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Do Beta-Adrenergic Blocking Agents Increase Coronary Flow Reserve?

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BACKGROUND Beta-adrenergic blocking agents are the cornerstone in the treatment of coronary artery disease (CAD). The exact pathophysiologic mechanism is not clear but depends largely on the oxygen-sparing effect of the drug. Thus, the effect of metoprolol on coronary flow reserve and coronary flow velocity reserve (CFVR) was determined in patients with CAD.

METHODS Coronary blood flow velocity was measured with the Doppler flow wire in 23 patients (age: 56 ± 10) undergoing percutaneous transluminal coronary angioplasty for therapeutic reasons. Measurements were carried out at rest, after 1-min vessel occlusion (postischemic CFVR) as well as after intracoronary adenosine (pharmacologic CFVR) before and after 5 mg intravenous metoprolol. In a subgroup (n = 15), absolute flow was measured from coronary flow velocity multiplied by coronary cross-sectional area.

RESULTS Rate-pressure product decreased after metoprolol from 9.1 to 8.0 × 10^3 mm Hg/min ($p < 0.001$). Pharmacologic CFVR was 2.1 at rest and increased after metoprolol to 2.7 ($p = 0.002$). Likewise, postischemic CFVR increased from 2.6 to 3.3 ($p < 0.001$). Postischemic CFVR was significantly higher than pharmacologic CFVR before as well as after metoprolol. Coronary vascular resistance decreased after metoprolol from 3.4 ± 2.0 to 2.3 ± 0.7 mm Hg × s/cm ($p < 0.02$).

CONCLUSIONS The following conclusions were drawn from this study. Metoprolol is associated with a significant increase in postischemic and pharmacologic CFVR. However, postischemic CFVR is significantly higher than pharmacologic CFVR. The increase in CFVR by metoprolol can be explained by a reduction in vascular resistance. The increase in CFVR (= increased supply) and the reduction in oxygen consumption (= decreased demand) after metoprolol explain the beneficial effect of this beta-blocker in patients with CAD. (J Am Coll Cardiol 2001;38:1866–71) © 2001 by the American College of Cardiology

The capacity of the coronary arteries to increase flow during hyperemia by a factor of three to four was described as early as in 1939 by Katz and Lindner (1). However, it was not until 1960 that the concept of coronary flow reserve (CFR) was introduced by Coffman and Gregg (2) to assess the capacity of coronary circulation to conduct maximal hyperemic blood flow. Pharmacologic agents commonly used to induce maximal vasodilation include papaverine (3–5), adenosine (4,6) and dipyridamole (4). Hyperemia can also be induced by transient vessel occlusion (7) or dynamic exercise (8).

Coronary flow reserve is the ratio of coronary blood flow during maximal vasodilation divided by resting flow. Because the pressure-flow relationship is linear and steep during maximal vasodilation, peak flow is a function of coronary resistance in the absence of epicardial coronary artery lesions (9). Therapeutic interventions may affect CFR by changing resting or maximal flow. A small increase in resting flow leads, however, to a large decrease in CFR, and vice versa.

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Metoprolol has been shown to reduce oxygen consumption of the myocardium and, thus, diminishes myocardial ischemia (= reduced demand). However, a preliminary report using positron emission tomography in healthy volunteers for coronary flow measurements also indicated an improvement in CFR after beta-adrenergic blockade (= increased supply), which was mainly due to an increase in hyperemic flow rather then a decrease in resting flow (10). Thus, the purpose of this study was to assess the effect of intravenous metoprolol on CFR, respectively, coronary flow velocity reserve (CFVR) in patients with coronary artery disease (CAD) using adenosine and postischemic hyperemia as stimulus for maximal flow increase.

METHODS

Patients. Twenty-three patients (age: 58 ± 10 years, all men) with one- (n = 17) or two-vessel (n = 6) disease are included in this analysis. Three of the 23 patients had previous myocardial infarction, but none of these patients had a Q-wave infarct (Table 1). All patients underwent percutaneous transluminal coronary angioplasty (PTCA) for clinical purposes (angina pectoris or positive exercise test with ST-segment depression). Patients with diffused or three-vessel disease were excluded from this analysis.

Abbreviations and Acronyms

CAD = coronary artery disease
CFR = coronary flow reserve
CFVR = coronary flow velocity reserve
i.c. = intracoronary
PTCA = percutaneous transluminal coronary angioplasty
QCA = quantitative coronary angiography

Coronary angiography. Patients underwent left heart catheterization for diagnostic purposes. Aortic and left ventricular pressure were measured with a pigtail catheter. Biplane left ventricular angiography was performed at the end of diagnostic coronary angiography. Coronary artery lesions were assessed quantitatively as percent diameter stenosis. Vessel diameter at the tip of the flow wire was measured by quantitative coronary angiography (QCA) using the ACA package on Philips DC/Integris system. Collateralization was assessed according to the Rentrop classification (11).

Doppler flow velocity measurements. Doppler flow velocity was measured with a 0.014 in. Doppler guide wire with a 12-MHz piezoelectric crystal at its tip (FloWire, EndoSonics, Rancho Cordova, California). The validation of this Doppler guide wire has been described previously (12).

Coronary flow velocity reserve was calculated from hyperemic peak flow velocity averaged over two cardiac cycles (averaged peak velocity = APV, cm/s) divided by resting flow velocity (Fig. 1). Pharmacologic CFVR was induced by an intracoronary bolus of 18 μg adenosine for the left and 12 μg for the right coronary artery (13). Postischemic hyperemia was induced by a 1-min balloon occlusion. Coronary vascular resistance was calculated from mean aortic pressure divided by mean coronary flow velocity (mm Hg $\times$ s/cm).

In a subgroup of 15 patients, coronary flow was calculated from coronary flow velocity multiplied by coronary artery dimension at the tip of the flow wire measured by QCA $\times$ 0.3. From these measurements CFR was determined.

Recent data (14,15) indicate that the standard (13) adenosine dose (18 μg for the left and 12 μg for the right coronary artery) may be submaximal in some patients. Therefore, in a group of six patients, the effect of two different adenosine doses (18 and 24 μg) on coronary flow reserve was tested.

Study protocol. The following study protocol were adhered to:

1. Diagnostic angiography
2. Intracoronary bolus of nitroglycerin (0.2 mg, repeated every 5 to 10 min)
3. PTCA
4. Control studies
   a. Rest measurements 1
   b. Measurements during hyperemia (adenosine, intracoronary [i.c.])
   c. Rest measurements 2
   d. Measurements during hyperemia (1-min coronary occlusion)
5. Administration of 5 mg metoprolol, intravenous
   a. Rest measurements 1
   b. Measurements during hyperemia (adenosine, i.c.)
   c. Rest measurements 2
   d. Measurements during hyperemia (1-min coronary occlusion).

The present study protocol was approved by the local ethics committee, and all patients gave informed consent.

Statistical analysis. Comparison of angiographic, hemodynamic and Doppler flow velocity data was performed by an unpaired two-sided Student *t* test. A two-way analysis of variance for repeated measurements was performed for comparison of hemodynamic and Doppler flow data. Correlation between CFVR and CFR (n = 15) was performed using the square method. The correlation coefficient (r) and the regression equation were calculated from these data. Statistical significance was defined at a p value of <0.05.

Table 1. Patient Characteristics

	n	%
Number of patients	23	—
Age (yr)	56 ± 10	—
Men	22	96
Cardiovascular risk factors		
Smoking	11	48
Diabetes mellitus	4	17
Family history of CAD	5	22
Obesity	3	13
Hypertension	10	43
Hypercholesterolemia	6	26
Medication		
Aspirin	19	83
Beta-blockers	0	0
Calcium antagonists	3	13
Lipid lowering agents	3	13
ACE inhibitors	7	30
Nitrates	8	35
Vessel studied		
LAD/LCX/RCA	12/4/7	52/17/30
% Diameter stenosis		
Pre-PTCA		83 ± 10
Post-PTCA		6 ± 8

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; PTCA = percutaneous transluminal angioplasty; RCA = right coronary artery.

RESULTS

Average number of diseased vessel was 1.3 per patient. No collateral flow was observed in the majority of patients (n = 18). However, in five patients there was mild collateral flow (grade 1) according to Rentrop classification (16).

Hemodynamics. There was a significant decrease in heart rate after metoprolol administration (Table 2, Fig. 2). Mean aortic pressure also dropped significantly after metoprolol, but this difference was lost during adenosine infusion. Consecutively, the rate-pressure product decreased significantly.

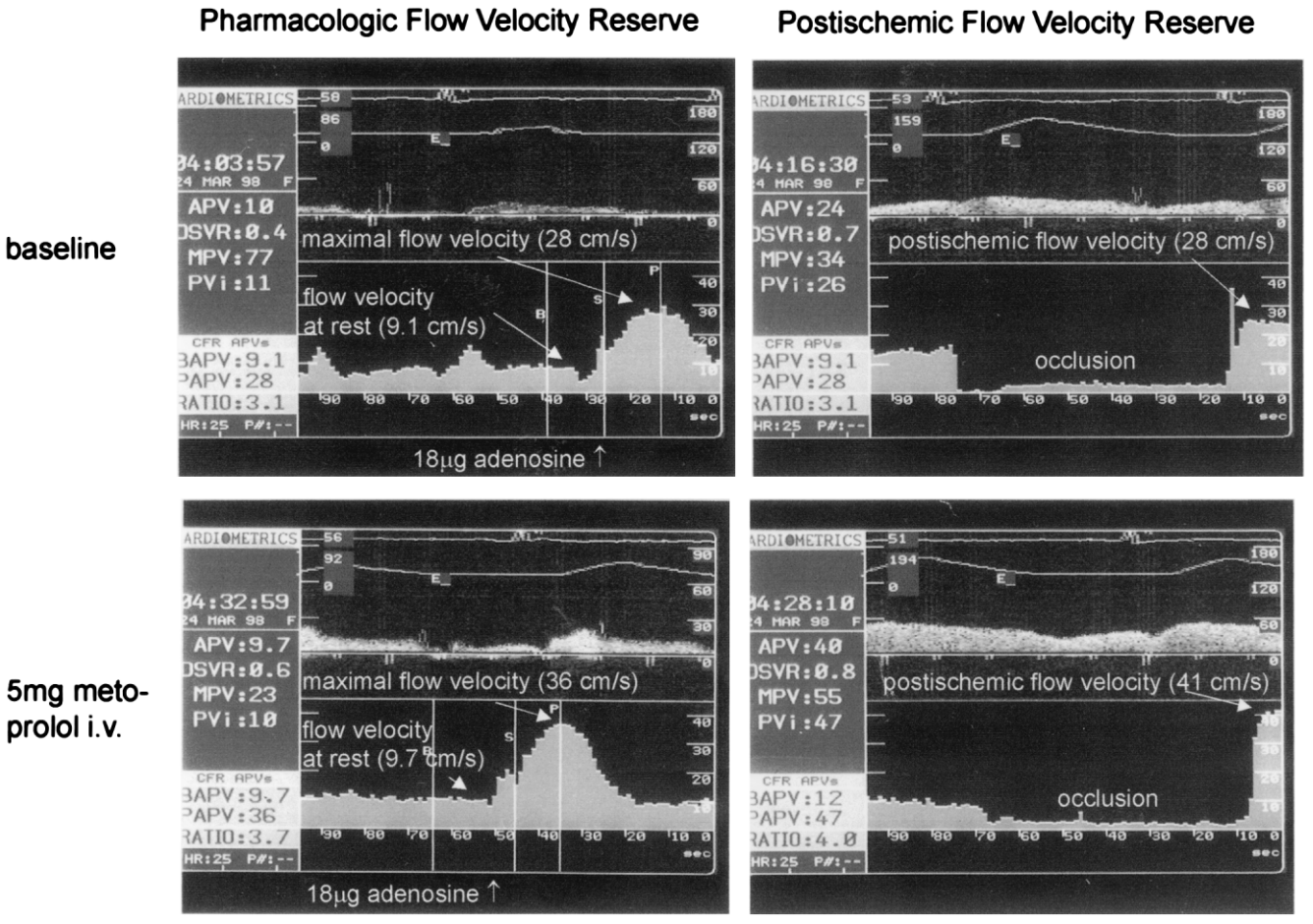

Figure 1. Representative recordings of coronary flow velocity signal in a patient with single-vessel disease undergoing percutaneous transluminal coronary angioplasty. The tracings are shown in the **panels from top to bottom**: electrocardiogram, aortic pressure, instantaneous flow velocity and flow velocity trend. Pharmacologic coronary flow velocity reserve (CFVR) **(left)**: flow velocity at rest = 9.1 cm/s, maximal flow velocity after administration of 18 μg adenosine = 28 cm/s; CFVR: 28/9.1 = 3.1. Determination of postischemic CFVR **(right)**: flow velocity after 1-min balloon occlusion = 28 cm/s; CFVR: 28/9.1 = 3.1. Pharmacologic CFVR after metoprolol **(lower panels)**: flow velocity at rest = 9.7 cm/s, maximal flow velocity after adenosine = 36 cm/s; CFVR: 36/9.7 = 3.7. Postischemic CFVR: postischemic flow velocity = 41 cm/s; CFVR: 41/9.7 = 4.2.

Coronary flow velocity and flow reserve. Basal coronary flow velocity remained unchanged after 5 mg metoprolol but increased significantly (+147%) during adenosine infusion after beta-blockade than after adenosine infusion alone (+94%; $p < 0.001$) (Table 2, Fig. 3). Conversely, the postischemic flow increase was significantly larger (+219%) after metoprolol than it was after ischemia alone (+153%; $p < 0.005$). Maximal flow velocity was significantly higher after metoprolol for both pharmacologic and postischemic vasodilation.

Table 2. Hemodynamics

	Control	Metoprolol	p Value
Coronary flow velocity reserve			
Pharmacologic	2.1 ± 0.6	2.6 ± 0.9	< 0.001
Postischemic	2.7 ± 0.8	3.3 ± 0.9	< 0.005
Coronary flow reserve (n = 15)			
Pharmacologic	1.8 ± 0.5	2.6 ± 0.9	< 0.001
Postischemic	2.5 ± 0.8	3.2 ± 0.9	< 0.05
Heart rate (beats/min)			
Rest	74 ± 10	70 ± 7	< 0.01
Adenosine	76 ± 9	70 ± 6	< 0.001
Ischemia	77 ± 7	68 ± 7	< 0.0001
Mean aortic pressure (mm Hg)			
Rest	96 ± 13	92 ± 11	< 0.01
Adenosine	91 ± 12	88 ± 12	NS
Ischemia	94 ± 13	89 ± 13	< 0.002

Similarly, both pharmacologic and postischemic CFVR increased significantly from 2.1 ± 0.6 to 2.6 ± 0.9, respectively, to 2.7 ± 0.8 to 3.3 ± 1.0 after intravenous administration of 5 mg metoprolol (Fig. 3). In two patients there was no change in pharmacologic CFVR, and in two patients CFVR even decreased after beta-blockade. Postischemic CFVR was significantly higher than pharmacologic CFVR.

In a subgroup of 15 patients, coronary cross-sectional area did not change significantly after 5 mg metoprolol (baseline: 6.5 ± 0.7 mm^2; after beta-blockade: 6.4 ± 0.5 mm^2; p = NS). Therefore, basal flow velocity and volumetric flow remained unchanged after metoprolol. In these patients CFR data were comparable to CFVR data.

The effect of 18 μg and 24 μg adenosine was studied in a group of six patients with normal coronary arteries. There

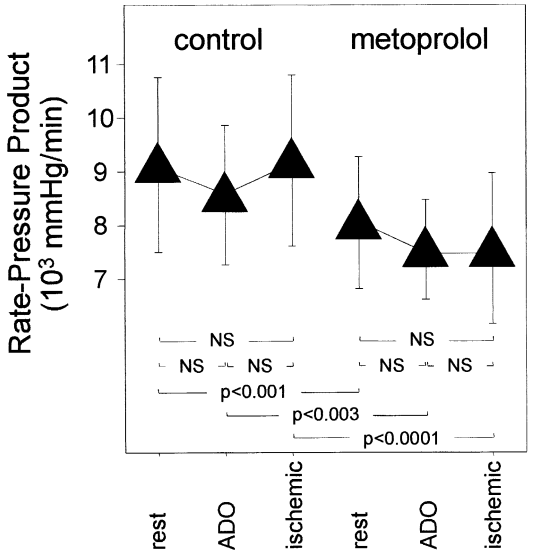

Figure 2. Rate-pressure product: before **(left)** and after **(right)** 5 mg metoprolol, intravenous, at rest as well as during hyperemia. There is a significant reduction in the rate-pressure product after beta-blockade. ADO = adenosine.

was no further flow increase with the higher adenosine dose (24 μg) than with the reported standard dose (18 μg). Coronary flow reserve in these patients was 2.99 ± 0.64 with 18 μg and 3.03 ± 0.73 with 24 μg (n = 23, n = NS).

Coronary vascular resistance. Coronary vascular resistance was slightly lower (n = NS) after metoprolol but significantly lower during pharmacologic, respectively, postischemic hyperemia (Fig. 4). Metoprolol further enhanced the drop in vascular resistance with pharmacologic, respectively, postischemic vasodilation (Fig. 4).

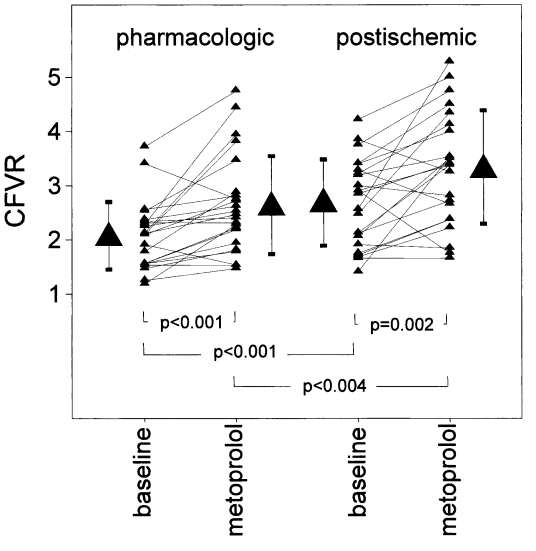

Figure 3. Pharmacologic and postischemic coronary flow velocity reserve (CFVR) increased significantly from 2.1 ± 0.6 to 2.6 ± 0.9, respectively, from 2.7 ± 0.8 to 3.3 ± 1.0 after intravenous administration of 5 mg metoprolol. In two patients, there was no change in pharmacologic CFVR, but in another two patients there was even a decrease in CFVR after beta-blockade. Postischemic CFVR was generally higher than pharmacologic CFVR.

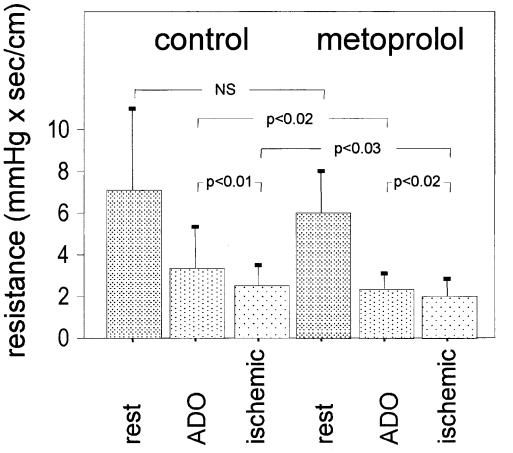

Figure 4. Coronary vascular resistance was slightly lower (NS) after metoprolol but significantly lower during pharmacologic, respectively, postischemic vasodilation. ADO = adenosine.

DISCUSSION

Changes in coronary hemodynamics associated with the administration of beta-blockers have been extensively studied in the past. Animal experiments have shown a reduction in coronary blood flow at rest, which has been explained by coronary vasoconstriction (17–19). Previous clinical data using coronary flow measurements suggest that beta-blockers lead to enhanced coronary vascular resistance during hyperemia due to unopposed alpha-adrenergic vasomotor tone (20). However, this study was performed using a nonselective beta-blocker, and only five of nine patients showed an increase of hyperemic coronary vascular resistance after propranolol, whereas, in four patients, coronary flow behaved similarly to our study. In part, this variability may have been related to the less precise method of flow determination by coronary sinus thermodilution. In 10 healthy volunteers, Boettcher and coworkers (10) have reported an increase in CFR after 50 mg oral metoprolol. Absolute coronary flow was measured noninvasively by positron emission tomography. The increase in CFR was achieved by a significant increase in maximal coronary flow, which was enhanced by a significant decrease in resting flow. In this study in patients with CAD, pharmacologically induced and postischemic flow velocity reserve increased after intravenous administration of 5 mg metoprolol due to an increase in maximal flow (Table 3, Fig. 3). At the same time, coronary vascular resistance decreased after beta-blockade but only during maximal vasodilation and not at rest (Fig. 4). The reduction in coronary vascular resistance can be explained by a diminution of the extravascular compressive forces either due to a reduced filling pressure or a decrease in myocardial contractility with a reduction in vascular tone. Comparison of the two vasodilatory stimuli, that is, pharmacologic vasodilation with adenosine versus postischemic vasodilation by 1-min balloon occlusion, clearly showed a stronger effect (Fig. 3) with ischemia. This can be either due to the duration and severity of the

Table 3. Coronary Flow Velocity Data

	Control		Metoprolol	
	Baseline	Change (Absolute and %)	Baseline	Change (Absolute and %)
Rest 1 (cm/s)	17 ± 7	–	17 ± 5	–
After adenosine (cm/s)	33 ± 12	+16 (94%)	42 ± 16	+26 (147%)
Rest 2 (cm/s)	17 ± 6	–	16 ± 5	–
After coronary occlusion (cm/s)	43 ± 15	+26 (153%)	51 ± 21	+35 (219%)

ischemic event or the dose of adenosine. Since no additional effect on CFR was observed with a higher (24 μg) than standard (18 μg) dose of adenosine, pharmacologic vasodilation was maximal with the standard dose used in this study.

Study limitations. Several limitations have to be considered for this article:

1) Changes in heart rate and mean aortic pressure may affect coronary flow velocity. Metoprolol decreases heart rate and aortic pressure, which might reduce coronary flow velocity. However, despite the decrease in heart rate and mean aortic pressure (Table 2), resting coronary flow velocity did not change in this study. Therefore, these effects seem to be of minor importance for the observed changes in flow velocity. On the other hand, adenosine as a strong vasodilator may lead to a drop in pressure and, thus, may decrease CFR. This was not the case in this analysis. Furthermore, all patients received the same dose at the same time of the study protocol.
2) The standard adenosine dose used for maximal hyperemia was 12 μg for the right and 18 μg for the left coronary artery. Recent data (14,15) suggest that these doses may be submaximal in some patients and, thus, may lead to an underestimation of CFR. This could explain why postischemic hyperemia might give higher CFR values than adenosine. Therefore, we measured CFR in a group of six patients after 18 and 24 μg adenosine, i.c. There was no significant difference in CFR (2.99 vs. 3.03, p = NS). Thus, the standard adenosine dose seems to be sufficient to induce maximal vasodilation in most patients.
3) Coronary flow velocity measurements may be limited by a change in sampling volume due to the motion of the flow wire within the coronary tree. We, therefore, assured that only patients with a stable and good flow signal were included in this analysis.
4) Changes in coronary artery diameter could, theoretically, affect flow velocity measurements. Thus, in 15 patients coronary artery diameter at the tip of the flow wire was measured, and absolute coronary blood flow was calculated from flow velocity and coronary cross-sectional area. Cross-sectional area remained unchanged after beta-blockade and, thus, did not account for changes in coronary flow velocity.
5) Cross-sectional area during maximal hyperemia with adenosine was not measured. However, in a previous study we have shown that, after intracoronary nitroglycerin, coronary dimensions did not change further, even with an extremely high dose (2.4 mg/min) of intracoronary adenosine (cross-sectional area before: 7.1 ± 2.6 mm^2; during adenosine infusion: 7.2 ± 2.8 mm^2). Thus, cross-sectional area is unchanged during adenosine infusion after maximal vasodilation with nitroglycerin and has no effect on coronary flow velocity.

Conclusions. Metoprolol is associated with a significant increase in CFR despite a reduction in heart rate and coronary perfusion pressure. This improvement in flow reserve is not only seen after pharmacologic vasodilation but also after postischemic hyperemia. The vasodilator response was, however, enhanced after myocardial ischemia when compared with adenosine. Apparently, ischemia seems to be a stronger vasodilator stimulus than adenosine.

In the daily routine, beta-blockers have a large therapeutic indication in the treatment of CAD due to their anti-ischemic and antiarrhythmic effect. The anti-ischemic effect of beta-blockers is based on the oxygen sparing mechanism with a reduction in the rate-pressure product (Fig. 2). However, the improvement in CFR indicates an improved oxygen supply due to the enhancement of maximal vasodilation after metoprolol with a potential reduction in ischemic events. This dual effect is probably responsible for an increase in blood supply and a reduction in oxygen demand rendering beta-blockers an ideal drug for treatment of CAD.

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