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Pharmacologic Myocardial Protection During Percutaneous Transluminal Coronary Angioplasty by Intracoronary Application of Dipyridamole: Impact on Hemodynamic Function and Left Ventricular Performance

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Objectives. **The aim of this study was to investigate whether intracoronary infusion of dipyridamole represents a suitable tool for preventing deterioration of left ventricular performance and hemodynamic function during percutaneous transluminal coronary angioplasty (PTCA).**

Background. **Coronary angioplasty represents a suitable model for establishing myocardial ischemia in humans. Balloon inflation is usually accompanied by significant deterioration in left ventricular systolic and diastolic properties. A brief episode of ischemia followed by reperfusion, termed *preconditioning,* has been identified as a mechanism for rendering the myocardium more resistant to ischemia. Adenosine is considered an important mediator of preconditioning. Dipyridamole is an important drug that interferes with myocardial adenosine metabolism by inhibiting its cellular reuptake.**

Methods. **In 20 patients undergoing elective coronary angioplasty of a major vessel, assessment of angiographic left ventricular performance and hemodynamic variables was performed before, during and after PTCA. Patients were randomly allocated to pretreatment with intracoronary infusion of dipyridamole before percutaneous transluminal coronary angioplasty (10 patients) or conventional pretreatment without dipyridamole (10 patients).**

Results. **Dipyridamole pretreatment resulted in significant preservation of systolic and diastolic left ventricular performance during percutaneous transluminal coronary angioplasty, as documented by an unaffected global ejection fraction (vs. a deterioration of 29.2% with conventional pretreatment, $p < 0.01$) and an increment in diastolic stiffness of only 12.7% (vs. an increment of 57.3% with conventional pretreatment, $p < 0.01$). Apart from one instance of coronary steal phenomenon, no significant side effects of dipyridamole infusion could be detected.**

Conclusions. **It is concluded that intracoronary application of dipyridamole may result in the induction of myocardial preconditioning by improving systolic and diastolic ventricular performance during percutaneous transluminal coronary angioplasty, thereby potentially reducing the risk of the angioplasty procedure.**

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Preconditioning has been defined as a mechanism that renders hearts more resistant to ischemia (1–3) and reduces myocardial infarct size and complications (4,5). Preconditioning is established by a preceding episode of provocation (e.g., coronary occlusion, atrial pacing). Adenosine has been identified as a crucial substance in the induction and maintenance of preconditioning (6). However, some investigators doubt that myocardial protection as a result of preconditioning can be established in humans (7).

Dipyridamole represents a well established medication that induces dilation of coronary arteries by inhibiting the degradation of adenosine. In the clinical setting, intravenous dipyridamole in a dosage of 0.5 mg/kg body weight allows the quantification of coronary flow reserve (8). Side effects of intravenous dipyridamole include headache, tachycardia and hypotension (9). Intravenous administration is accompanied by a high rate of plasma protein binding (10) of up to 99%, which might counteract a sufficient local cardiac effect (coronary circulation, myocardium, microcirculation, interstitium). Intracoronary dipyridamole administration might result in a higher local concentration, with consecutive reduction of side effects, potentiation of coronary flow and enhancement of local adenosine concentration (11).

A recently published study from our department (12) documented that intracoronary dipyridamole infusion induces a significant gain in tolerance to ischemia during percutaneous transluminal coronary angioplasty (PTCA), indicating that intracoronary dipyridamole might represent a determinant of myocardial preconditioning. The purpose of the present study was to evaluate whether intracoronary dipyridamole infusion is accompanied by a reduction in systolic and diastolic dysfunction (13) and augmentation of hemodynamic performance during PTCA. The data presented indicate that ventricular

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Abbreviations and Acronyms

dP/dt max	=	maximal rate of increase of left ventricular pressure
dP/dt max/IP	=	dP/dt max at a developed pressure of 40 mm Hg
dP/dt min	=	maximal rate of decline of left ventricular pressure
dP/dV	=	diastolic stiffness
ECG	=	electrocardiogram
LVEDP	=	left ventricular end-diastolic pressure
MNSER	=	mean normalized systolic ejection fraction
P syst/ESV	=	systolic arterial blood pressure divided by end-systolic volume
PTCA	=	percutaneous transluminal coronary angioplasty
VCF	=	velocity of circumferential fiber shortening

dysfunction during PTCA can be prevented by intracoronary dipyridamole.

Methods

Patients. Twenty patients undergoing elective PTCA were randomly selected to receive either conventional pretreatment consisting of aspirin and heparin or additional pretreatment with dipyridamole before PTCA. Written informed consent was obtained from all patients. The investigator (B.E.S.) performing the PTCA was aware of the pretreatment administered. Dipyridamole infusion was preferred to adenosine because of possible negative chronotropic and dromotropic (atrioventricular blockade) side effects of intracoronary adenosine. Coronary angioplasty was performed according to the standard criteria of our department (14). Patient inclusion criteria included 1) stable angina pectoris; 2) isolated stenosis in the proximal two-thirds of a major coronary artery without angiographic evidence of collateral channels; 3) electrocardiogram (ECG) with stable sinus rhythm and without signs of ischemia or bundle branch block; 4) primary successful balloon inflation resulting in residual stenosis <30%.

Patients demonstrating local impairment of left ventricular function because of a history of myocardial infarction were only admitted if PTCA was performed in an artery supplying myocardium with normal ventricular performance. No patient had a history of diabetes mellitus or coronary artery bypass grafting.

Angiography and PTCA. For left ventricular angiography and measurement of left ventricular and aortic pressures, a pigtail catheter was placed through the left femoral artery, using fluid-filled catheter systems for measurement of phasic pressures. Coronary angiography and angioplasty were performed through the right femoral artery. After documentation of baseline hemodynamic variables, biplane angiography using the 30° left anterior oblique and 60° right anterior oblique projections and coronary angiography were performed. All patients received intravenous heparin (15,000 IU) and aspirin (500 mg). In 10 patients, dipyridamole was infused in a dosage of 0.5 mg/kg body weight over 5 min into the vessel undergoing PTCA. In this group, PTCA was initiated after reestablishment of baseline hemodynamic variables (mean time 233 ± 10 s). Immediately before termination of PTCA, left ventricular angiography and measurement of left ventricular hemodynamic variables were again performed. Angioplasty was terminated if severe angina pectoris or significant cardiac arrhythmias occurred, according to the judgment of the investigator. A maximal balloon inflation time of 300 s was allowed in patients with little or no pain. The investigation was completed after left ventricular angiography and final measurement of left ventricular hemodynamic variables were performed for the third time.

Hemodynamic variables. Using commercial software (Kontron Cardio 500) end-diastolic and end-systolic volumes and global left ventricular ejection fraction were calculated, and quantitative coronary angiography measuring % diameter stenosis of the target vessel and non-PTCA arteries was performed by an investigator (U.E.H.) with no knowledge of the pretreatment administered. The angiogram demonstrating the largest end-diastolic volume, coinciding with the R wave of the surface ECG, was considered to demonstrate end of diastole. The first angiogram after closure of the aortic valve was considered to demonstrate the end of systole, synchronous with the dicrotic notch of the aortic pressure curve. For assessment of regional left ventricular function, 10 perpendicular chords (m1 to m10) were constructed (15). Fractional myocardial shortening was calculated for each chord. For further analysis, mean fractional shortening of ischemic myocardium was calculated and compared with mean fractional shortening of nonjeopardized myocardium. Furthermore, the velocity of circumferential fiber shortening (VCR), mean normalized systolic ejection rate (MNSER), tension time index and the index of contractility were evaluated. The VCR was calculated as EDD − ESD/EDD × LVET; MNSER as EF/LVET; and the index of contractility as arterial systolic pressure divided by end-systolic volume (P syst/ESV), where EDD = end-diastolic diameter; ESD = end-systolic diameter; and LVET = left ventricular ejection time. Using the recordings of left ventricular and aortic pressures, we determined the following isovolumetric indexes: maximal rate of increase of left ventricular pressure (dP/dt max); maximal rate of decline of left ventricular pressure (dP/dt min); dP/dt max at a developed pressure of 40 mm Hg (dP/dt max/IP). Additionally, left ventricular end-diastolic pressure (LVEDP), diastolic stiffness (dP/dV) and end-systolic and end-diastolic wall stress were quantified. End-systolic wall stress was calculated according to Laplace and defined as $T = p \times r/2d$, where p = systolic left ventricular pressure minus LVEDP; r = internal radius of the left ventricle; d = wall thickness of the left ventricle in a segment of the anterior wall 4 cm long. End-diastolic wall stress was defined analogously, with p = LVEDP. The surface ECG was recorded, and RR interval measurement was performed during the complete diagnostic and interventional

Table 1. Clinical Characteristics of 20 Study Patients

	Dipyridamole Pretreatment (n = 10)	Conventional Pretreatment (n = 10)	p Value
Age (yr)	64.2 ± 3.5	61.3 ± 3.2	NS
Male/female	9/1	9/1	
Extent of CAD			
1 VD	3	5	
2 VD	5	4	
3 VD	2	1	
Vessel dilated			
LAD	4	6	
LCx	3	2	
RCA	3	2	
Lesion site			
Proximal	5	6	
Mid	5	4	
Distal	0	0	
CABG	0	0	
% diameter stenosis	63.5 ± 2.47	62.5 ± 2.45	NS

Data presented are mean value ± SE or number of patients. CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery; VD = vessel disease.

procedure. Immediately before termination of balloon inflation, patients were asked to quantify the intensity of anginal pain as absent, little, moderate or severe. There were no significant differences with regard to oral antianginal medication (dipyridamole pretreatment: nitrates in six patients, beta-adrenergic blocking agents in seven, calcium channel antagonists in two; conventional pretreatment: nitrates in seven patients, beta-blockers in five, calcium channel antagonists in four). Oral antianginal medication was discontinued at least 12 h before angioplasty. All interventions were performed by the same investigator (B.E.S.) in the same catheterization laboratory.

Statistical analysis. Results are expressed as mean value ± SE. Data were analyzed by two-way repeated measures analysis of variance. For statistical analysis, only between-group comparison of hemodynamic variables (before PTCA vs. during PTCA and before PTCA vs. after PTCA) was performed. The Tukey test was applied for multiple comparisons of hemodynamic data. Statistical analysis was performed by means of PC-SAS software version 6.10. Significance was accepted at $p < 0.05$.

Results

Demographic data. Patients were randomly selected to receive either conventional pretreatment consisting of aspirin and heparin (nine men, one woman; mean age 61.3 ± 3.2 years, range 38 to 71) or additional pretreatment with dipyridamole (nine men, one woman; mean age 64.2 ± 3.5 years, range 39 to 77, p = NS) before PTCA (Table 1). The dipyridamole group included five patients with two-vessel disease and two patients with three-vessel disease (mean diameter stenosis of non-PTCA arteries 52.3 ± 2.9%; five proximal, one mid and three distal lesions). The conventional pretreatment group included four patients with two-vessel disease and one patient with three-vessel disease (mean diameter stenosis of non-PTCA arteries 55.8 ± 3.4%; three proximal, two mid and one distal lesion).

Global and regional ejection fraction and volumes. Dipyridamole pretreatment prevented significant reduction of global ejection fraction (Fig. 1) during PTCA (68.0 ± 4.0% vs. 68.1 ± 3.7%), which could be documented in patients receiving conventional pretreatment (77.2 ± 2.3% vs. 54.6 ± 3.1%, $p < 0.01$). After termination of balloon inflation, dipyridamole induced a significant increase in global ejection fraction of 79.9 ± 1.7% compared with conventional pretreatment ($p < 0.01$). The reduction of global ejection fraction in patients receiving conventional pretreatment (Table 2) was due to a significant increase in end-systolic volume during PTCA (20.1 ± 2.3 vs. 44.6 ± 4.3 ml/m^2), whereas end-systolic volume in patients receiving dipyridamole was not altered significantly during PTCA ($p < 0.01$) and was significantly lower after PTCA ($p < 0.05$). In dipyridamole-pretreated patients, fractional shortening in the jeopardized area was reduced during PTCA (from 0.44 ± 0.05% to 0.29 ± 0.05%) and reached maximal values after termination of PTCA (0.52 ± 0.05%). In conventional pretreatment, reduction of fractional shortening was more dramatic (from 0.54 ± 0.06% to 0.15 ± 0.02%, $p < 0.05$), and baseline values were only slightly augmented after PTCA (0.57 ± 0.04%, p = NS). In the nonjeopardized area, dipyridamole induced a compensatory increase in fractional shortening (from 0.41 ± 0.04% to 0.51 ± 0.05%), with further augmentation to 0.56 ± 0.03% after balloon deflation. In conventional pretreatment, no significant alteration in fractional shortening in the nonjeopardized area could be documented (0.45 ± 0.03% before PTCA vs. 0.43 ± 0.03% during PTCA vs. 0.41 ± 0.03% after PTCA), resulting in a significant increase in fractional shortening during ($p < 0.05$) and after PTCA ($p < 0.01$) by dipyridamole.

Isovolumetric phase indexes and indexes of contractility. In patients receiving conventional pretreatment, a dramatic reduction of MNSER and P syst/ESV could be seen during PTCA, whereas dipyridamole prevented a significant deterioration. After termination of balloon inflation, a significant increase in VCF, MNSER and P syst/ESV compared with baseline values was achieved by dipyridamole. A significant reduction in dP/dt max and dP/dt max/IP during PTCA (Table 3) could be prevented by intracoronary dipyridamole; dP/dt max was reduced by conventional treatment from 1,721 ± 106 to 1,402 ± 89 mm Hg/s, whereas dipyridamole pretreatment caused only a moderate, insignificant reduction, from 1,503 ± 74 to 1,410 ± 79 mm Hg/ml ($p < 0.05$).

Indexes of diastolic function and wall stress. Independent of pretreatment used, no significant difference in the increase of LVEDP and diastolic wall stress was observed during PTCA. Dipyridamole prevented a significant increase in diastolic stiffness dP/dV (Fig. 2) that occurred in patients receiving conventional therapy during PTCA (0.233 ± 0.019 vs.

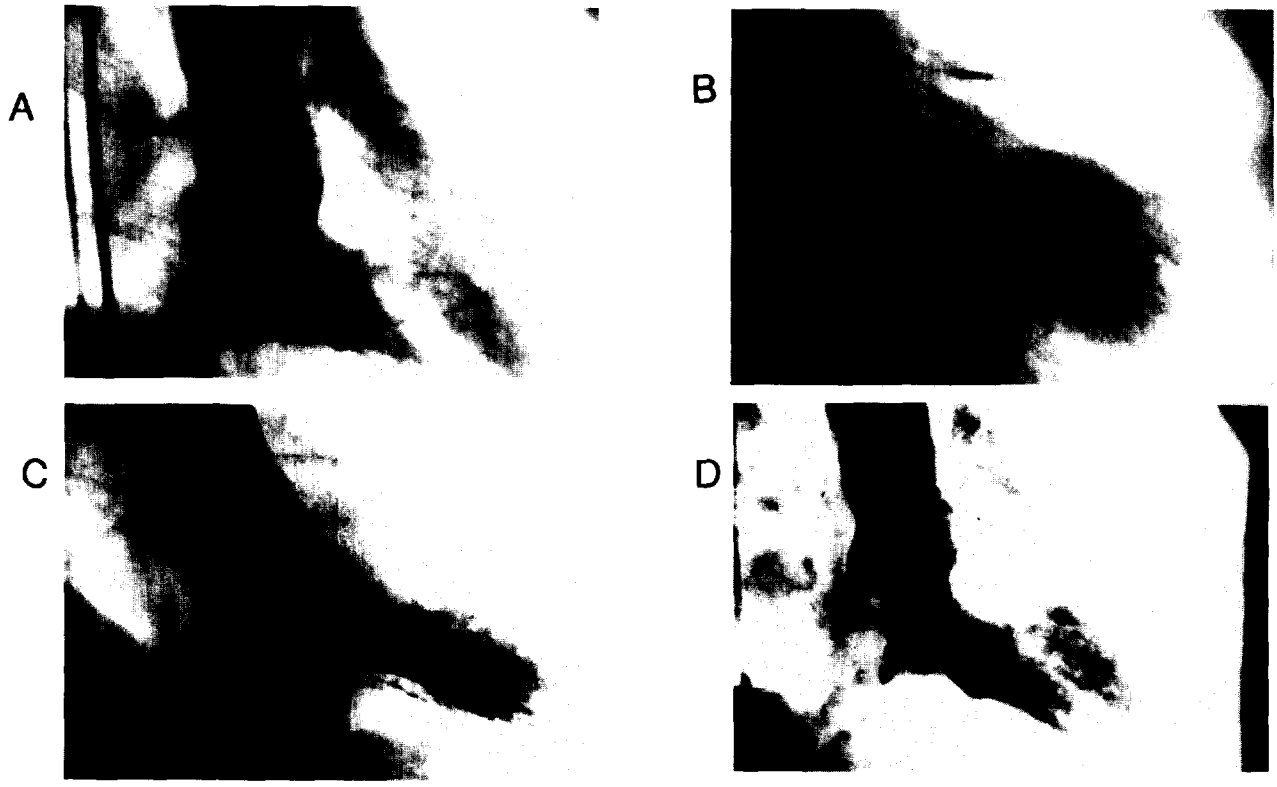


Figure 1. End-systolic left ventricular angiograms before (**A**) and during (**B**) PTCA of the left anterior descending coronary artery in a 56-year old patient receiving conventional pretreatment and before (**C**) and during (**D**) PTCA of the left anterior descending coronary artery in a 64-year old patient receiving dipyridamole pretreatment.

0.267 ± 0.016 mm Hg/ml, $p < 0.01$) and was followed by a significant reduction after performance of PTCA (0.16 ± 0.012 mm Hg/ml, $p < 0.01$) compared with baseline values. During the interventional procedure, no significant alteration of end-systolic wall stress was noted.

Blood pressure, heart rate, arrhythmias, ST segment shift and balloon inflation time. Independent of pretreatment used, no significant alteration of arterial blood pressure and heart rate could be documented (Table 4). Dipyridamole itself induced an insignificant lowering of systolic blood pressure from 146.9 ± 4.6 to 138.3 ± 3.8 mm Hg, accompanied by a transient increase in heart rate (77.9 ± 4.6 vs. 83.5 ± 6.1 beats/min), whereas diastolic blood pressure was not altered (69.3 ± 2.9 vs. 68.9 ± 3.2 mm Hg). In one patient, dipyridamole pretreatment was followed by moderate anginal pain, indicating coronary steal phenomenon. Severity of anginal pain, balloon inflation pressure and ST segment shift (dipyridamole pretreatment: 0.17 ± 0.03 mV conventional pretreatment: 0.20 ± 0.04 mV, p = NS) did not differ significantly. In the dipyridamole pretreatment group, two patients developed ventricular premature beats during balloon inflation; one patient demonstrated premature atrial complexes. After conventional pretreatment, five patients presented with ventricular premature beats, with one additional patient developing ventricular tachycardia. In one patient, premature atrial beats were noted. Dipyridamole pretreatment induced a significant prolongation of tolerated balloon inflation time of 48.4% (205.1 ± 7.2 s vs. 138.2 ± 6.7 s, $p < 0.01$).

Discussion

Study results. These data indicate that preinterventional treatment with dipyridamole results in a marked preservation of left ventricular function and hemodynamic variables: 1) global left ventricular function is mostly preserved; 2) regional ischemic left ventricular function deteriorates to a highly significant lesser extent, whereas regional left ventricular function in the nonjeopardized area is augmented; 3) isovolumetric indexes are not altered significantly; 4) diastolic properties are affected less dramatically than in patients treated conventionally.

Implications for local drug delivery. This study used intracoronary infusion of dipyridamole. Apart from one patient who experienced moderate anginal pain due to coronary steal phenomenon, no significant side effects were noted. Systolic blood pressure was lowered insignificantly, accompanied by a transient increase in heart rate. Baseline values were reestablished in <4 min, indicating that these transient hemodynamic alterations had no influence on the subsequent response to ischemia. Dipyridamole administered intravenously is accompanied by a relatively high rate of side effects (e.g., blood pressure decrease, increase in heart rate) and plasma protein

Table 2. Indexes of Volume, Contractility, Global Left Ventricular Ejection Fraction and Wall Stress*

	Dipyridamole Pretreatment			Conventional Pretreatment		
	Before PTCA	During PTCA	After PTCA	Before PTCA	During PTCA	After PTCA
EDV (ml/m^2)						
Mean	90.7	99.5	95.4	88.9	97.5	91.4
SE	5.9	5.4	5.3	5.0	5.0	7.6
p value		NS	NS			
ESV (ml/m^2)						
Mean	29.4	31.8	18.8	20.1	44.6	21.3
SE	4.7	4.7	1.4	2.3	4.3	2.9
p value		<0.01	<0.05			
EF (%)						
Mean	68.0	68.1	79.9	77.2	54.6	76.3
SE	4.0	3.7	1.7	2.3	3.1	2.9
p value		<0.01	<0.01			
VCF (circ/s)						
Mean	1.3	1.05	1.97	1.21	0.59	1.2
SE	0.21	0.19	0.22	0.1	0.08	0.09
p value		NS	<0.05			
MNSER (vol/s)						
Mean	1.66	1.66	1.96	1.97	1.38	1.97
SE	0.1	0.1	0.07	0.05	0.06	0.06
p value		<0.01	<0.01			
T syst (1,000 dynes/cm^2)						
Mean	333.7	293.1	345.1	309.3	292.3	289.1
SE	14.9	21.5	16.6	18.5	16.6	20.9
p value		NS	NS			
T diast (1,000 dynes/cm^2)						
Mean	35.0	46.7	29.4	25.4	45.1	28.9
SE	3.8	3.9	2.6	3.0	6.9	3.1
p value		NS	<0.01			

*Significance is defined as $p < 0.05$ and analyzed as between-group comparison related to baseline values (before percutaneous transluminal coronary angioplasty [PTCA] vs. during PTCA and before PTCA vs. after PTCA). circ = circumference; EDV = end-diastolic volume; EF = global ejection fraction; ESV = end-systolic volume; MNSER = mean normalized systolic ejection ratio; T diast = end-diastolic wall stress; T syst = end-systolic wall stress; VCF = velocity of circumferential fiber shortening.

binding, thus preventing sufficient local concentration. Intracoronary infusion of dipyridamole does not result in these side effects (12); moreover, it is most likely essential for induction of myocardial protection.

Postulated mechanism of action. Dipyridamole inhibits the cellular uptake (erythrocyte, endothelial cell) and degradation of adenosine, increasing its interstitial concentration. After binding to adenosine-A1 receptors (16), a pharmacologic cascade (17) is initiated. As a consequence of dipyridamole-induced preservation of left ventricular function, myocardial protection is achieved. Dipyridamole induced preservation of left ventricular function in the ischemic zone and, furthermore, exhibited a compensatory increase in fractional shortening in the nonjeopardized regions during and after PTCA. Thus, left ventricular function also improved regionally outside the distribution of the ischemic area, indicating that improvement of myocardial performance also occurs outside the jeopardized zone (18). This effect is presumably due to increased blood flow by dipyridamole. The beneficial effect of intracoronary dipyridamole can only be obtained when dipyridamole-induced myocardial protection prevails over PTCA-induced ischemia. After a mismatch between ischemia and myocardial protection, left ventricular performance cannot be preserved in severe ischemia such as induced by PTCA of dominant vessels.

Norepinephrine is released by efferent sympathetic nerves during ischemia (19). Its liberation can be inhibited by adenosine (20). Blockade of adenosine receptors enhances the liberation of norepinephrine, thus facilitating arrhythmias (21) and further compromizing the jeopardized myocardium (22). Furthermore, affection of potassium and calcium channels results in calcium overload of the ischemic myocardium. Reperfusion after PTCA is accompanied by a liberation of free radicals and lactate (23). Enhancement of adenosine during ischemia therefore might inhibit calcium overload of the myocardium and induce a scavenger effect (24) on free radicals. Activation of cardiac adenosine-A1 receptors by intracoronary dipyridamole infusion thus might result in reduction of noradrenalin release, enhancement of tolerance to ischemia,

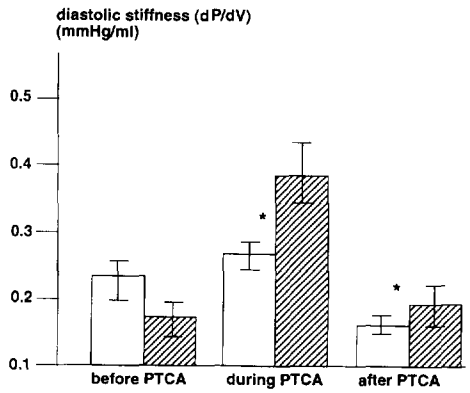
Table 3. Isovolumetric Phase Indexes, Diastolic Stiffness and Tension Time Index*

	Dipyridamole Pretreatment			Conventional Pretreatment		
	Before PTCA	During PTCA	After PTCA	Before PTCA	During PTCA	After PTCA
P syst/ESV (mm Hg/ml per m^2)						
Mean	5	4.29	7.21	7.35	3.15	6.43
SE	0.51	0.44	0.68	0.81	0.42	0.71
p value		<0.05	<0.01			
dP/dt max (mm Hg/s)						
Mean	1,503	1,410	1,526	1,721	1,402	1,554
SE	74	79	85	106	89	62
p value		<0.05	NS			
dP/dt min (mm Hg/s)						
Mean	1,357	1,295	1,384	1,632	1,345	1,482
SE	71	75	68	78	67	65
p value		NS	NS			
dP/dt max/IP (1/s)						
Mean	37.6	35.3	38.2	43.0	35.0	38.9
SE	1.9	2.0	2.1	2.7	2.2	1.6
p value		<0.05	NS			
dP/dV (mm Hg/ml)						
Mean	0.233	0.267	0.16	0.167	0.391	0.192
SE	0.019	0.016	0.012	0.021	0.095	0.024
p value		<0.01	<0.01			
TTI (P syst × HR)						
Mean	10,386	9,367	10,993	10,918	9,577	10,138
SE	421	701	509	1,030	890	1,115
p value		NS	NS			

*Significance defined as $p < 0.05$ and analyzed as between-group comparisons related to baseline values (before percutaneous transluminal coronary angioplasty [PTCA] vs. during PTCA and before PTCA vs. after PTCA). dP/dt max = maximal rate of increase of left ventricular pressure; dP/dt max/IP = dP/dt max at a developed pressure of 40 mm Hg; dP/dt min = minimal rate of decline of left ventricular pressure; dP/dV = diastolic stiffness; P syst/ESV = systolic arterial pressure divided by end-systolic volume; P syst × HR = systolic arterial pressure times heart rate; TTI = tension time index.

prevention of calcium accumulation and reduction of arrhythmias (25) and energy imbalance (26). During baseline conditions, adenosine exerts no impact on contractility. During ischemia, adenosine establishes an antiadrenergic effect, accompanied by a reduction in myocardial oxygen demand and an improvement of oxygen supply to the ischemic and nonjeopardized myocardium (18) (stimulation of adenosine-A2 receptors). Because of its antiadrenergic effects, intracoronary dipyridamole infusion can contribute to a reduction in the catecholamine-mediated increase in myocardial oxygen demand. This effect can be achieved by direct stimulation of adenosine-A1 receptors, as well as by stimulation of presynaptic adenosine-A1 receptors, thus inhibiting release of catecholamines.

Figure 2. Effect of PTCA on diastolic stiffness (dP/dV) according to pretreatment dipyridamole **(solid bars)** or conventional **(hatched bars)**. *$p < 0.01$, between-group comparison and related to before PTCA, with significance defined as $p < 0.05$.



The beneficial effect of dipyridamole on global and regional left ventricular systolic performance can be attributed to 1) enhancement of coronary perfusion (27,28), especially in the nonjeopardized region, as induced by dipyridamole "garden hose effect" (29), may exert a positive inotropic effect; 2) a direct positive inotropic effect of dipyridamole cannot be excluded; 3) reduction of systemic afterload with consecutive reduction of systolic wall stress and enhancement of ejection fraction in the ischemic and in the nonjeopardized region might be of importance; 4) improvement of myocardial energetics (26) as a result of adenosine enhancement in the ischemic area may occur; and 5) reduction of myocardial

Table 4. Hemodynamic Variables and Balloon Inflation Time*

	Dipyridamole Pretreatment			Conventional Pretreatment		
	Before PTCA	During PTCA	After PTCA	Before PTCA	During PTCA	After PTCA
P syst (mm Hg)						
Mean	146.9	136.4	135.6	147.8	140.7	136.9
SE	4.6	6.9	5.9	8.8	6.9	8.2
p value		NS	NS			
P diast (mm Hg)						
Mean	69.3	73	67.2	82.5	84.3	77.4
SE	2.9	3.3	2.5	4.6	4.7	4.3
p value		NS	NS			
MAP (mm Hg)						
Mean	95.2	92.4	93.3	104.3	103.1	97.2
SE	2.5	4.1	3.4	5.9	4.9	5.1
p value		NS	NS			
HR (beats/min)						
Mean	77.9	80.8	83.7	78.2	77.5	77.7
SE	4.6	3.7	3.3	5.2	5.6	5.3
p value		NS	NS			
LVEDP (mm Hg)						
Mean	14.7	18.8	13.9	11.2	18.5	12.3
SE	1.2	1.3	1.2	1.3	2.6	1.3
p value		NS	NS			
Inflation time (s)						
Mean		205.1			138.2	
SE		7.2			6.7	
p value		<0.01				

*Significance defined as $p < 0.05$ versus baseline values. HR = heart rate; LVEDP = left ventricular end-diastolic pressure; MAP = mean arterial blood pressure; P diast = diastolic arterial blood pressure; P syst = systolic arterial blood pressure; PTCA = percutaneous transluminal coronary angioplasty.

calcium accumulation after dipyridamole infusion may play a role.

Another potential mechanism refers to the possible recruitment of collateral channels by dipyridamole. Despite the failure of angiography to document collateral circulation, a vasoactive effect of intracoronary dipyridamole on preexisting collateral vessels cannot be completely excluded. Opening of collateral vessels with consecutive improvement of the oxygen supply to the jeopardized myocardium might induce a beneficial action on left ventricular performance, thus mimicking the postulated effect of myocardial protection. At present, it is not yet possible to quantify the potential effect of improved collateral circulation and to differentiate it from the proclaimed induction of myocardial preconditioning.

Intracoronary dipyridamole infusion induces a less pronounced diastolic dysfunction during PTCA, as documented by diastolic stiffness, indicating that diastolic dysfunction and its negative effect on systolic function can be attenuated during PTCA. Apart from a dipyridamole-induced protection of the ischemic myocardial segments, this phenomenon can be attributed to an accelerated restorage of the cardiac adenosine triphosphate pool. Further explanations include inhibition of adenosine transport and improvement of microvascular perfusion. These effects are comparable to the role of adenosine in the setting of the stunned myocardium (30,31).

Potential methodologic limitations. One hemodynamic limitation of this study is the use of fluid-filled catheters (pigtail) for evaluation of isovolumetric indexes. However, all the indexes (isovolumetric, auxotonic ejection phase indexes) analyzing contractility demonstrated comparable and similar changes during PTCA, indicating that miscalculation can be characterized as negligible. Furthermore, additional quantification of pressure-independent contractile indexes (VCF, MNSER, ejection fraction, P syst/ESV) demonstrated the favorable effects of dipyridamole use. Due to the uniform augmentation of hemodynamic variables, dipyridamole use induces significant improvement of left ventricular performance.

Baseline values of global ejection fraction, MNSER, end-diastolic wall stress, P syst/ESV, dP/dt min, dP/dV, diastolic arterial blood pressure and LVEDP differed significantly ($p < 0.05$) in patients receiving conventional pretreatment versus those receiving dipyridamole. Dipyridamole-pretreated patients presented with lower baseline values for ejection fraction, MNSER, P syst/ESV, dP/dt min and diastolic arterial pressure and higher values for end-diastolic wall stress, dP/dV and LVEDP. Because of the uniform improvement of hemodynamic variables during intracoronary dipyridamole, misinterpretation of values during and after PTCA as a result of different baseline values can be considered negligible.

Analysis of our data shows that dipyridamole seems to exert a positive influence on balloon inflation time tolerated by the patients. However, our study was not performed in double-blind manner, resulting in a possible bias on the part of the investigator performing the PTCA. For this reason, an increased tolerance to ischemia by intracoronary dipyridamole, as indicated by a prolonged balloon-inflation time, cannot be proved by our data.

Clinical implications. With regard to mechanism of action, intracoronary infusion of dipyridamole seems to prove the central role of adenosine in the setting of ischemic preconditioning. With regard to its therapeutic implications, myocardial protection with a consecutive reduction in ischemic complications seems to play a central role.

Summary. Dipyridamole infusion induces a significant amelioration of global and regional left ventricular performance during ischemia. Diastolic dysfunction during PTCA is reduced markedly by dipyridamole. Apart from one patient who experienced moderate anginal pain, no significant side effects of dipyridamole medication could be detected.

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