic and end-systolic images obtained by angiographic ventriculography and digitally recorded for offline analysis in Xcelera workstation (Philips Medical Systems, Amsterdam, the Netherlands). Double product was calculated as central systolic BP×HR. Time-tension index, another index of myocardial oxygen consumption,<sup>16</sup> was calculated as follows: time-tension index=[(systolic time interval/RR interval)×mean central systolic BP]×HR.

The initial invasive procedure was followed by the 6-month treatment period initiated by a 1-week placebo run-in phase in all patients. Ivabradine was initiated at a dose of 5 mg/d and up-titrated as appropriate, with the goal to reduce resting HR to 60/min (maximum dose for ivabradine of 7.5 mg twice/d or an identically looking tablet for placebo). Concomitant baseline medication was continued unchanged throughout the study except for  $\beta$ -blockers that were tapered over 5 days prior the baseline examination and then stopped over the study period. The follow-up examination at the end of the 6-month treatment period consisted of measurements identical to those described above.

## Study Protocol

Patient study inclusion occurred 5 days before the baseline invasive examination because tapering and stop of the treatment with  $\beta$ -blockers had to take place over the study period. The initial invasive measurement was followed by the 6-month treatment period initiated by a 1-week placebo run-in phase in all patients. For the determination of resting HR at baseline, a 24-hour ECG monitoring was performed the day after the invasive procedure. At the start of week 2, the study drug was started as randomly assigned. The study drug was begun at a lower dose and increased with the aim to reduce resting HR to 60/min. Prior follow-up, another 24-hour ECG was performed. For more details please refer Gloekler et al.<sup>13</sup>

## Statistical Analysis

A sample size calculation was performed on the basis of previously reported data.<sup>13</sup> Assuming an intraindividual difference in central systolic BP of 10 mmHg as a clinically significant change (standard

deviation of 16 mmHg, power >0.80;  $\alpha=0.05$ ), we calculated that 23 subjects were required assuming no dropout.

Statistical analysis was done with the GraphPad Prism 5 software package (GraphPad Software Inc, San Diego, CA). Between-group comparison of continuous data was performed by a 2-sided unpaired Student's *t* test and comparison of categorical data by a  $\chi^2$  test. Intraindividual comparison of hemodynamic parameters obtained at follow-up versus baseline examination was performed by paired Student's *t* test. Linear regression analysis was used for assessing the relation between HR change as the independent variable and central systolic pressure and stroke volume. A value of  $P<0.05$  was considered to indicate statistical significance. Unless otherwise indicated, data are given as mean±standard deviation (SD).

## Results

Baseline characteristics of 2 groups were comparable (Table 1). Hemodynamic data at baseline and follow-up are shown in Table 2. Using the flash flush test,  $F_n$  was found to be 23 Hz and  $\beta$ , 0.44. Compared with baseline, patients on ivabradine showed a significant decrease in HR of 8±12 bpm with an increase of 11 mmHg in central systolic pressure from 129±22 to 140±26 mmHg ( $P=0.02$ ) after 6 months. Central mean arterial pressure also increased by 6 mmHg from 92±11 to 98±14 mmHg ( $P=0.02$ ; Figure 1). At follow-up, brachial-central systolic BP significantly decreased ( $P=0.005$ ). Central diastolic pressure in the ivabradine group did not increase significantly, and the increase in central pulse pressure failed to achieve statistical significance ( $P=0.07$ ). Stroke volume increased significantly in the ivabradine group (Table 2), whereas cardiac output did not significantly change (Table 2). In the placebo group, central systolic pressure, diastolic pressure, mean arterial pressure, pulse pressure, stroke volume, and cardiac output remained unchanged. Despite the decrease in HR by 8±12 bpm, no significant change in the double product (central systolic pressure×HR) was seen in the ivabradine group (8950±2179 versus 8998±2477 mmHg×bpm;  $P=0.91$ ). Time-tension index, an index for myocardial oxygen consumption, did not significantly change, neither in placebo ( $P=0.30$ ) nor in the ivabradine group ( $P=0.21$ ; Table 2). Central systolic pressure inversely correlate with HR in the whole study population ( $r=-0.33$ ,  $P=0.0026$ ; Figure 2). Additionally, we observed an inverse linear correlation ( $r=-0.41$ ,  $P=0.009$ , Figure 3) between the change of HR from baseline to follow-up and the concomitant change in central systolic pressure and stroke volume ( $r=-0.61$ ,  $P=0.0008$ ) and a positive relationship between change of HR and brachial-central systolic BP ( $r=0.34$ ,  $P=0.03$ ).

## Discussion

The principal findings of our study in hypertensive patients with stable CAD are that after a follow-up of 6 months, HR lowering with ivabradine was associated with an increase of 11 mmHg in directly measured central systolic pressure. Further, there was an inverse correlation between the decrease in HR and the increase in central systolic pressure, indicating that the greater the negative chronotropic effect of ivabradine, the greater was the increase in central pressure. Moreover, the HR-lowering effect of ivabradine was associated with an increase in stroke volume without significant changes in cardiac output. Conceivably, the observed increase in central pressure could be because of a ventricular-vascular mismatch or of an increase in stroke volume.<sup>17</sup> Under physiological conditions, when there is ventricular-vascular

**Table 1. Baseline Characteristics of the Included Patients**

Characteristics	Placebo (n=23)	Ivabradine (n=23)	P Value
Age, y	63±8	65±10	0.46
Male sex, n (%)	20 (87)	21 (90)	0.73
Body mass index, kg/m <sup>2</sup>	29±6	30±7	0.57
Smoking, n (%)	3 (14)	2 (11)	0.77
Diabetes mellitus, n (%)	4 (18)	1 (4)	0.48
Dyslipidemia, n (%)	23 (100)	23 (100)	0.95
Hypertension, n (%)	22 (96)	21 (90)	0.91
Angina pectoris, n (%)	15 (65)	15 (65)	1.0
Prior myocardial infarction, n (%)	7 (30)	7 (30)	1.0
<b>Medication</b>			
ACE inhibitor/ARBs, n (%)	18 (78)	13 (57)	0.15
Calcium channel blockers, n (%)	2 (9)	6 (24)	0.24
Diuretics, n (%)	2 (9)	5 (23)	0.41
β-Blockers, n (%)	15 (66)	12 (52)	0.65
Nitrates, n (%)	8 (36)	6 (24)	0.41
Statin, n (%)	13 (57)	21 (90)	0.16
CAD, number of vessels diseased			0.18
1, n (%)	9 (39)	6 (26)	
2, n (%)	10 (43)	9 (39)	
3, n (%)	4 (17)	8 (35)	
<b>Hemodynamic data</b>			
Left ventricular ejection fraction, %	62±7	58±10	0.12
Heart rate, bpm	76±10	73±9	0.27
<b>Brachial blood pressure, mm Hg</b>			
Systolic	131±16	136±21	0.44
Diastolic	72±11	71±8	0.83
Mean	95±11	97±11	0.72
<b>Central blood pressure, mm Hg</b>			
Systolic	126±17	129±22	0.66
Diastolic	71±11	66±9	0.21
Mean	94±12	92±11	0.71

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; and CAD, coronary artery disease.

coupling, the reflected pulse wave returns to the left ventricle in diastole and serves to increase coronary perfusion. When HR is slowed down by a negative chronotropic drug, the reflected pulse wave returns to the ventricle at a time when it is still in systole, thereby serving to augment central systolic pressure. In line with this concept, several studies showed that HR reduction by β-blockers (with the exception of the vasodilating ones) was associated with an increase in wave reflection.<sup>9-12</sup>

Of note, bradycardia increases diastolic filling time of the ventricle, thereby increasing stroke volume. Conceivably, the observed increase in central pressure could also be related at

least in part to an increased stroke volume pumped into an aorta with compromised Windkessel function. In line with this concept, we found that stroke volume was increased in the ivabradine group and that the decrease in HR from baseline to follow-up directly correlated with the increase in stroke volume.

Pulse wave velocity is positively related to HR.<sup>18-20</sup> This may at least in part be linked to the visco-elastic vessel properties: higher HR shortens relaxing time of the vessel, resulting in increasing stiffness. Conversely, through decreased mechanical stress, long-term reduction in HR may promote a favorable remodeling, particularly if there is no changes in inotropy associated with HR reduction. In our study, HR reduction was associated with increased stroke volume and consequent increased vascular mechanical stress. This may have blunted the favorable HR-lowering effect of ivabradine on vascular remodeling.

The present data corroborate and extend previous studies, showing an inverse correlation between HR and pulse pressure, using either pacing<sup>18,19</sup> or ivabradine experimentally.<sup>21</sup>

Williams et al reported a similar phenomenon with β-blockade in the CAFÉ study.<sup>22,23</sup> For the same brachial BP, a 4.3 mmHg higher central aortic systolic BP was noted with atenolol-based treatment compared with the amlodipine-based treatment. Moreover, the brachial–central BP difference decreased linearly with the fall in HR; the slower the HR, the greater the relative increase in central BP. In line with this concept, we found that in the ivabradine group, brachial–central BP difference significantly decreased, suggesting that at lower HR, central systolic BP get closer to brachial systolic BP.

Williams et al proposed that HR reduction with atenolol was the mechanism accounting for less effective central aortic pressure reduction per unit change in brachial pressure (pseudo antihypertensive effect of β-blockers).<sup>23</sup> This in turn was presumably the principle reason in ASCOT for atenolol-based therapy being less efficacious than amlodipine-based therapy in reducing morbidity and mortality.<sup>24</sup>

Our findings are apparently in contrast with the recently published study of Dillinger et al,<sup>25</sup> who in controlled hypertensive patients with CAD failed to observe an increase in central pressure after HR reduction with ivabradine. This could be explained by some important clinical and methodological differences between their study and our findings. First, their study period was significantly shorter (3 weeks) when compared with ours (6 months). Second, Dillinger et al continued concomitant β-blocker therapy throughout the study, whereas our patients after tapering and before baseline BP measurements were no longer exposed to β-blockade. BP effects of β-blockers are multifactorial (HR and sympathetic nervous activity reduction, renin–angiotensin–aldosterone system inhibition) and, therefore, is difficult to speculate on the withdrawal effects. Because β-blockers’ treatment is expected to reduce more significantly brachial than central BP,<sup>23</sup> we speculate that withdrawal had a greater impact on peripheral than central BP. Nevertheless, percentage of patients treated with β-blockers was comparable between the placebo and the ivabradine group, and at baseline, after withdrawal of β-blocker’s treatment, both brachial and central BP were comparable between placebo and ivabradine group.

Third, we measured central pressure directly by left heart catheterization. In contrast, Dillinger et al indirectly estimated central pressure by applanation tonometry of the radial artery

**Table 2. Hemodynamic Data at Baseline and Follow-Up**

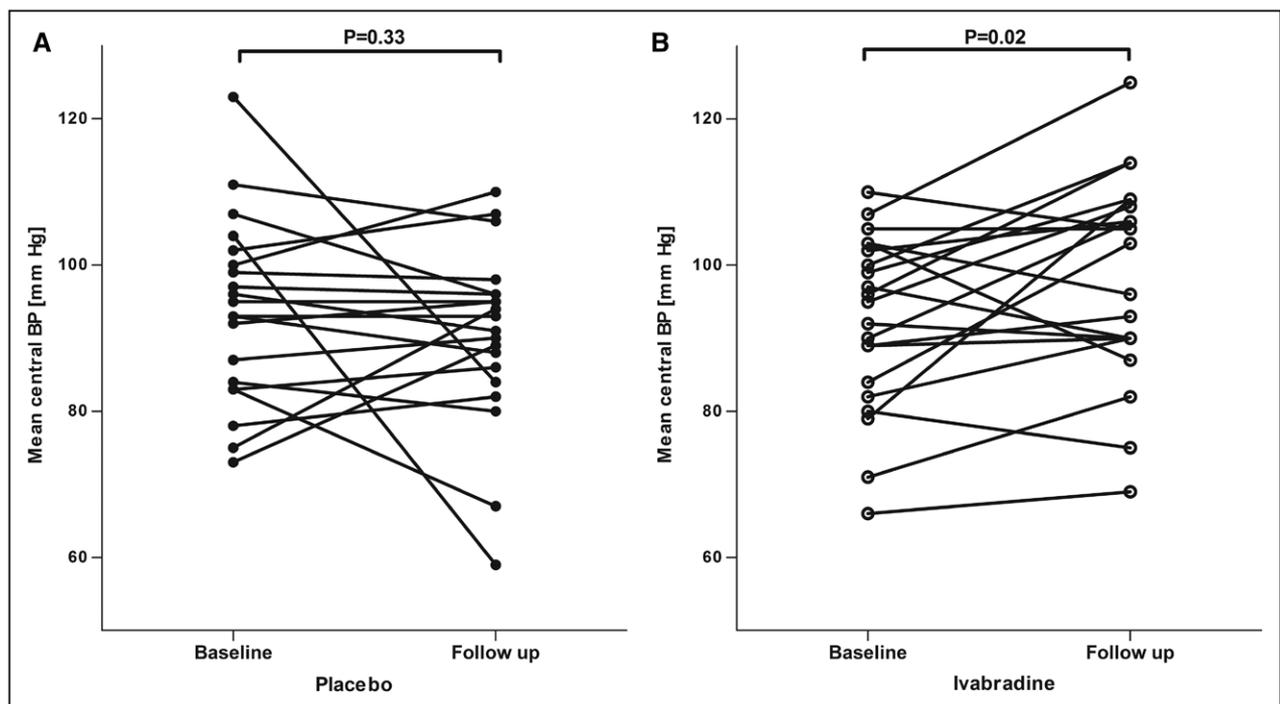
Variable	Placebo (n=23)		P Value	Ivabradine (n=23)		P Value
	Baseline	Follow-Up		Baseline	Follow-Up	
Heart rate, bpm	76±10	75±10	0.91	73±9	64±10	0.003
Brachial systolic BP, mm Hg	131±16	128±16	0.51	136±21	142±25	0.12
Brachial diastolic BP, mm Hg	72±11	70±8	0.49	71±8	74±11	0.21
Brachial pulse pressure, mm Hg	59±14	58±10	0.73	65±18	68±21	0.23
Brachial mean BP, mm Hg	95±11	93±10	0.47	97±11	101±15	0.21
Central systolic BP, mm Hg	126±17	123±18	0.52	129±22	140±26	0.02
Central diastolic BP, mm Hg	71±11	67±9	0.21	66±9	70±10	0.13
Central pulse pressure, mm Hg	56±13	56±14	0.90	63±19	71±25	0.07
Central mean BP, mm Hg	94±12	90±12	0.33	92±11	98±14	0.02
Brachial-Central systolic BP, mm Hg	4.5±4.1	4.8±4.6	0.78	6.5±4.9	2.1±4.5	0.005
Central double product, mm Hg×bpm	8897±1841	8741±1331	0.71	8950±2179	8998±2477	0.91
Time-tension index, mm Hg×bpm	3300±692	3127±527	0.30	3275±794	3071±674	0.21
Stroke volume, mL	87.5±18.7	89.1±19.5	0.66	86.0±21.8	107.2±30.0	0.002
Cardiac output, L/min	6.35±1.16	6.34±1.37	0.96	6.44±1.83	6.96±1.84	0.13

BP indicates blood pressure.

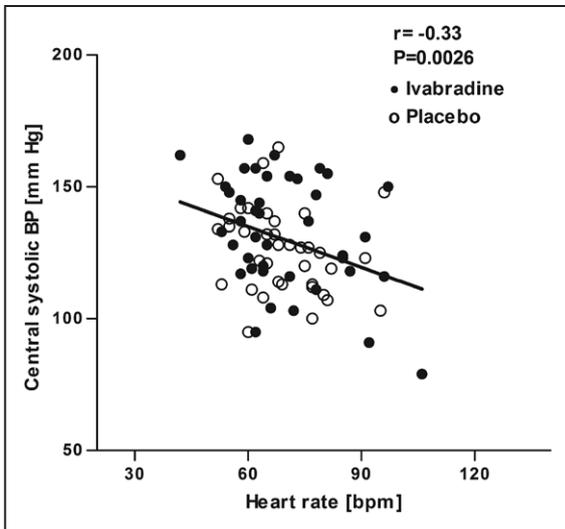
after calibration of the device using the brachial BP estimated by cuff. Finally, our study was single-blind; however, analysis of the recorded invasive measurements, as well as stroke volume measurements, were assessed by blinded investigators (S.F. Rimoldi and D. Cerny).

We previously evaluated the negative chronotropic effect of β-blockers in a meta-analysis of 22 randomized controlled trials with >60000 hypertensive patients.<sup>26</sup> In contrast to patients with myocardial infarction and heart failure, β-blocker-associated reduction in HR increased the risk of cardiovascular events in

hypertension; the slower the HR, the greater the risk for the end points of all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, or heart failure. Similarly, in the EXPLOR study, Boutouyrie et al<sup>27</sup> showed that atenolol, when combined with amlodipine, reduced central systolic and pulse pressure to a lesser extent than when combined with valsartan. Surprisingly, even in endurance athletes, the slow HR secondary to conditioning has been shown to be associated with higher carotid systolic BP and pulse pressure compared with nonathletic controls, despite brachial BP being similar in the 2 groups.<sup>28</sup>

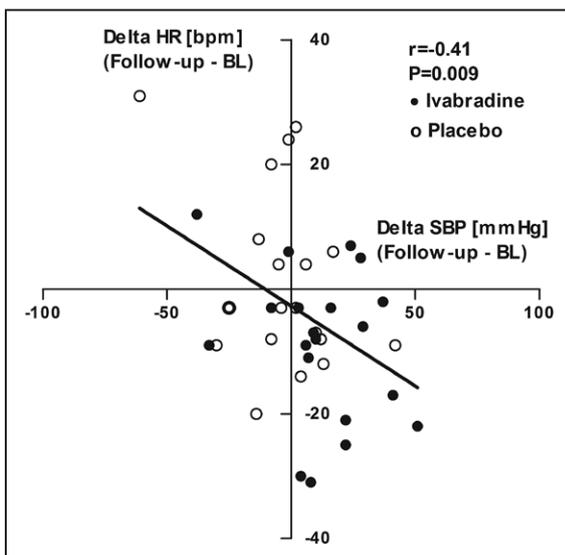


**Figure 1.** Mean central arterial pressure with placebo (A) and ivabradine (B) at baseline and after 6 months follow-up.



**Figure 2.** Correlation between central systolic pressure and heart rate in the whole study population.

One may ask at this juncture why the Kjekshus hypothesis, which is based on  $\beta$ -blockade in the prereperfusion area, is no longer applicable to contemporary CAD patients treated with ivabradine. Two main issues may account for this: first, in the prereperfusion era, lack of reperfusion and contemporary medical therapy likely resulted in extensive myocardial scarring, thereby providing a substrate for re-entrant circuits and fatal ventricular arrhythmias.  $\beta$ -Blockers were beneficial in this setting by reducing sympathetic activity and preventing sudden death, which was the major cause of mortality in the prereperfusion era. In the reperfusion era, prompt reperfusion and contemporary medical therapy reduce the likelihood of extensive scar formation. Thus, given the increase in central pressure with the decrease in HR, the risk-benefit ratio of a negative chronotropic intervention may no longer be favorable in hypertensive patients with CAD. Conceivably, some of these pathophysiologic factors could account for the increase



**Figure 3.** Correlation between baseline to 6-month follow up difference in heart rate (HR) and difference in central systolic blood pressure (SBP).

in primary end point among patients with angina of Canadian Cardiovascular Society class II or higher who were randomized to ivabradine in the study assessing the morbidity-mortality benefits of the  $I_f$  inhibitor ivabradine in patients with coronary artery disease (SIGNIFY).<sup>3</sup> Current guidelines of the European Society of Cardiology (ESC) on the management of stable CAD<sup>29</sup> recommend ivabradine as second-line agent (mostly on top of  $\beta$ -blockers) in patients with no satisfactorily controlled angina pectoris. In view of these large study results and the present data, we suggest that in hypertensive patients with stable CAD and preserved left ventricular function, ivabradine should be combined with vasodilatory antihypertensive agents to avoid HR-related increase in central BP.

Second, systolic BP multiplied by the HR is often called the double product and is an index of myocardial oxygen consumption. In our study, HR decreased by  $\approx 8$  bpm in the ivabradine group, whereas central systolic BP increased by 11 mmHg. These hemodynamic changes amounted to a mere decrease in the double product of  $<2\%$ , which is unlikely to have any impact on the risk of myocardial ischemia. Similarly, time-tension index, another parameter to estimate myocardial oxygen consumption, was unchanged with ivabradine therapy.

The fact that HR lowering with ivabradine turned out to be beneficial in patients with heart failure with reduced systolic function as shown by Swedberg et al<sup>7</sup> should not surprise. In many patients with heart failure, arterial BP is low and, in contrast to hypertensive patients, they are likely to tolerate or may even benefit from an increase in central BP. Reil et al<sup>30</sup> even documented markedly improved ventricular-arterial coupling, resulting in a higher stroke volume in ivabradine-treated patients. Moreover, the authors speculated that this could also be because ivabradine-treated patients with HR reduction of  $\approx 10$  bpm may have had slightly higher central systolic BP levels compared with controls.

### Perspectives

HR is a powerful determinant of central BP, particularly in hypertensive patients. The present study showed that the decrease in HR after 6 months of ivabradine treatment, a pure negative chronotropic agent without effects on other BP-regulating mechanisms, was associated with a significant increase in stroke volume and central systolic BP. This increase in central pressure is prone to mitigate the potential benefits of a HR-lowering intervention and may account at least in part for failure to reduce outcome in hypertensive CAD patients. Future studies in hypertensive CAD patients should assess the impact of HR-lowering treatment on cardiovascular morbidity and mortality. Negative chronotropic drugs, such as ivabradine, may have to be combined with specific antihypertensive drugs as to safeguard the benefits of HR lowering.

### Disclosures

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## Novelty and Significance

### What Is New?

- Heart rate is an important determinant of central blood pressure. Heart rate lowering with ivabradine causes a ventricular–vascular mismatch and an increase in stroke volume both of which lead to a substantial increase in central blood pressure.

### What Is Relevant?

- These findings confirm that heart rate reduction with a pure negative chronotropic agent translates into increased central systolic blood pressure in hypertensive coronary artery disease patients.

### Summary

This study highlights that in hypertensive coronary artery disease patients, heart rate reduction with ivabradine results in a significant increase in stroke volume and consequent central systolic blood pressure. Negative chronotropic drugs, such as ivabradine, may have to be combined with specific antihypertensive drugs as to safeguard the benefits of heart rate lowering.

## Selective Heart Rate Reduction With Ivabradine Increases Central Blood Pressure in Stable Coronary Artery Disease

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