



Clinical research

# Coronary collateral perfusion in patients with coronary artery disease: effect of metoprolol

Michael Billinger, Lorenz Raeber, Christian Seiler, Stephan Windecker, Bernhard Meier, Otto M. Hess\*

Cardiology, Swiss Cardiovascular Centre, University Hospital, CH-3010 Bern, Switzerland

Received 17 April 2003; revised 30 January 2004; accepted 5 February 2004

See page 537 for the editorial comment on this article<sup>†</sup>

## KEYWORDS

Coronary collateral flow;  
Coronary artery disease;  
Doppler flow velocity;  
Coronary angiography;  
PTCA

**Background** The use of ultrathin Doppler angioplasty guidewires has made it possible to measure collateral flow quantitatively. Pharmacologic interventions have been shown to influence collateral flow and, thus, to affect myocardial ischaemia.

**Methods** Twenty-five patients with coronary artery disease undergoing PTCA were included in the present analysis. Coronary flow velocities were measured in the ipsilateral ( $n = 25$ ) and contralateral ( $n = 6$ ; two Doppler wires) vessels during PTCA with and without i.v. adenosine ( $140 \mu\text{g}/\text{kg} \cdot \text{min}$ ) before and 3 min after 5 mg metoprolol i.v., respectively. The ipsilateral Doppler wire was positioned distal to the stenosis, whereas the distal end of the contralateral wire was in an angiographically normal vessel. The flow signals of the ipsilateral wire were used to calculate the collateral flow index (CFI). CFI was defined as the ratio of flow velocity during balloon inflation divided by resting flow.

**Results** Heart rate and mean aortic pressure decreased slightly (ns) after i.v. metoprolol. The collateral flow index was  $0.25 \pm 0.12$  (one fourth of the resting coronary flow) during the first PTCA and  $0.27 \pm 0.14$  (ns versus first PTCA) during the second PTCA, but decreased with metoprolol to  $0.16 \pm 0.08$  ( $p < 0.0001$  vs. baseline) during the third PTCA.

**Conclusions** Coronary collateral flow increased slightly but not significantly during maximal vasodilatation with adenosine but decreased in 23 of 25 patients after i.v. metoprolol. Thus, there is a reduction in coronary collateral flow with metoprolol, probably due to an increase in coronary collateral resistance or a reduction in oxygen demand.

© 2004 Published by Elsevier Ltd on behalf of The European Society of Cardiology.

## Introduction

Coronary collateral circulation is an important pathophysiological mechanism to supply blood to a myocardial

area jeopardised by an occluded or stenotic artery. The functional relevance of coronary collaterals in humans has been a matter of debate for many years.<sup>1–3</sup> Previous studies have demonstrated a protective role of collaterals in patients with coronary artery disease, which show a smaller infarct size,<sup>4</sup> less ventricular aneurysm formation, improved ventricular function,<sup>4,5</sup> and better survival<sup>6</sup> compared to patients without collaterals. Much of the controversy about collaterals is due to inadequate

\* Corresponding author. Tel.: +41-31-632-9652/3693; fax: +41-31-632-4771.

E-mail address: otto.martin.hess@insel.ch (O.M. Hess).

† doi:10.1016/j.ehj.2003.11.005.

## List of Abbreviations

CAD	Coronary artery disease	PTCA	Percutaneous transluminal coronary angioplasty
CFI	Collateral flow index		
ic	Intracoronary		

methods to determine collateral blood flow. Semiquantitative (angiographic) methods have been used to estimate the extent of coronary collaterals<sup>1</sup> or acutely recruitable collaterals during angioplasty.<sup>7,8</sup> Intracoronary Doppler wires have been used to measure flow velocity in patients with coronary stenosis<sup>9–11</sup> and collaterals.<sup>12–15</sup> The theoretical basis for the use of intracoronary flow velocity measurements to determine collateral flow relates to the fact that velocity signals distal to an occluded stenosis almost invariably originate from collaterals.

Physical exercise, mental stress, and drugs influence collateral flow. The effect of cardioselective β-blockers such as metoprolol has not yet been studied, although this class of drugs favourably influences the occurrence of myocardial ischaemia by reducing myocardial oxygen consumption. On the other hand, β-blockers increase coronary vascular resistance<sup>16</sup> and thus may diminish collateral perfusion, aggravating myocardial ischaemia. Thus, the purpose of the present study was to assess coronary collateral flow before and after adenosine infusion and with and without intravenous β-blockade.

## Methods

### Patients

Twenty-five patients (age  $58 \pm 10$  years, all men) with one- or two-vessel disease were included in the present analysis (Table 1). Five of the 25 patients had previous myocardial infarction in the non-PTCA perfusion territory and none of these patients had a Q-wave infarct. All patients underwent percutaneous transluminal coronary angioplasty (PTCA) for clinical motives (angina pectoris or positive exercise test with ST-segment depression). The percent diameter stenosis of the dilated vessel was  $83 \pm 10\%$  before and  $6 \pm 8\%$  after the intervention. Cardiovascular risk factors and preintervention medication are summarised in Table 1.

**Inclusion criteria:** Patients with coronary artery disease and angina pectoris, age 18–80 years, indication for PTCA, written informed consent, and absence of allergy to adenosine or metoprolol.

**Exclusion criteria:** Unstable angina pectoris and myocardial infarction (<2 months), hypertension with left ventricular hypertrophy, tortuous coronary arteries, women of childbearing age, or β-blocker treatment.

This investigation was approved by the local ethics committee.

### Power calculation

The appropriate sample size for the present study was assessed by power analysis. A decrease in collateral flow index from 0.25 to 0.20 after metoprolol would require a sample size of 10 patients (assuming a standard deviation of the difference between

the two CFI values of 0.05; power: 80%;  $p < 0.05$ ).<sup>15</sup> With 16 patients, a power of 96% would be achieved.

### Coronary angiography

Patients underwent left heart catheterisation for diagnostic purposes. Aortic pressure was measured using the PTCA guiding catheter. Biplane left ventricular angiography was performed followed by diagnostic coronary angiography. Coronary artery lesions were estimated quantitatively as percent diameter reduction. Coronary collateral flow was assessed by the Rentrop score.<sup>8</sup>

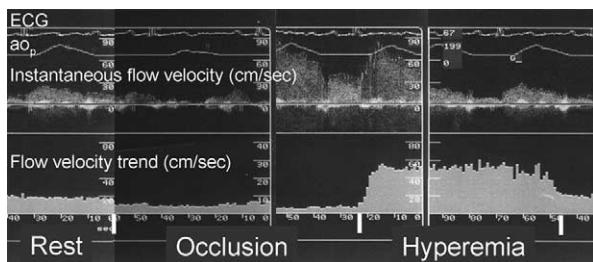
### Doppler flow velocity measurements

Doppler flow velocity measurements were performed using a 0.014 inch (1/3 mm in diameter) PTCA Doppler guidewire with a 12-MHz piezoelectric crystal at its tip (FloWire®, EndoSonics, Rancho Cordova, California, USA). The validation of this Doppler guidewire has been described previously.<sup>10</sup>

The collateral flow index (CFI) was determined as the ratio of the flow velocity time integral distal to the occluded artery during balloon dilatation divided by baseline flow velocity obtained at the same location prior to PTCA (Fig. 1).<sup>15</sup> In a subgroup of 6 patients, contralateral and ipsilateral flow velocity was measured in a normal (contralateral) and a "stenotic" (ipsilateral) vessel segment. A peripheral vein was used for fluid application and adenosine infusion.

Table 1

	n	%
Number of patients	25	—
Age (years)	$58 \pm 10$	—
Men	24	96
<i>Cardiovascular risk factors</i>		
Smoking	11	44
Diabetes mellitus	4	16
Family history of CAD	6	24
Obesity	3	12
Hypertension	11	44
Hypercholesterolemia	6	24
<i>Medication</i>		
Aspirin	21	84
β-Blockers	0	0
Calcium antagonists	3	12
Lipid lowering agents	4	16
ACE inhibitors	7	28
Nitrates	8	32
<i>Vessel studied</i>		
LAD/LCX/RCA	12/5/8	48/20/32
<i>% Diameter stenosis</i>		
Pre-PTCA (%)	$83 \pm 10$	
Post PTCA (%)	$6 \pm 8$	



**Fig. 1** Representative recordings of a flow velocity signal in a patient with single vessel disease undergoing PTCA. From left to right, the flow signal is shown at rest, during balloon occlusion, and after balloon deflation with postischaemic hyperaemia. The following tracings are shown from top to bottom: electrocardiogram (ECG), aortic pressure ( $ao_p$ ), instantaneous flow velocity, and flow velocity trend. Please, note that during balloon occlusion, coronary flow velocity drops from 18 to 6.9 cm/s but increase after balloon deflation to 53 cm/s. The collateral flow index for this patients is 0.41.

## Study protocol

After diagnostic coronary angiography, an interval of at least 10 min was allowed for dissipation of the effect of the nonionic contrast medium (iopamidol 755 mg/300 mg iodine) on coronary flow velocity and vasomotion. An intracoronary (ic) bolus of 0.2 mg of nitroglycerin was given to keep the calibre of the epicardial coronary artery constant, and thus eliminate dimensional changes in the epicardial vessels that could influence flow indices. The Doppler guidewire was positioned distal to the stenosis to be dilated, and coronary flow velocity reserve measurements were obtained. Flow velocity was measured in 12 patients in the left anterior descending, in 5 in the circumflex, and in 8 in the right coronary artery (Table 1). Collateral flow velocity was measured continuously during the first balloon occlusion without adenosine (PTCA 1) and during a second occlusion with i.v. adenosine (PTCA 2). Then, 5 mg metoprolol was administered intravenously over 5 min. After an interval of 5 min, collateral flow velocity was determined during a third balloon occlusion, at first without and then with i.v. adenosine (PTCA 3, Fig. 2). Before each balloon inflation, resting flow velocity was determined at the same location as during balloon occlusion (baseline measurement). Intravenous adenosine infusion was associated with an increase in coronary flow as early as 15–20 s. An intracoronary ECG was recorded from the Doppler

guidewire and 3 standard ECG leads were recorded. Blood pressure was measured continuously with the guiding catheter at the ostium of the coronary artery. During balloon occlusion, 16 of the 25 patients showed ST-segment changes in the intra-coronary ECG but only half of them had clinical symptoms (anginal pain).

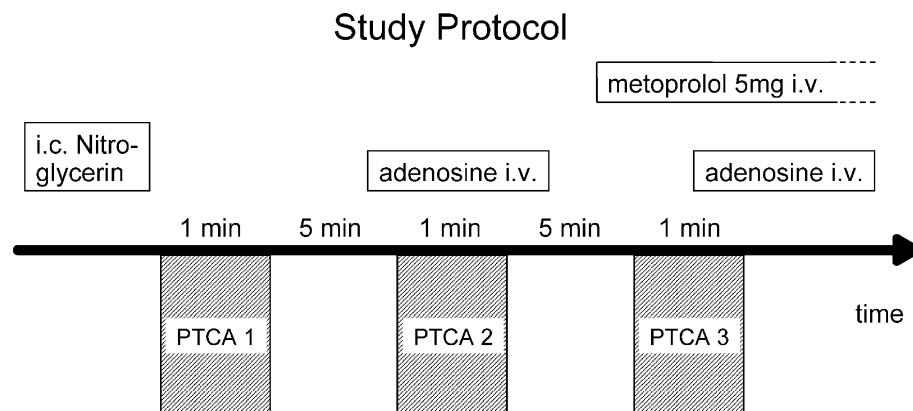
In 6 of the 25 patients a second Doppler wire was introduced in the contralateral vessel to study flow changes in an angiographically normal vessel segment. Coronary flow velocity was measured at rest and during PTCA and adenosine infusion in both the ipsilateral and contralateral vessel segments. The contralateral vessel segment served as a control region for flow changes during the study protocol.

## Statistical analysis

Comparison of angiographic, haemodynamic, and Doppler flow velocity data was performed by an analysis of variance (ANOVA) for repeated measurements. Data were analysed at baseline, after adenosine infusion, and after metoprolol administration. Only fixed, no random, effects were included. There was one treatment group. A saturated model was used with different estimates of the mean, but no assumption was made as to whether a time point was baseline or a PTCA measurement. The covariance structure was used to account for the dependence of coronary collateral flow between different measurements of a single patient. Regarding the covariance matrix, a check of the correlation coefficients between the different measurements indicated that compound symmetry is a reasonable assumption. In addition to the model-based estimates as given in the manuscript, we also calculated empirical standard errors, for which it has been shown that the results are valid even if the covariance matrix is misspecified. There was no material difference in the results. Statistical significance was defined as a  $p$ -value of  $<0.05$ .

## Results

Representative flow velocity recordings during and after balloon inflation are shown in Fig. 1. During balloon occlusion (left panel), flow velocity dropped from 18 to 6.9 cm/s but increased after balloon deflation (=postischaemic hyperaemia; middle panel) to 53 cm/s. After



**Fig. 2** Study protocol: Prior to coronary flow measurements, 200  $\mu$ g nitroglycerin is administered for maximal vasodilatation. Then three consecutive balloon inflations (60 s each) are performed (PTCA 1–3). 1st PTCA: Control inflation, 2nd PTCA: Adenosine infusion, 3rd PTCA: Metoprolol administration followed by adenosine infusion during balloon inflation.

returning to baseline (right panel), the resting flow velocity was 18 cm/s. The collateral flow index for this patient was 0.41.

## Haemodynamics

There was a significant decrease in the rate-pressure product after metoprolol infusion compared to baseline 1 or PTCA 1. Heart rate and mean aortic pressure decreased slightly, although not significantly, after metoprolol infusion (Table 2). Collateral assessment according to Rentrop<sup>8</sup> showed good collateral flow (Rentrop 2–3) in 13 patients and poor collateral flow (Rentrop 0–1) in 12 patients. The collateral flow index was  $0.30 \pm 0.13$  in patients with Rentrop 2–3 and  $0.19 \pm 0.08$  in those with Rentrop 0–1 ( $p = 0.01$ ). The response to metoprolol or adenosine was similar in these 2 groups.

## Flow velocity data

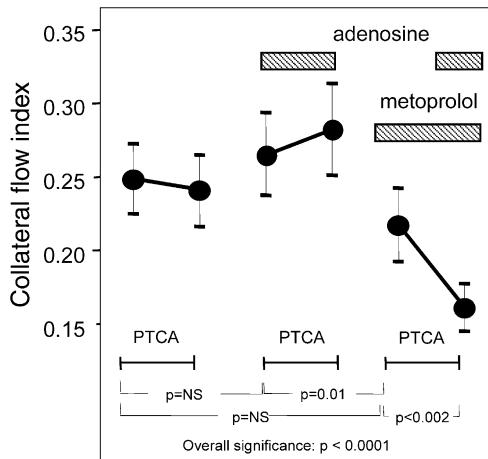
Flow velocity decreased significantly during PTCA 1, 2 and 3, respectively. Coronary flow was unchanged between balloon inflations, i.e., there was no significant change in coronary flow between baseline 1–4 (Table 3). Adenosine had only a minor effect on coronary flow velocity during PTCA. However, in 8 patients there was a mild decrease in coronary flow velocity, which was not significant when compared to the other patients. After 5 mg intravenous metoprolol, coronary flow velocity decreased in 23 of the 25 patients during PTCA. This flow velocity (PTCA 3) was significantly lower than during PTCA 1 or 2. Baseline flow velocity remained, however, unchanged during metoprolol. There were no differences between vascular beds, i.e., between the left anterior descending and right coronary artery.

In 6 of the 25 patients, the coronary flow velocity of the ipsilateral ("stenotic") and contralateral (normal) vessel was measured simultaneously. Despite a significant increase in the flow velocity of the contralateral vessel (from  $19 \pm 7$  to  $41 \pm 9$  cm/s), no effect on ipsilateral flow velocity was observed after i.v. adenosine, but a significant drop in ipsilateral flow velocity (from

**Table 3** Flow velocity during baseline, respectively, PTCA 1–3

	Flow velocity (cm/s)
Baseline 1	$11.6 \pm 4.6$
PTCA 1 after 5 s	$3.9 \pm 1.8$
PTCA 1 after 50 s	$3.8 \pm 1.9$
Baseline 2	$16.8 \pm 5.5$
PTCA 2 after 5 s (adenosine)	$4.2 \pm 2.1$
PTCA 2 after 50 s (adenosine)	$4.5 \pm 2.4$
Baseline 3	$16.7 \pm 4.9$
PTCA 3 after 5 s (metoprolol)	$3.2 \pm 1.7$
PTCA 3 after 50 s (metoprolol and adenosine)	$2.5 \pm 1.3^*$
Baseline 4	$15.8 \pm 4.4^\dagger$

PTCA = percutaneous transluminal coronary angioplasty; \* $p < 0.002$  vs. PTCA 1 and 2 after 5 and 50 s and vs. PTCA 3 after 5 s.  $^\dagger p = \text{NS}$  vs. baseline 1 and 2.



**Fig. 3** Collateral flow index (collateral flow velocity divided by resting flow velocity). There is a slight, but non-significant, increase in collateral flow index during adenosine infusion (PTCA 2), but a significant drop during adenosine infusion after metoprolol administration (PTCA 3).

$3.6 \pm 1.9$  to  $2.5 \pm 1.5$  cm/s) was found after metoprolol during pharmacologic hyperaemia (Fig. 4).

## Collateral flow index

The collateral flow index was similar during PTCA 1 ( $0.25 \pm 0.20$ ) and 2 ( $0.27 \pm 0.14$ ) with and without adenosine. However, after metoprolol infusion, adenosine led to a significant fall in collateral flow index ( $0.16 \pm 0.06$ ), indicating a reduction in coronary collateral flow following i.v.  $\beta$ -blockade (Fig. 3).

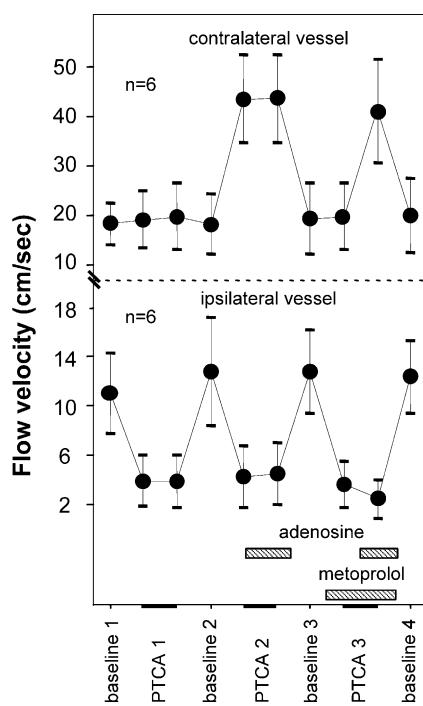
## Discussion

Coronary collateralisation plays an important role in the pathophysiology of myocardial ischaemia and limits the size of myocardial infarction in patients with coronary artery disease. Sudden occlusion of the supply

**Table 2** Hemodynamic variables during baseline, respectively, PTCA 1–3

	Heart rate ( $\text{min}^{-1}$ )	Mean aortic pressure (mmHg)	Rate pressure product ( $10^3 \text{ mmHg min}^{-1}$ )
Baseline 1	$74 \pm 10$	$97 \pm 13$	$7.2 \pm 1.4$
PTCA 1	$75 \pm 8$	$96 \pm 12$	$7.2 \pm 1.2$
Baseline 2	$74 \pm 10$	$96 \pm 12$	$7.1 \pm 1.3$
PTCA 2	$75 \pm 10$	$96 \pm 11$	$7.2 \pm 1.4$
Baseline 3	$75 \pm 10$	$96 \pm 10$	$7.2 \pm 1.2$
PTCA 3 (with metoprolol)	$73 \pm 9$	$94 \pm 12$	$6.9 \pm 1.3^*$
Baseline 4	$73 \pm 10$	$95 \pm 13$	$6.9 \pm 1.4$

PTCA = percutaneous transluminal coronary angioplasty. \* $p < 0.02$  vs. PTCA 1.



**Fig. 4** Flow data from 2 Doppler wires ( $n = 6$ ): One flow wire is in the contralateral (normal) and one in the ipsilateral (PTCA) vessel. Please note that coronary flow velocity increases significantly during adenosine infusion (contralateral vessel), whereas flow velocity remains unchanged in the ipsilateral vessel during balloon inflation. Following adenosine infusion (after metoprolol), flow velocity increases only in the contralateral (normal) vessel, but decreases in the ipsilateral (occluded) vessel.

artery (plaque rupture) is usually associated with larger infarcts than in chronic coronary artery disease because coronary circulation does not have enough time to develop collaterals. Coronary collaterals may occur with repeated ischaemia<sup>17</sup> or during exercise training.<sup>18</sup> In the presence of a high-grade stenosis However, collateral flow is dependent on coronary vasoconstrictor tone and decreases with vasoconstrictor agents or changes in coronary perfusion pressure. Thus, the purpose of the present study was to assess coronary collateral perfusion before and after  $\beta$ -blockade in patients with coronary artery disease undergoing PTCA for therapeutic reasons. Collateral flow velocity was measured with a Doppler wire during balloon inflation using i.v. adenosine to induce maximal coronary vasodilatation of collateral-dependent and collateral-supplying arteries.

### Coronary collateral flow with metoprolol

The coronary collateral flow index increased slightly during the intravenous administration of adenosine (Fig. 3) in 13 of 25 patients, but remained unchanged or even decreased in 12 patients. These changes did, however, not reach statistical significance. After metoprolol, the collateral flow index decreased significantly when adenosine was given intravenously (Fig. 3). Two thirds ( $n = 16$ ) of all patients showed ST-segment changes in the intracoronary ECG during balloon occlusion.

Half of these patients developed anginal pain which was due to either ischaemia or adenosine-induced chest discomfort that could not be differentiated. Despite the fall in collateral flow after metoprolol, during adenosine infusion no more patients developed anginal pain. This can be explained either by the small extension of the ischaemic zone or by the preponderance of the oxygen-saving mechanism of metoprolol with a significant reduction in the rate-pressure product (Table 2). The fall in collateral flow could be due either to metoprolol directly (increase in resistance) or due to the decrease in oxygen requirements (decrease in the rate-pressure product). Other mechanisms may also have been involved, such as preconditioning of the ischaemic myocardium by repeated balloon inflation or stunning of the myocardium at risk. Previous experimental and clinical data have shown that during sympathetic activation coronary collateral perfusion increases due to the reduction in the pressure gradient across the collateral vessel.<sup>19</sup> By analogy, the application of a  $\beta$ -blocker leads to an increase in coronary collateral resistance. This may explain why collateral flow velocity decreases after metoprolol. However, in the daily clinical setting,  $\beta$ -blockers have been rarely associated with an increase in symptoms. Therefore, the decrease in coronary collateral flow may be associated with a reduction in myocardial oxygen consumption induced by the decrease in the rate-pressure product.

In 6 of the 25 patients, the coronary flow velocity of the ipsilateral ("stenotic") and contralateral (normal) vessels was measured simultaneously. Despite a significant increase in flow velocity of the contralateral vessel (from  $19 \pm 7$  to  $41 \pm 9$  cm/s), the collateral flow of the ipsilateral vessel did not increase during balloon occlusion after i.v. adenosine. In contrast, there was a drop in ipsilateral flow velocity from  $3.6 \pm 1.9$  to  $2.5 \pm 1.5$  cm/s after metoprolol during adenosine (Fig. 4). Thus, the contralateral vessel shows a typical hyperaemic response, whereas the ipsilateral occlusive flow velocity (i.e., collateral flow) decreased after metoprolol in 23 of the 25 patients.

Thus, the reduction in coronary collateral flow after metoprolol appears to be due to a vasoconstrictive response of the collateral vessel with an increase in vascular resistance.

### Limitations

Several potential limitations of the present study should be considered.

- (1) The exact mechanism responsible for the reduction in coronary collateral flow after metoprolol is not clear but may require adjustment of the heart rate and blood pressure to keep one of the determinants of collateral flow constant.
- (2) The effect of i.v. metoprolol on heart rate and blood pressure was relatively modest. This would favour the hypothesis of a direct effect of metoprolol on collaterals rather than a secondary decrease in

collateral flow due to the decrease in the rate-pressure product.

## References

- Helfant RH, Vokonas PS, Gorlin R. Functional importance of the human coronary collateral circulation. *N Engl J Med* 1971;284:1277–81.
- Piek JJ, Becker AE. Collateral blood supply to the myocardium at risk in human myocardial infarction: a quantitative postmortem assessment. *J Am Coll Cardiol* 1988;11:1290–6.
- Gorlin R. Coronary Artery Disease. Philadelphia: W.B. Saunders Co; 1976. p. 69.
- Habib GB, Heibig J, Forman SA et al. Influence of coronary collateral vessels on myocardial infarct size in humans. Results of phase I thrombolysis in myocardial infarction (TIMI) trial. The TIMI Investigators. *Circulation* 1991;83:739–46.
- Hirai T, Fujita M, Nakajima H et al. Importance of collateral circulation for prevention of left ventricular aneurysm formation in acute myocardial infarction. *Circulation* 1989;79:791–6.
- Hansen J. Coronary collateral circulation: clinical significance on survival in patients with coronary artery occlusion. *Am Heart J* 1989;117:290–5.
- Rentrop KP, Cohen M, Blanke H et al. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. *J Am Coll Cardiol* 1985;5:587–92.
- Rentrop KPJT, Feit F, VanBuskirk M. Determinants and protective potential of coronary arterial collaterals as assessed by an angioplasty model. *Am J Cardiol* 1988;61:677–84.
- Donohue TJ, Kern MJ, Aguirre FV et al. Assessing the hemodynamic significance of coronary artery stenoses: analysis of translesional pressure-flow velocity relations in patients. *J Am Coll Cardiol* 1993;22:449–58.
- Doucette JDC, Payne H et al. Validation of a Doppler guide wire for intravascular measurement of coronary artery flow velocity. *Circulation* 1992;85:1899–911.
- Pijls NH, De Bruyne B, Peels K et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med* 1996;334:1703–8.
- Oflili E, Kern MJ, Tatineni S et al. Detection of coronary collateral flow by a Doppler-tipped guide wire during coronary angioplasty. *Am Heart J* 1991;122:221–5.
- Kern MJ, Donohue TJ, Bach RG et al. Quantitating coronary collateral flow velocity in patients during coronary angioplasty using a Doppler guidewire. *Am J Cardiol* 1993;71:34D–40D.
- Bach RG, Donohue TJ, Caracciolo EA et al. Quantification of collateral blood flow during PTCA by intravascular Doppler. *Eur Heart J* 1995;16:74–7.
- Seiler C, Fleisch M, Garachemani A et al. Coronary collateral quantitation in patients with coronary artery disease using intravascular flow velocity or pressure measurements. *J Am Coll Cardiol* 1998;32:1272–9.
- Kern MJ, Ganz P, Horowitz JD et al. Potentiation of coronary vasoconstriction by  $\beta$ -adrenergic blockade in patients with coronary artery disease. *Circulation* 1983;67:1178–85.
- Billinger M, Fleisch M, Eberli FR et al. Is the development of myocardial tolerance to repeated ischemia in humans due to preconditioning or to collateral recruitment. *J Am Coll Cardiol* 1999;33:1027–35.
- Senti S, Fleisch M, Billinger M et al. Long-term physical exercise and quantitatively assessed human coronary collateral circulation. *J Am Coll Cardiol* 1998;32:49–56.
- Busch PDA, Heusch G. Sympathetic effects on segmental coronary resistances and their role in coronary collateral perfusion. *J Appl Cardiol* 1988;3:145–60.