INTERVENTIONAL CARDIOLOGY AND SURGERY

Myocardial viability, coronary flow reserve, and in-hospital predictors of late recovery of contractility following successful primary stenting for acute myocardial infarction

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Objective: To assess the relation between myocardial viability, coronary flow reserve, and recovery of myocardial contractility after stenting for acute myocardial infarction.

Design: Consecutive sample prospective study.

Setting: University hospital.

Patients: 41 patients with single vessel disease and successful primary stenting for a first acute myocardial infarction.

Interventions: ²⁰¹Tl single photon emission computed tomography, contrast ventriculography, and intracoronary Doppler performed 7 (1) days after primary stenting.

Main outcome measures: Regional contractility recovery assessed by contrast ventriculography at 6 (1) months' follow up.

Results: On univariate analysis, contractility recovery was correlated to prereperfusion anterograde and collateral flow grades ($r = 0.41$, $p = 0.03$ and $r = 0.55$, $p = 0.0004$), viability index ($r = 0.55$, $p = 0.04$), peak creatine kinase concentrations ($r = -0.55$, $p = 0.0005$), left ventricular ejection fraction ($r = 0.45$, $p = 0.005$), end diastolic pressure ($r = -0.62$, $p < 0.0001$), end systolic volume index ($r = -0.47$, $p = 0.01$), and the extent of hypokinetic area ($r = -0.48$, $p = 0.003$), but not the coronary flow reserve. On multivariate analysis, independent predictors of late contractility recovery were prereperfusion anterograde and collateral flow grades and viability index. Relative coronary flow reserve, reflecting the culprit vessel's microvascular function, was correlated only to the extent of the infarct risk area ($r = -0.45$, $p = 0.003$).

Conclusions: Independent predictors of contractility recovery between the seventh day and the sixth month after successful stenting for acute myocardial infarction are prereperfusion anterograde and collateral flows and myocardial viability. The culprit vessel's microvascular dysfunction is independent of myocardial viability and contractility and correlated to the extent of "jeopardised microvasculature".

Percutaneous transluminal coronary angioplasty with systematic stenting is considered to be the ideal primary treatment after acute myocardial infarction (AMI). This confers the advantages of conventional balloon angioplasty, compared with thrombolytic treatment, in terms of coronary flow restoration, major ischaemic events, and death, with lower restenosis rates.¹⁻⁵ However, clinical outcome and recovery of myocardial contractility after successful reperfusion are influenced by the extent of microvascular damage and the persistence of viable myocardium.⁶⁻⁸ While the relation between microvascular obstruction following coronary reperfusion (assessed by the incomplete regression of ST segment elevation or myocardial contrast echocardiography), myocardial viability, and contractility is established, the relation between the persistent reduction of coronary artery flow reserve (CFR)^{9,10} and myocardial viability or contractility remains controversial.

The purpose of this study was to analyse the relation between CFR and myocardial viability, assessed 7 (1) days after successful primary stenting for AMI by intracoronary Doppler and ²⁰¹Tl single photon emission computed tomography (SPECT), and their impact on the late recovery of myocardial contractility.

METHODS

Study population and protocol

The study group consisted of 41 patients successfully treated by primary angioplasty followed by systematic stenting of the

proximal portion of a coronary artery for their first anterior or inferior AMI within six hours after onset of the symptom.

The diagnosis of AMI was based on chest pain lasting > 30 minutes and ST segment elevation of > 0.2 mV in at least two contiguous ECG leads. Patients with cardiogenic shock, isolated lateral wall infarction, left main or multivessel disease, unidentified or diffusely diseased infarct related artery, distal coronary occlusion, and complicated in-hospital course were not included. All patients had a 12 lead ECG before the procedure and 30 minutes after restoration of TIMI (thrombolysis in myocardial infarction) grade 3 flow.¹¹ The ST segment was measured in the lead showing maximal elevation before and after reperfusion. ST segment elevation regression was calculated and expressed as a percentage of the initial elevation.

Predischarge (7 (1) days after reperfusion) ²⁰¹Tl SPECT followed within 24 hours by coronary and left ventricular angiography was performed in all patients. Both tests were also scheduled for the six month follow up. Intracoronary Doppler assessment of CFR was performed during the predischarge catheterisation (8 (1) days after reperfusion).

Abbreviations: AMI, acute myocardial infarction; CFR, coronary flow reserve; SPECT, single photon emission computed tomography; TIMI, thrombolysis in myocardial infarction

Angiography and stenting procedure

Before the procedure, all patients received heparin (100 IU/kg) and aspirin (500 mg) intravenously. Coronary angiography was performed according to the Judkins technique after intracoronary injection of 1 mg of linsidomine chlorhydrate. Anterograde and collateral coronary flows were graded according to the TIMI and Rentrop classifications.¹² Balloon angioplasty followed by systematic stenting was performed with standard techniques. After the stenting all patients received ticlopidine (500 mg/day) and aspirin (100 mg/day) for 30 days followed by aspirin alone indefinitely. Intravenous heparin infusion was continued ≥ 72 hours after the procedure (activated partial thromboplastin time 60–80 seconds).

Coronary dimensions were measured on line by the CAAS system (Pie Medical Systems, Maastricht, Netherlands).¹³ Left ventricular ejection fraction was quantified off line in the 30° right anterior oblique projection by one observer blinded to all other data. Regional left ventricular systolic shortening was assessed in 20 segments based on Slager's method quantifying the regional contribution of each segment to the global ejection fraction.^{14, 15} Segments were considered to be hypokinetic when they were < 2 SD below the mean of corresponding segments of a reference population (30 patients with chest pain and normal coronary arteries).

Based on the definition of stunned myocardium, a recovery index was defined by the following equation⁸:

$$\frac{n \text{ hypokinetic segments at pre-discharge} - n \text{ hypokinetic segments at follow up}}{n \text{ hypokinetic segments at pre-discharge}}$$

²⁰¹Tl SPECT

SPECT was performed using a pharmacological stress-reinjection protocol.¹⁶ A 4.5 MBq $\times$ body mass index dose of ²⁰¹Tl was injected 2 minutes after intravenous infusion of dipyridamole and a 1.5 MBq $\times$ body mass index dose 4 hours later. Images were acquired 5–10 minutes after ²⁰¹Tl injection by an APEX SPX-4 HR (Elsint, Haifa, Israel) gamma camera. ²⁰¹Tl uptake was analysed in 20 segments as previously reported.¹⁷ A four grade scale (0 = normal, 1 = mild, 2 = moderate, 3 = severely decreased uptake) was used for the qualitative analysis of viability. Segments with a reinjection score ≥ 2 were considered to be necrotic and those with a score < 2 to be viable. Images were analysed by one observer blinded to all other data. Segments were secondarily assigned to the infarct related artery based on the coronary angiogram. Infarct risk area was defined as the number of segments assigned to the infarct related artery. Myocardial viability was assessed by an index defined as the ratio of the number of viable segments within the infarct risk area to the size of the risk area.¹⁸

Intracoronary flow measurements

Intracoronary flow was measured with a 0.014 inch Doppler tipped flow wire (12 MHz, FloWire, Cardiometrics Inc, Mountain view, California, USA) in the culprit vessel, with the tip at the distal extremity of the stent, and in a normal remote artery.¹⁹ Time averaged peak velocities were measured at baseline and after intracoronary administration of adenosine (12–18 μ g). Absolute CFR was calculated as the ratio of baseline to hyperaemic averaged peak velocity. Relative CFR was defined as the ratio of infarct related to remote artery CFR.

Statistical analysis

Continuous variables are presented as mean (SD) and analysed by a one way analysis of variance between the patient groups or a simple regression model. A multivariate analysis was performed using a multiple regression model

including all univariate parameters with a value of $p < 0.05$. A χ^2 test was used to analyse qualitative variables. A p value < 0.05 was considered significant.

RESULTS

Patient population and procedural outcome

Forty one patients fulfilled the inclusion criteria and were included in the study. Clinical follow up was completed in all patients. Follow up SPECT and angiography were performed in 37 (90%) patients 6 (1) months after the myocardial infarction. Four asymptomatic patients refused the follow up tests. At follow up no death, myocardial infarction, or unstable angina had occurred. Exertion angina occurred in seven patients (17.1%), related in all to restenosis, and were treated by balloon angioplasty. Four asymptomatic patients with evidence of ischaemia at the follow up SPECT underwent angioplasty, for restenosis in one and for progression of the lesions in three. Rates of target lesion revascularisation and total revascularisation were 19.5% (8 patients) and 26.8% (11 patients), respectively.

On the basis of the median recovery index (50%) the study population was divided into two groups, with or without contractility recovery. Table 1 reports the baseline characteristics of the two patient groups.

Angiographic and scintigraphic data

The culprit vessel was the left anterior descending in 16, a dominant left circumflex in 5, and a dominant right coronary artery in 20 patients. Initial TIMI flow grades of 0, 1, and 2 were found in 31, 5, and 5 patients, and Rentrop grades 0, 1, 2, and 3 in 13, 9, 10, and 9 patients, respectively. TIMI flow grade 3 was found in all vessels and no collateral blood flow was visualised at predischARGE and follow up.

Mean diameter stenosis was 6 (7)% immediately after stenting, 6 (7)% at predischARGE, and 37 (27)% at follow up ($p < 0.0001$). The six month binary restenosis rate (diameter stenosis $> 50\%$) was 27%. Compared with predischARGE, at follow up there was an improvement in left ventricular ejection fraction (60 (11) ν 63 (10), $p = 0.02$) and a decrease in the number of hypokinetic segments (4.7 (3.5) ν 3.1 (3.2), $p < 0.0001$).

Intracoronary Doppler measurements

Hyperaemic averaged peak velocity and CFR were higher in the remote artery than in the infarct related artery (table 2). There was a strong correlation between the CFR measured in the culprit vessel and CFR in the remote artery ($r = 0.76$, $p = 0.0001$).

Table 1 Baseline characteristics of patients with versus those without recovery index $\geq 50\%$

Characteristic	Recovery index $\geq 50\%$	Recovery index $< 50\%$
Number of patients	22	15
Age (years)	55 (7)	57 (11)
Male sex	17 (77%)	12 (80%)
Hypercholesterolaemia	10 (45%)	6 (40%)
Systemic hypertension	3 (14%)	5 (33%)
Diabetes mellitus	2 (9%)	1 (7%)
Current smokers	14 (64%)	8 (53%)
Infarct location		
Anterior	7 (32%)	9 (60%)
Inferior	15 (68%)	6 (40%)
Symptom to reperfusion time (min)	223 (97)	201 (99)
ST segment elevation		
Baseline (mm)	3.2 (1.3)	3.8 (1.2)
After stenting (mm)	0.8 (1)	1.5 (1.6)
Regression (%)	75 (28)	66 (31)
Peak creatine kinase (IU/l)	1733 (1631)	3538 (2420)*

Data are mean (SD). * $p=0.01$.

Table 2 Intracoronary Doppler measurements

	Infarct related artery	Remote artery	p Value
Reference diameter (mm)	3.1 (0.3)	3 (0.4)	NS
Averaged peak velocity (cm/s)			
Baseline	20 (6)	22 (8)	NS
Hyperaemic	45 (17)	57 (18)	<0.0001
Coronary flow reserve	2.3 (0.6)	2.7 (0.6)	<0.0001

In-hospital factors correlated to the CFR of the culprit vessel were age ($r = -0.4$, $p = 0.01$), residual ST segment elevation and its decrease after stenting ($r = -0.53$, $p = 0.0004$ and $r = 0.51$, $p = 0.0008$), heart rate ($r = -0.39$, $p = 0.01$), left ventricular end diastolic pressure ($r = -0.39$, $p = 0.02$) and volume index ($r = -0.32$, $p = 0.04$), number of hypokinetic segments ($r = -0.51$, $p = 0.0006$), viability index ($r = 0.49$, $p = 0.001$), and infarct risk area ($r = -0.58$, $p = 0.0001$). On multivariate analysis only left ventricular end diastolic volume index ($p = 0.008$) and infarct risk area ($p = 0.02$) were correlated to the CFR in the culprit vessel.

Relative CFR was correlated to the extent of infarct risk area ($r = -0.45$, $p = 0.003$).

Recovery index

Recovery index was 95 (12)%, 60 (35)%, 31 (56)%, and 31 (33)% for prereperfusion Rentrop grades 3 to 0 ($p = 0.003$) and 97 (8)%, 59 (54)%, and 44 (42)% for prereperfusion TIMI grades 2 to 0 ($p = 0.04$), respectively. Recovery index was comparable in patients with or without restenosis (53 (42) v 52 (45)%) and in those with or without ischaemia at follow up SPECT (57 (43) v 49 (45)%). Table 3 reports angiographic, scintigraphic, and CFR characteristics of patients with and without a recovery index $\geq 50\%$.

Among factors significantly correlated to the recovery index on univariate analysis (table 4), the multivariate analysis identified prereperfusion anterograde and collateral blood flows and the scintigraphic viability index as independent predictors of late contractility recovery. The magnitude of postreperfusion ST segment elevation regression, and absolute

Table 4 Univariate and multivariate analysis of in-hospital factors associated with the recovery index

In-hospital factor	Univariate		Multivariate p value
	r	p Value	
Prereperfusion			
TIMI grade	0.41	0.01	0.025
Rentrop grade	0.55	0.0004	0.0005
Peak creatine kinase (IU/l)	-0.55	0.0005	0.8
Viability index (%)	0.55	0.0004	0.044
Left ventricular data			
End diastolic pressure (mm Hg)	-0.62	<0.0001	0.1
Ejection fraction (%)	0.45	0.005	0.15
End systolic volume index (ml/m ²)	-0.47	0.03	0.38
Hypokinetic segments (n)	-0.48	0.003	0.23

and relative CFR were not significantly correlated to the recovery index ($r = 0.14$, $r = 0.17$, and $r = 0.015$, respectively).

DISCUSSION

The present study shows that the improvement of myocardial contractility between the seventh day and the sixth month after primary stenting for AMI is independently correlated to the quality of the residual anterograde and collateral blood flow before reperfusion and to myocardial viability. Postreperfusion regression of ST segment elevation and predischARGE absolute CFR are correlated to the myocardial viability but not to the late recovery of contractility. Relative CFR is correlated to the extent of the infarct risk area but neither to myocardial viability nor to contractility recovery.

To our knowledge, this is the first study of the relation between acute phase and predischARGE predictors of myocardial viability and contractility, CFR, and the late improvement of myocardial contractility.

By design, this study included patients at low risk compared with previous studies.^{4,5} The rates of angiographic restenosis and target lesion revascularisation were nevertheless comparable with those previously reported.

Table 3 In-hospital and follow up angiographic, scintigraphic, and coronary flow reserve characteristics of patients with and without a recovery index $\geq 50\%$

Characteristic	Recovery index $\geq 50\%$ (n=22)	Recovery index $<50\%$ (n=15)	p Value
Prereperfusion Rentrop grade	2.7	1.9	0.04
Prereperfusion TIMI grade	1.6	1.1	0.03
Viable segments			
In-hospital (n)	5.5 (2.6)	3.1 (3.2)	0.02
Follow up (n)	6.7 (2.8)	4.3 (4.5)	0.04
Viability index (%)	72 (29)	33 (37)	0.001
In-hospital left ventricular data			
End diastolic pressure (mm Hg)	12 (6)	18 (9)	0.02
Ejection fraction (%)	63 (9)	55 (11)	0.02
End diastolic volume (ml/m ²)	67 (15)	75 (24)	NS
End systolic volume (ml/m ²)	25 (8)	34 (14)	0.01
Hypokinetic segments (n)	3.7 (3.2)	6.7 (3.2)	0.008
Coronary flow reserve			
Absolute	2.4 (0.6)	2.1 (0.6)	NS
Relative	0.9 (0.2)	0.8 (0.2)	NS
Follow up left ventricular data			
End diastolic pressure (mm Hg)	10 (6)	12 (5)	NS
Ejection fraction (%)	68 (7)	55 (9)	<0.0001
End diastolic volume (ml/m ²)	71 (12)	73 (21)	NS
End systolic volume (ml/m ²)	23 (7)	34 (14)	0.003
Hypokinetic segments (n)	1.1 (1.7)	5.9 (2.8)	<0.0001
Recovery index (%)	83 (22)	8 (26)	<0.0001

TIMI, thrombolysis in myocardial infarction.

Myocardial viability, infarct size, and contractility recovery

The relation between ²⁰¹Tl SPECT assessed myocardial viability and the recovery of late contractility supported in our study has been widely established, as well as the benefit of primary angioplasty in terms of infarct size reduction and contractility improvement.^{20, 21}

The distinction between myocardial viability and infarct size is artificial, as they represent two views—half empty or half full glass—of the same concept. Nevertheless, the infarct size is indirectly correlated to the recovery of contractility through its complementarity with myocardial viability. Moreover, there is a complex relation between viability and contractility with a spectrum of contractile dysfunction related not only to the balance between necrosis and viability but also to the extent of metabolic damage in viable myocytes. This explains the recovery of contractility in some but not all of the regions with preserved metabolic viability.²¹ Consequently, on multivariate analysis, the recovery index is independently correlated to the myocardial viability but not to the infarct size.

In the present study, among multiple factors reflecting the extent of the infarction, in-hospital left ventricular end diastolic pressure was most strongly correlated to the recovery index on univariate analysis. Left ventricular end diastolic pressure may be the expression of the balance between viability and necrosis, reflecting not only the systolic function but also the diastolic function. Hence, low left ventricular end diastolic pressure may be used as a predictor of reversible contractile dysfunction.

Preexisting collateral and antegrade flow and late contractility

Sabia and colleagues²² reported an association between collateral blood flow detected by myocardial contrast echocardiography, but not angiography, and contractility recovery after angioplasty of totally occluded vessels for recent (48 hours to 5 weeks) myocardial infarction. The authors blame the inability to visualise vessels smaller than 100 μ m on the low resolution of angiography. In our study collateral blood flow was assessed after systematic intracoronary injection of vasodilators, which may have improved visibility. Furthermore, collateral blood flow functional during the first six hours after a myocardial infarction may disappear during the following days as the microvascular obstruction extends.²³ Other studies underline the importance of preangioplasty residual antegrade or collateral flow as predictors of in-hospital infarct size after myocardial infarction.^{24, 25} Our study shows a direct and independent correlation between prereperfusion collateral and antegrade blood flows and late contractility recovery. These findings indirectly support the potential benefit of primary stenting facilitated by previous antithrombotic treatment, reported to improve the prereperfusion TIMI grade.²⁶

Microvascular dysfunction and recovery of contractility

CFR after coronary occlusion has been studied in animal models and a few human studies. Apparently controversial results concerning the relation between CFR and contractility have been reported.

In vitro studies first showed evidence of microvascular dysfunction following prolonged or short ischaemia.^{27, 28} Bolli and colleagues²⁹ reported a prolonged impairment of CFR after a 15 minute coronary occlusion in dogs, introducing the concept of microvascular stunning. In their study, the microvascular dysfunction appeared to be independent of wall thickening. A persistent limitation of CFR has also been reported after coronary revascularisation in the absence of infarction.^{30, 31}

Persistence of impaired CFR of the infarct related artery after primary angioplasty, compared with a non-infarct population, has been reported to last as long as six months after the

myocardial infarction, with no evidence of a correlation between CFR and wall motion in 14 patients.⁹ On the contrary, another study using angiographic measurements of CFR immediately after intracoronary thrombolysis followed by balloon angioplasty reported a significant correlation between postangioplasty and predischage CFR and in-hospital wall motion improvement in 22 patients.¹⁵ Improved CFR 24 hours after primary angioplasty for AMI has also been reported to be correlated to myocardial contrast echocardiography score 24 hours, and echocardiographic wall motion index four weeks, after an AMI in 25 patients.³²

Being based on parameters measured during the first 24 hours after myocardial infarction, the previous studies assessed the combined effect of the microvascular obstruction and the vasodilator reserve limitation. During these first 24 hours, microvascular obstruction, reflected by the incomplete regression of ST segment elevation or myocardial contrast echocardiography, leads to necrosis, absence of contractility recovery, and poor clinical outcome.^{6, 7} The higher vascular resistance and the modifications of baseline flow velocity patterns reported immediately after reperfusion reflect also the microvascular obstruction.^{33, 34}

To assess microvascular dysfunction without the effects of microvascular obstruction, which has been reported to increase in the first 48 hours after reperfusion,²³ we measured CFR 7 (1) days after reperfusion in patients with angiographically normalised coronary arteries and treated for ≥ 72 hours by intravenous heparin. In such patients, without coronary stenosis, the CFR reflects the microvascular function.

Several factors such as age, heart rate, and haemodynamic factors^{18, 35} modify both infarct related and remote artery vasodilator reserves in a common direction. Moreover, a reduction of both infarct related artery and normal remote arteries has been reported one week after AMI as a response to systemic and local neurohormonal constrictor stimuli.¹⁰ Postreperfusion microvascular dysfunction in the culprit vessel is more specifically assessed by the relative CFR, excluding the effects of parameters that globally modify CFR in all coronary arteries, than by the absolute CFR. In our study relative CFR was correlated only to the extent of the infarct risk area. This finding supports the concept of a microvascular dysfunction correlated to the extent of “jeopardised microvasculature” but independent of infarct size or myocardial viability. The more important amount of resistance vessels in arteries with extended vascular territories may explain the more severe limitation of the vasodilator reserve in response to the neurohormonal constrictor stimuli in such arteries than in those with less extended territories.¹⁰ This results in higher hyperaemic resistance and consequently lower relative CFR in arteries with extended territories than in those with small territories.

The comparable baseline averaged peak velocities in the infarct related and the remote arteries are suggestive of a sufficient baseline flow in the culprit vessel, allowing for recovery of rest contractility despite a decreased vasodilator reserve. Nevertheless, a limitation of inotropic contractile reserve, not assessed by our study, could not be excluded.

Limitations of the study

Although our study was larger than previous studies, it is still limited by the number of patients included and the selective inclusion criteria. Our results cannot be extended to all cases of reperfused myocardial infarction.

To assess late recovery of contractility we used an index that reflects the amount of stunned myocardium regardless of the extent of the infarction. Although the clinical relevance of such an index in a given patient should be viewed with caution, it is an independent and quantitative tool for the assessment of stunned myocardium. The strong correlation between the recovery index and the follow up left ventricular ejection fraction underlines its reliability.

Conclusions

Our results show that microvascular dysfunction persists in the infarct related artery seven days after successful stenting for AMI. This microvascular dysfunction is independent of myocardial viability or rest contractility but correlated to the extent of the infarct risk area. Independent predictors of improvement in contractility between the seventh day and the sixth month after primary stenting for AMI are persistence of viable myocardium on predischARGE SPECT and preserved prereperfusion anterograde and collateral blood flows, supporting the benefit of primary stenting facilitated by preprocedural antithrombotic treatment.

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REFERENCES

- Grines CL, Browne KF, Marco J, *et al*. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The primary angioplasty in myocardial infarction study group. *N Engl J Med* 1993;**328**:673-9.
- Zijlstra F, Hoorntje JC, de Boer MJ, *et al*. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1999;**341**:1413-9.
- Zijlstra F, de Boer MJ, Hoorntje JC, *et al*. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med* 1993;**328**:680-4.
- Grines CL, Cox DA, Stone GW, *et al*. Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent primary angioplasty in myocardial infarction study group. *N Engl J Med* 1999;**341**:1949-56.
- Maillard L, Hamon M, Khalife K, *et al*. A comparison of systematic stenting and conventional balloon angioplasty during primary percutaneous transluminal coronary angioplasty for acute myocardial infarction. STENTIM-2 Investigators. *J Am Coll Cardiol* 2000;**35**:1729-36.
- Claeys MJ, Bosmans J, Veenstra L, *et al*. Determinants and prognostic implications of persistent ST-segment elevation after primary angioplasty for acute myocardial infarction: importance of microvascular reperfusion injury on clinical outcome. *Circulation* 1999;**99**:1972-7.
- Agati L, Voci P, Hickie P, *et al*. Tissue-type plasminogen activator therapy versus primary coronary angioplasty: impact on myocardial tissue perfusion and regional function 1 month after uncomplicated myocardial infarction. *J Am Coll Cardiol* 1998;**31**:338-43.
- Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. *Circulation* 1982;**66**:1146-19.
- Ishihara M, Sato H, Tateishi H, *et al*. Time course of impaired coronary flow reserve after reperfusion in patients with acute myocardial infarction. *Am J Cardiol* 1996;**78**:1103-8.
- Uren NG, Crake T, Lefroy DC, *et al*. Reduced coronary vasodilator function in infarcted and normal myocardium after myocardial infarction. *N Engl J Med* 1994;**331**:222-7.
- TIMI Study Group. The thrombolysis in myocardial infarction (TIMI) trial. Phase I findings. *N Engl J Med* 1985;**312**:932-6.
- 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.
- Reiber JH, Serruys PW, Kooijman CJ, *et al*. Assessment of short-, medium-, and long-term variations in arterial dimensions from computer-assisted quantitation of coronary cineangiograms. *Circulation* 1985;**71**:280-8.
- Slager CJ, Hooghoudt TE, Serruys PW, *et al*. Quantitative assessment of regional left ventricular motion using endocardial landmarks. *J Am Coll Cardiol* 1986;**7**:317-26.
- Suryapranata H, Zijlstra F, Macleod DC, *et al*. Predictive value of reactive hyperemic response on reperfusion on recovery of regional myocardial function after coronary angioplasty in acute myocardial infarction. *Circulation* 1994;**89**:1109-17.
- Dilsizian V, Rocco TP, Freedman NM, *et al*. Enhanced detection of ischemic but viable myocardium by the reinjection of thallium after stress-redistribution imaging. *N Engl J Med* 1990;**323**:141-6.
- Beygui F, Le Feuvre C, Maunoury C, *et al*. Detection of coronary stenosis by exercise electrocardiography thallium-201 perfusion imaging and coronary angiography in asymptomatic patients after percutaneous transluminal coronary angioplasty. *Am J Cardiol* 2000;**86**:35-40.
- Claeys MJ, Vrints CJ, Bosmans J, *et al*. Coronary flow reserve during coronary angioplasty in patients with a recent myocardial infarction: relation to stenosis and myocardial viability. *J Am Coll Cardiol* 1996;**28**:1712-9.
- Doucette JW, Corl PD, Payne HM, *et al*. Validation of a Doppler guide wire for intravascular measurement of coronary artery flow velocity. *Circulation* 1992;**85**:1899-911.
- Lomboy CT, Schulman DS, Grill HP, *et al*. Rest-redistribution thallium-201 scintigraphy to determine myocardial viability early after myocardial infarction. *J Am Coll Cardiol* 1995;**25**:210-7.
- Panza JA, Dilsizian V, Laurienzo JM, *et al*. Relation between thallium uptake and contractile response to dobutamine. Implications regarding myocardial viability in patients with chronic coronary artery disease and left ventricular dysfunction. *Circulation* 1995;**91**:990-8.
- Sabia PJ, Powers ER, Ragosta M, *et al*. An association between collateral blood flow and myocardial viability in patients with recent myocardial infarction. *N Engl J Med* 1992;**327**:1825-31.
- Rochitte CE, Lima JA, Blumke DA, *et al*. Magnitude and time course of microvascular obstruction and tissue injury after acute myocardial infarction. *Circulation* 1998;**98**:1006-14.
- Christian TF, Schwartz RS, Gibbons RJ. Determinants of infarct size in reperfusion therapy for acute myocardial infarction. *Circulation* 1992;**86**:81-90.
- Clements IP, Christian TF, Higano ST, *et al*. Residual flow to the infarct zone as a determinant of infarct size after direct angioplasty. *Circulation* 1993;**88**:1527-33.
- Herrmann HC, Moliterno DJ, Ohman EM, *et al*. Facilitation of early percutaneous coronary intervention after reteplase with or without abciximab in acute myocardial infarction: results from the SPEED (GUSTO-4 Pilot) trial. *J Am Coll Cardiol* 2000;**36**:1489-96.
- Ku DD. Coronary vascular reactivity after acute myocardial ischemia. *Science* 1982;**218**:576-8.
- VanBenthuyzen KM, McMurtry IF, Horwitz LD. Reperfusion after acute coronary occlusion in dogs impairs endothelium-dependent relaxation to acetylcholine and augments contractile reactivity in vitro. *J Clin Invest* 1987;**79**:265-74.
- Bolli R, Triana JF, Jeroudi MO. Prolonged impairment of coronary vasodilation after reversible ischemia. Evidence for microvascular "stunning". *Circ Res* 1990;**67**:332-43.
- Spyrou N, Khan MA, Rosen SD, *et al*. Persistent but reversible coronary microvascular dysfunction after bypass grafting. *Am J Physiol Heart Circ Physiol* 2000;**279**:H2634-40.
- Rimoldi O, Spyrou N, Foale R, *et al*. Limitation of coronary reserve after successful angioplasty is prevented by oral pretreatment with an alpha-adrenergic antagonist. *J Cardiovasc Pharmacol* 2000;**36**:310-5.
- Lepper W, Hoffmann R, Kamp O, *et al*. Assessment of myocardial reperfusion by intravenous myocardial contrast echocardiography and coronary flow reserve after primary percutaneous transluminal coronary angioplasty in patients with acute myocardial infarction. *Circulation* 2000;**101**:2368-74.
- Wakatsuki T, Nakamura M, Tsunoda T, *et al*. Coronary flow velocity immediately after primary coronary stenting as a predictor of ventricular wall motion recovery in acute myocardial infarction. *J Am Coll Cardiol* 2000;**35**:1835-41.
- Akasaka T, Yoshida K, Kawamoto T, *et al*. Relation of phasic coronary flow velocity characteristics with TIMI perfusion grade and myocardial recovery after primary percutaneous transluminal coronary angioplasty and rescue stenting. *Circulation* 2000;**101**:2361-7.
- Wieneke H, Haude M, Ge J, *et al*. Corrected coronary flow velocity reserve: a new concept for assessing coronary perfusion. *J Am Coll Cardiol* 2000;**35**:1713-20.