

Sympathetic stimulation using the cold pressor test increases coronary collateral flow¹

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Summary

Background: Little is known about the vasomotor function of human coronary collateral vessels. The purpose of this study was to examine collateral flow under a strong sympathetic stimulus (cold pressor test, CPT).

Methods: In 30 patients (62 ± 12 years) with coronary artery disease, two subsequent coronary artery occlusions were performed with random CPT during one of them. Two minutes before and during the 1 minute-occlusion, the patient's hand was immersed in ice water. For the calculation of a perfusion pressure-independent collateral flow index (CFI), the aortic (P_{ao}), the central venous (CVP) and the coronary wedge pressure (P_{occl}) were measured: $CFI = (P_{occl} - CVP) / (P_{ao} - CVP)$.

Results: CPT lead to an increase in P_{ao} from 98 ± 14 to 105 ± 15 mm Hg ($p = 0.002$). Without and with CPT, CFI increased during occlusion from $14\% \pm 10\%$ to $16\% \pm 10\%$ ($p = 0.03$) and

from $17\% \pm 9\%$ to $19\% \pm 9\%$ ($p = 0.006$), respectively, relative to normal flow. During CPT, CFI was significantly higher at the beginning as well as at the end of the occlusion compared to identical instants without CPT. CFI at the end of the control occlusion did not differ significantly from the CFI at the beginning of occlusion with CPT.

Conclusions: During balloon occlusion, collateral flow increased due to collateral recruitment independent of external sympathetic stimulation. Sympathetic stimulation using CPT additionally augmented collateral flow. The collateral-flow-increasing effect of CPT is comparable to the recruitment effect of the occlusion itself. This may reflect a coronary collateral vasodilation mediated by the sympathetic nervous system.

Keywords: coronary collateral circulation; ischaemic preconditioning; walking through angina; sympathetic nervous system; cold pressor test

Introduction

The “walking through phenomenon” in angina pectoris describes a condition of chest pain after the beginning of physical activity and subsequent relief during persistent physical exercise [1, 2]. Similar symptoms can be found in patients with intermittent claudication. Thulesius showed in patients with “walking through phenomenon” in intermittent claudication, that during exercise of the affected musculature a vasodilation of collateral vessels occurs [3]. Traditionally, “walking through” angina has been interpreted as coronary collateral channel opening during exercise-induced myocardial ischaemia [4–6]. However, this could not be demonstrated by coronary angiography [7]. Recently, it has been demonstrated

that repeated episodes of ischaemia during percutaneous transluminal coronary angioplasty (PTCA) result in an increase in collateral flow as assessed by coronary wedge-pressure measurements [8], either caused by opening of preexisting underperfused or by dilation of already perfused collateral vessels. Although coronary collateral recruitment could never be demonstrated using coronary angiography, the positive results of this study [8] can largely be attributed to the high sensitivity of the method for the assessment of collateral flow [9, 10].

Little is known about vasomotor properties of human coronary collateral vessels, in particular the role of sympathetic nervous activation, such as during exercise or during myocardial ischaemia. Experimental studies have indicated that increased sympathetic tone results in augmented collateral flow [11–13]. The purpose of this study was to test clinically the hypothesis that activation of the sympathetic nervous system using the cold pressor test (CPT) causes an increase in coronary collateral flow.

Abbreviation list

CAD	coronary artery disease
CFI	collateral flow index
CPT	cold pressor test
CVP (mm Hg)	central venous pressure
P_{ao} (mm Hg)	mean aortic pressure
P_{occl} (mm Hg)	mean coronary wedge-pressure
PTCA	percutaneous transluminal coronary angioplasty

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Methods

Patients

Thirty patients (age 62 ± 12 years, 24 men, 6 women) with one or two vessel coronary artery disease (CAD) were included in the study. All patients underwent routine percutaneous transluminal coronary angioplasty (PTCA) of a single lesion. Patients were included if the following inclusion criteria were fulfilled: absence of unstable angina pectoris, absence of acute or previous myocardial Q-wave infarction, absence of total coronary occlusion. The magnitude of collateral vessels visualized during coronary angiography was not a criterion for inclusion or exclusion.

The patients gave informed consent to participate in the study.

Coronary angioplasty, assessment of haemodynamic parameters, and ischaemia

Diagnostic coronary angiography was performed from the right femoral approach using 5F Judkins catheters for both, left and right coronary arteries. For PTCA 6F guiding catheters were used. Mean coronary wedge pressure measurements (P_{occl}) were performed using PTCA guide wires equipped with pressure sensors at the tip of the wire (WaveWire®, Endosonics, Rancho Cordova, California USA) (figure 1). Mean aortic pressure (P_{ao}) was measured via the guiding catheter. Central venous pressure was measured from a second catheter in the right atrium. An intracoronary ECG obtained from the guide wire was recorded in 26 patients in addition to three standard limb leads (figure 1). The ST-segment changes were normalized for the respective R-wave amplitude. Heart rate was assessed from the ECG and the pressure-rate product ($P_{\text{ao}} \times \text{heart rate}$) was calculated. All parameters were recorded continuously. Measurements were performed at the beginning and at the end of each 1-minute coronary balloon occlusion.

Coronary collateral assessment

Collateral flow index (CFI) was calculated as the distal perfusion pressure during vessel occlusion, normalized to the perfusion pressure during vessel patency, according to the following formula:

$$\text{CFI} = (P_{\text{occl}} - \text{CVP}) / (P_{\text{ao}} - \text{CVP}).$$

This method has recently been validated against intracoronary Doppler flow velocity measurements for the assessment of collateral flow [10].

Study protocol

Coronary angiography and biplane ventricular angiography were performed before inclusion into the study. In order to avoid overlapping effects, no nitroglycerin was given until completion of the study protocol. All patients underwent two balloon occlusions of 1 minute duration, during which simultaneous aortic and coronary pressure measurements were performed to assess the CFI (figure 1). CPT, consisting of immersing the patient's hand in ice water, has frequently been validated for activation of the sympathetic nervous system [14, 15]. The sympathetic activation increases immediately after beginning of the CPT. After two minutes, a very consistent elevation is achieved [14, 15]. In our study, the test was started 2 minutes before and continued during the 1-minute coronary occlusion. Since collateral recruitment occurs with each occlusion [8], the CPT was randomly assigned to one of the two occlusions.

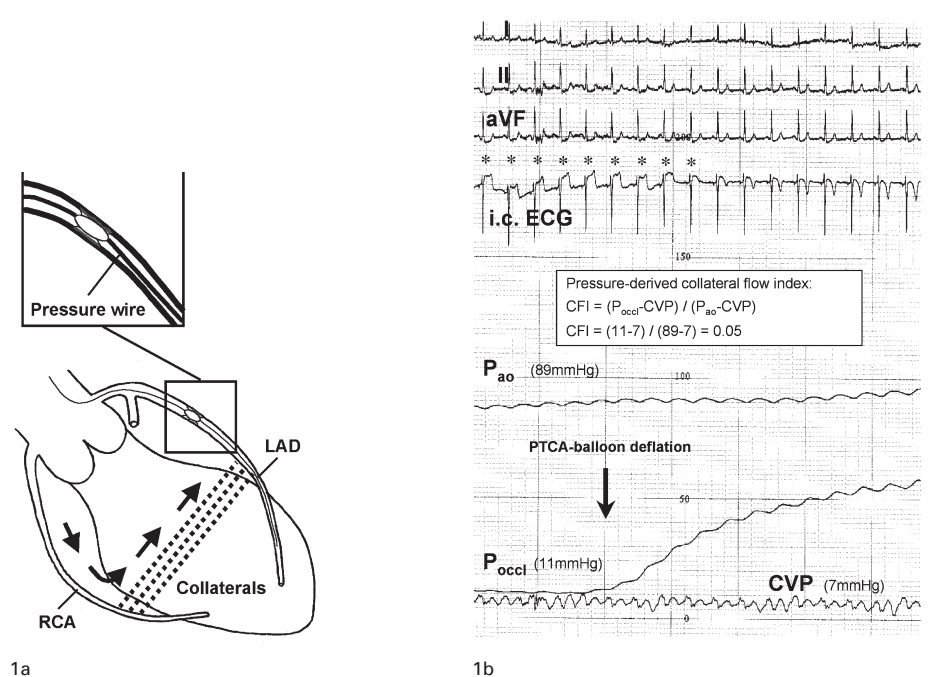
Statistical analysis

For comparisons of continuous variables between groups, unpaired Student's t-tests were performed. For intraindividual comparisons of hemodynamic data with and without CPT, paired Student's t-tests were used. Mean values \pm standard deviations are given. To assess the correlation between continuous variables, linear regression analyses were performed. Statistical significance was defined at a p value <0.05 .

Figure 1

Figure 1a shows the inflated balloon across a stenosis in the LAD in a patient with coronary collaterals insufficient to prevent myocardial ischemia. Coronary perfusion pressure determined by the blood flow distal to the occluded stenosis (i.e. collateral flow) is measured (P_{occl}) via the pressure wire located distal to the stenosis. Collateral flow index (CFI) is calculated as indicated in figure 1b. ST-segment elevations are observed in the intracoronary ECG during balloon occlusion (asterixes).

Abbreviations: CFI = collateral flow index, CVP = central venous pressure, LAD = left anterior descending coronary artery, RCA = right coronary artery, P_{ao} = mean aortic pressure, P_{occl} = coronary wedge pressure.



Results

Patient characteristics

Patient characteristics are summarized in table 1. Seventeen patients were on beta-blocking agents, 4 patients on ACE-inhibitors or angiotensin-antagonists and 8 patients on calcium

antagonists at the time of the study. In twelve patients, CPT was performed during the first of the two occlusions.

Effects of cold pressor test (CPT)

Average data of CFI, coronary wedge pressure (P_{occl}), mean aortic pressure (P_{ao}), heart rate, pressure-rate product, central venous pressure, and ST-segment changes (normalized to the respective R-wave amplitude) on intracoronary ECG are given in table 2. There was a significant increase of CFI during each occlusion, reflecting collateral recruitment during ischaemia (figure 2). In addition, when comparing CFI without and with CPT at the beginning as well as at the end of occlusion, a significant increase in CFI could be observed (figure 2). No differences in CFI were found between the end of occlusion without CPT and the beginning of occlusion with CPT. Differences in heart rate between the beginning and the end of occlusion without and with CPT differed significantly except for the change during the occlusion with CPT (table 2). Mean aortic pressure showed a pattern similar to the heart rate regarding CPT-induced changes. Again, the changes during the occlusion with CPT were not significant (table 2). Consequently, the pressure-rate product also in-

Table 1

Patient characteristics.

Age (years)	62 ± 12
Gender (male / female)	24 / 6
Systolic aortic pressure (mm Hg)	128 ± 10
Diastolic aortic pressure (mm Hg)	70 ± 10
Mean aortic pressure (mm Hg)	91 ± 12
Central venous pressure (mmHg)	6 ± 3
Heart rate (beats per minute)	70 ± 13
Left ventricular ejection fraction (%)	64 ± 8
1-/2-vessel disease	22 / 8
Target lesion for PTCA (LAD / LCX / RCA)	15 / 5 / 10
Resting transstenotic gradient (mm Hg)	17 ± 22
Collateral flow index (%)	14 ± 10
No intracoronary ECG changes during PTCA	24 / 26

Continuous variables are given in mean ± standard deviation. Abbreviations: LAD = left anterior descending coronary artery, LCX = left circumflex coronary artery, PTCA = percutaneous transluminal coronary angioplasty, RCA = right coronary artery.

Figure 2

Collateral flow index (CFI, vertical axis) at the beginning and at the end of 1 minute balloon occlusions without and with cold pressor test (CPT), respectively. The CFI changes are additionally given for each individual (solid lines). A significant overall increase in CFI due to the CPT can be observed, although the CFI did not change or even decrease after CPT in a number of patients. Furthermore, collateral recruitment during each occlusion could be demonstrated, independent of the presence or absence of sympathetic stimulation. Abbreviations: CFI = collateral flow index, CPT = cold pressor test

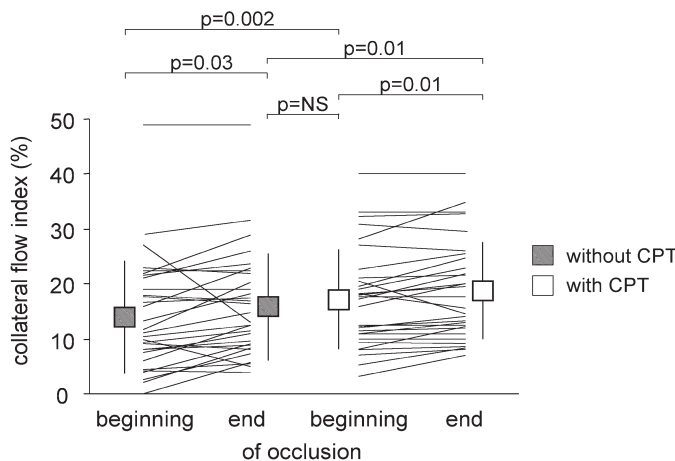


Table 2

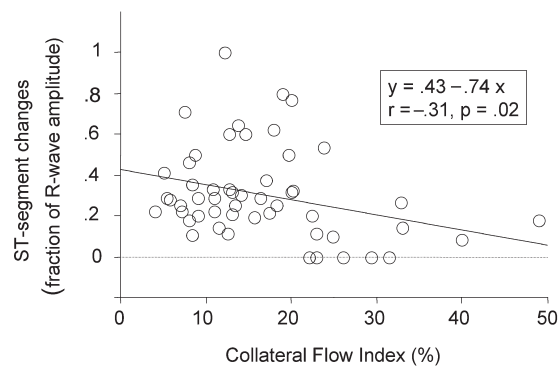
Parameters at the beginning and at the end of occlusion without and with CPT.

	Occlusion without CPT		Occlusion with CPT	
	beginning	end	beginning	end
CFI (%)	14.0 ± 10.3	15.9 ± 9.8 ^a	17.3 ± 9.1	18.7 ± 8.9
P_{occl} (mm Hg)	18.5 ± 9.0	21.0 ± 8.8 ^a	22.4 ± 10.2	24.7 ± 9.9
P_{ao} (mm Hg)	99 ± 14 ^b	100 ± 13	105 ± 15 ^c	105 ± 15
HR (bpm)	65.2 ± 13.9	67.3 ± 14.2	71.3 ± 16.2 ^c	70.8 ± 16.8
PRP (mm Hg × bpm)	6461 ± 1825	6800 ± 1901	7583 ± 2444 ^c	7483 ± 2425
CVP (mm Hg)	6.5 ± 2.6 ^d	7.6 ± 2.8	6.8 ± 2.6 ^d	8.0 ± 2.4
ST		0.31 ± 0.24 ^c		0.30 ± 0.21

Abbreviations: CFI = collateral flow index, CVP = central venous pressure, HR = heart rate, P_{ao} = mean aortic pressure, P_{occl} = coronary wedge pressure, PRP = pressure-rate product, ST = ST-segment changes in intracoronary ECG (normalized for respective R-wave amplitude). All changes in hemodynamic data are significant, if not indicated otherwise (^a p>0.05 vs. beginning of occlusion with CPT; ^b p>0.05 vs. end of occlusion without CPT; ^c p>0.05 vs. end of occlusion with CPT; ^d p>0.05 vs. end of occlusion).

Figure 3

Correlation between ST-segment changes (vertical axis) and collateral flow index (horizontal axis) at the end of occlusion. There is a significant inverse linear relationship between signs of ischaemia and collateral supply during vessel occlusion with and without cold pressor test. Abbreviations: CFI = collateral flow index, ST = ST-segment changes in intracoronary ECG (changes normalized for respective R-wave amplitude)



creased during the occlusion without CPT and as a result of the CPT, but not during the occlusion with CPT (table 2). The central venous pressure significantly increased during both occlusions, significantly diminished between the end of occlusion without and with CPT, but remained unchanged when the effect of the CPT was analysed (table 2). P_{occl} behaved similarly regarding CFI changes and statistical significance levels (table 2).

No intracoronary ECG ST-segment changes were observed at the beginning of any occlusion. Overall, ST-segment changes did not differ statistically between the two occlusions at their end point (table 2).

Determinants of ischaemia

The CFI was inversely and linearly related to ST-segment changes at the end of both occlusions as well as in an overall analysis of occlusions without and with CPT ($r = -0.31$, $p = 0.02$, figure 3).

No associations were found between CPT-induced changes in intracoronary ECG ST-segment and pressure-rate product, drug intake, heart rate, target lesion, number of contralateral stenotic lesions and initial transstenotic pressure gradient using univariate analysis.

Discussion

This study demonstrated in a model using the CPT in humans that sympathetic activation produces an increase in coronary collateral flow independently of collateral recruitment and ischaemic preconditioning caused by repeated episodes of ischaemia.

Stimulation of peripheral cold receptors have been shown to strongly activate the sympathetic nervous system [11]. In particular, the activation of the muscle sympathetic nerve activity, i.e. the system regulating the systemic blood pressure, could be demonstrated directly using microneurography within the peroneal nerve in humans [11–16]. In cardiac sympathetic fibers, there is indirect evidence that the CPT increases their activity [11]. In humans, only indirect evidence of sympathetic effects on coronary vessels can be assessed, such as vasomotion in angiography or changes of coronary pressure or flow velocity. The coronary vasomotor response to sympathetic stimulation is a result of a complex interaction between adrenergic receptor activation and local metabolic changes. The functional integrity of the endothelium plays an important role for the reaction of the coronary vessels to sympathetic stimuli [17–20].

Few experimental investigations on vasomotor properties of coronary collateral vessels have been published [21, 22]. These studies suggest that the sympathetic nervous system might predominantly (or exclusively) exert beta-receptor-mediated (i.e.

vasodilative) effects on coronary collaterals. Other mediators for vasodilatation, like adenosine triphosphate release by sympathetic nerve endings or local metabolites, cannot be excluded [23].

Active collateral vasodilation vs. passive collateral flow increase

An increase in collateral flow can either be initiated by collateral vasodilation with subsequent reduction of the collateral vascular resistance, or by collateral channel opening (i.e. collateral recruitment) and passive reduction of the overall collateral vascular resistance. If the latter mechanism was operative in our study, the sympathetic nervous system-induced vasoconstriction in the collateral-supplying microvascular bed (contralateral area) must have been more pronounced than in the collateral-receiving vascular bed (ipsilateral area), causing a more pronounced intracoronary pressure drop ipsi- than contralateral. Since vasoconstrictor response is largely dependent on endothelial function [17], the degree of endothelial dysfunction must have been systematically more severe in the contralateral coronary artery than in the artery referred for PTCA. Our study patients, however, had more severe ipsilateral coronary artery disease: only 8 patients had concomitant contralateral stenoses. Thus, it seems unlikely that unequal microvascular vasoconstriction between ipsi- and contralateral vascular beds may have led

to an increase in collateral flow during the cold pressor test, but rather a sympathetic-mediated collateral vasodilation.

Myocardial ischaemia during sympathetic stimulation

The inverse relation between CFI and ST-segment changes reflects the potentially protective role of collaterals during vessel occlusion (figure 3); a well known phenomenon [8, 9, 24, 25]. Sympathetic stimulation using the CPT was associated with a significant increase of the pressure-rate product, thus indirectly demonstrating that myocardial oxygen demand was increased. Since myocardial ischaemia results from an imbalance between oxygen supply and myocardial oxygen demand, our results suggest that the overall effect of CPT-induced increase of the pressure-rate product on myocardial ischaemia is counterbalanced but not overcompensated by the concomitant increase in collateral flow (table 2). Myocardial protection by collateral flow stimulation may thus be an adaptive mechanism when the cardiovascular system is aroused by the sympathetic nervous system.

Study limitations

No test was performed to assess coronary endothelial function, such as analysis of the ability of the vasculature to dilate in response to intracoronary acetylcholine, an endothelium-dependent vasodilator [19]. Impaired vasodilation or even vasoconstriction would have given the possibility to estimate the regional endothelial dysfunction, hence the regional vasoconstrictor sensitivity to sympathetic stimulation. As mentioned above, however, our results suggest that vasomotion of the ipsi- and contralateral coronary vascular bed in response to the sympathetic activation may have counterbalanced rather than supported the observed increase in collateral flow.

There is a considerable proportion of patients in whom CFI did not change or even decreased during CPT. This decrease in CFI in response to a sympathetic stimulus was also observed in a study using positron emission tomography for calculation of regional myocardial blood flow in collateral dependent and remote myocardium [26]. In that study, only three out of nine patients had a collateral flow increase during the CPT. The small num-

ber of patients studied, considering the high variability of collateral vessel response, might explain the contradictory results when compared with our study.

Since myocardial ischaemia itself can produce either reflex-sympathetic excitation or depression and vagal activation, mostly depending on the affected myocardial region, the total sympathetic drive to the coronary vessels cannot be considered a result of the effect of the CPT alone. In our study, however, the CPT-induced increase in heart rate indicates that the cardiac sympathetic nervous system was activated.

The majority of patients (17/30) were under beta-blocking agents at the time of cardiac catheterization. Considering this subgroup separately, CFI was not statistically different at the end of a strong 3-minute sympathetic stimulus (i.e. CPT). This observation is consistent with the concept of beta-receptor mediated collateral vasodilatation through sympathetic stimulation as the cause of increased CFI. However, because of the small study group, no further statistically relevant subgroup analysis was possible.

Conclusions

Cardiac sympathetic stimulation induces an increase in collateral flow. This effect is most likely attributable to collateral vasodilation, strong enough to counterbalance possible vascular redistribution effects of unevenly constricting resistance vessels in collateral receiving and supplying myocardial areas. Despite increased myocardial oxygen demand during sympathetic stimulation, no increase in myocardial ischaemia was observed. The development of myocardial tolerance to ischaemia during persistent physical exercise may thus be supported by a sympathetic-induced dilatation of collateral vessels with subsequent increase in collateral flow.

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