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Clinical research

Reciprocal relationship between left ventricular filling pressure and the recruitable human coronary collateral circulation

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KEYWORDS
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Coronary imaging

Aims The aim of our study in patients with coronary artery disease (CAD) and present, or absent, myocardial ischaemia during coronary occlusion was to test whether (i) left ventricular (LV) filling pressure is influenced by the collateral circulation and, on the other hand, that (ii) its resistance to flow is directly associated with LV filling pressure.
Methods and results In 50 patients with CAD, the following parameters were obtained before and during a 60 s balloon occlusion: LV, aortic (P_{ao}) and coronary pressure (P_{occl}), flow velocity (V_{occl}), central venous pressure (CVP), and coronary flow velocity after coronary angioplasty ($V_{Ø\text{-}occl}$). The following variables were determined and analysed at 10 s intervals during occlusion, and at 60 s of occlusion: LV end-diastolic pressure (LVEDP), velocity-derived (CFI_v) and pressure-derived collateral flow index (CFI_p), coronary collateral (R_{coll}), and peripheral resistance index to flow (R_{periph}). Patients with ECG signs of ischaemia during coronary occlusion (insufficient collaterals, $n = 33$) had higher values of LVEDP over the entire course of occlusion than those without ECG signs of ischaemia during occlusion (sufficient collaterals, $n = 17$). Despite no ischaemia in the latter, there was an increase in LVEDP from 20 to 60 s of occlusion. In patients with insufficient collaterals, CFI_v decreased and CFI_p increased during occlusion. Beyond an occlusive LVEDP > 27 mmHg, R_{coll} and R_{periph} increased as a function of LVEDP.
Conclusion Recruitable collaterals are reciprocally tied to LV filling pressure during occlusion. If poorly developed, they affect it via myocardial ischaemia; if well grown, LV filling pressure still increases gradually during occlusion despite the absence of ischaemia indicating transmission of collateral perfusion pressure to the LV. With low, but not high, collateral flow, resistance to collateral as well as coronary peripheral flow is related to LV filling pressure in the high range.

Introduction

Detours around a blocked coronary artery may not only affect left ventricular (LV) filling pressure via variable degrees of ischaemia, but also via the collateral perfusion pressure itself, and filling pressure may influence collateral flow (*Figure 1*).

The entire filling of an occluded, collateral-receiving coronary artery from a collateral-supplying vessel (*Figure 2*) exemplifies that the area at risk for infarction (AR) is closely and inversely dependent on collateral flow, to the extent that AR becomes zero in the presence of well-grown collaterals. The validity of this concept has

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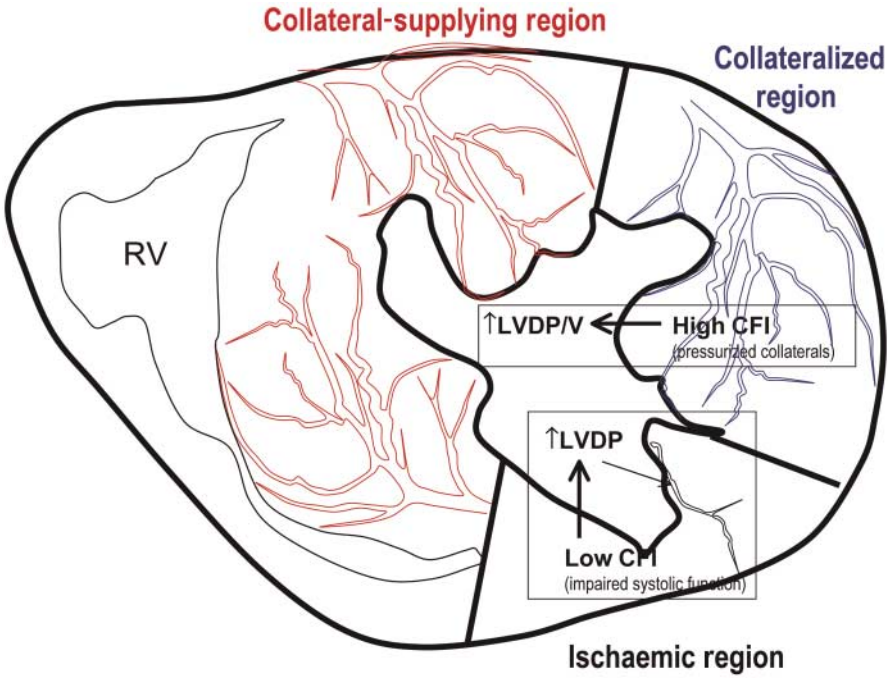

Figure 1 Drawing of a short axis view of the left (LV) and right ventricle (RV) to illustrate the concept of a reciprocal relation between LV diastolic pressure (LVDP) and the coronary collateral circulation (blue and black vessels). The black, straight lines mark the borders between three LV vascular territories, of which one is the collateral-supplying region (red area, patent left anterior descending coronary artery) to the second, collateral-receiving or collateralized area (blue area, occluded left circumflex coronary artery, LCX). The third region (black area, occluded right coronary artery) receives only minimal collateral flow and is ischaemic. The low CFI in the ischaemic area leads to increased LVDP via impaired systolic LV function of the inferior and posterior wall (arrow). The increased LVDP itself may influence the flow in the sparse collateral vessels of that area (thin arrow; waterfall phenomenon). In the collateralized LCX region, high CFI, or rather the 'pressurized' collaterals, may render the myocardial wall less distensible against diastolic filling ((LVDP per volume of filling) when compared with the ischaemic region.

been confirmed by documenting that patients with well-developed collaterals and timely reperfusion of a coronary occlusion do not show reduced infarct size (or a better wall motion recovery index) during follow-up when compared with patients undergoing delayed reperfusion.[1] Another sign of the relevance of well-grown collaterals, aside from alleviating ischaemia, is that they mitigate the consequences of infarction (e.g. LV remodelling) even when developing only after the time window for myocardial salvage.[2]

The clinical significance of the coronary collateral circulation in limiting the extent of myocardial ischaemia has been well established in recent years.[3] Conversely, the concept of an 'erectile' function of collaterals to reduce LV diastolic distensibility and thus LV remodelling following infarction has been investigated without accurately accounting for collateral flow (*Figure 1*).[4] A further issue of the importance of sparse coronary collaterals with elevated LV filling pressure has been investigated only experimentally and relates to the fact that it may alter collateral resistance to flow (*Figure 1*).[5]

The purpose of our study in patients with coronary artery disease (CAD) and present or absent myocardial ischaemia during coronary occlusion was to test the hypotheses that (i) LV filling pressure is influenced by the collateral circulation and, on the other hand, that (ii) its resistance to flow is directly associated with LV filling pressure.

Methods

Patients

Fifty patients (age 63 $\pm$ 10 years, 36 men, 14 women) with one- to three-vessel CAD were included in the study. All underwent percutaneous coronary intervention (PCI) of one stenotic lesion because of symptoms related to stable CAD. Patients were prospectively selected on the basis of the following criteria: (i) no previous Q-wave infarction in the myocardial area undergoing PCI; (ii) no baseline ECG ST-segment abnormalities; and (iii) right dominance in the case of collateral measurement in the right coronary artery. The present investigation was approved by the institutional ethics committee, and patients gave informed consent to participate in the study.

The study population was divided into two groups according to the presence or absence of intracoronary or surface lead ECG signs of myocardial ischaemia (i.e. insufficient collaterals, $n = 33$, or sufficient collaterals, $n = 17$, respectively) as obtained at the end of the first 60 s balloon occlusion of the stenosis to be revascularized.

Cardiac catheterization and coronary angiography

Patients underwent left heart catheterization for diagnostic purposes. Biplane left ventriculography was performed followed by coronary angiography. Continuous LV pressure recording was obtained via a second femoral artery line aside from that used

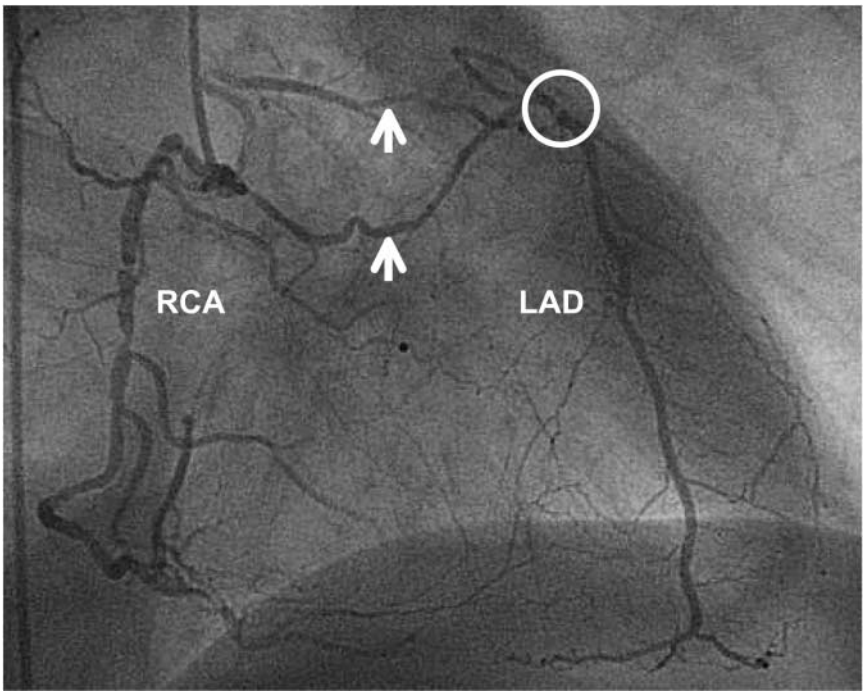

Figure 2 Coronary angiogram of a patient with contrast injection into the right coronary artery (RCA) and complete filling via collateral arteries (arrows) of the chronically occluded left anterior descending coronary artery (LAD). The large area at risk for infarction of the proximally occluded LAD is zero, since it is entirely supplied by the RCA via collaterals.

for PCI and collateral measurements. Central venous pressure (CVP) was measured via the femoral vein. Offline measurements: coronary artery stenoses were estimated quantitatively as percentage diameter reduction using the guiding catheter for calibration. AR at the stenotic lesion undergoing PCI was determined quantitatively as the ratio between the summed coronary artery branch lengths distal to the stenosis divided by the summed branch lengths of the entire coronary artery.[6]

Coronary collateral assessment

The following parameters for coronary collateral assessment were determined every 10 s during and/or at the end of the first 60 s balloon occlusion of the stenotic lesion undergoing PCI: presence or absence of angina pectoris, intracoronary (obtained from the angioplasty guidewire) or surface ECG ST-segment changes > 0.1 mV (i.e. signs of ischaemia), simultaneously obtained Doppler and pressure sensor-derived collateral flow index (CFI_v and CFI_p), collateral and coronary peripheral vascular resistance index (R_{coll} and R_{periph}).

Sensor-derived collateral measurements: in all study patients, recruitable coronary collateral flow during vascular balloon occlusion relative to normal antegrade flow through the non-occluded coronary artery (CFI, no unit) was determined using simultaneous intracoronary velocity and pressure measurements. Doppler-derived CFI has been validated in comparison with pressure-derived CFI and ECG signs of ischaemia.[7] Compared with velocity-derived measurements of CFI, the standard error of estimate using pressure measurements was 0.08.[7]

Intracoronary Doppler measurements were performed using a 0.014 inch 20 MHz Doppler crystal-tipped angioplasty guidewire (FloWire®, Vulcano Therapeutics, Belgium). The Doppler guidewire was positioned distal to the stenosis undergoing PCI and CFI_v was determined as the ratio of coronary occlusive average peak flow velocity (V_{occl}, cm/s) to the velocity at an identical wire position after PCI and cessation of reactive hyperaemia ($V_{Ø\text{-}occl}$, cm/s; *Figure 2*): $CFI_v = V_{occl}/V_{Ø\text{-}occl}$. A 0.014 inch fibre optic pressure monitoring wire (Wavewire®, Vulcano Therapeutics, Belgium) was set at zero, calibrated, advanced through the guiding catheter, and positioned distal to the stenosis to be dilated. The pressure-derived CFI was determined by simultaneous measurement of mean aortic pressure (P_{ao}, mmHg, via the angioplasty guiding catheter) and the distal coronary occlusive pressure (P_{occl}, mmHg, *Figure 3*).[7,8] CVP was measured sequentially after obtaining P_{occl} and P_{ao}, but before angioplasty balloon deflation. Pressure-derived CFI was calculated using:

$$CFI_p = (P_{occl} - CVP)/(P_{ao} - CVP).$$

Study protocol

Following diagnostic coronary angiography, an interval of at least 10 min was allowed for dissipation of the effect of the contrast medium on coronary vasomotion. Before PCI, 5000 units of heparin were given. In all patients, continuous LV pressure was obtained before and during coronary balloon occlusion (*Figure 3*). It was performed via a 5-French pigtail catheter placed in the left ventricle through a second introducer sheath. The Doppler and pressure guidewires were positioned distal to the stenosis to be dilated. During the entire protocol, an intracoronary ECG obtained from the pressure guidewire and a three-lead surface ECG were recorded (*Figure 3*). Two puffs of oral nitroglycerine spray were given shortly before coronary occlusive measurements. Simultaneous recording of LV pressure, P_{occl}, V_{occl} (on video), P_{ao}, and four ECG leads was started before and continued throughout the 60 s vascular balloon occlusion. Immediately before balloon deflation, occlusive CVP was obtained.

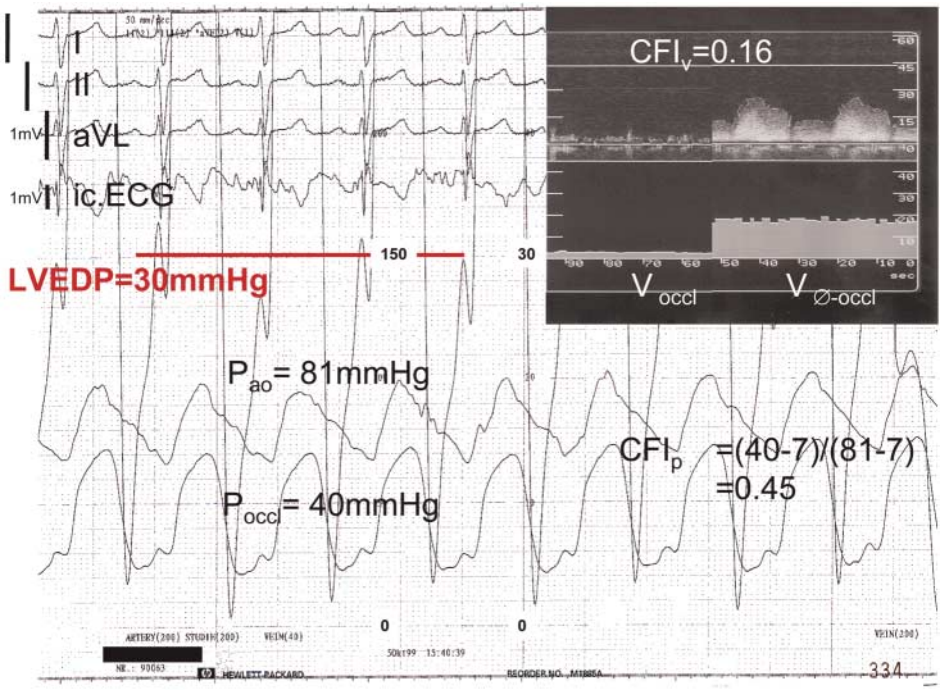

Figure 3 Simultaneous recordings in a patient with insufficient collateral flow of four ECG leads (surface leads and intracoronary, i.c., lead), LVEDP (scale 40 mmHg), phasic aortic pressure (P_{ao}, scale 200 mmHg), phasic coronary occlusive pressure (P_{occl}, scale 200 mmHg) and coronary occlusive flow velocity (V_{occl}, cm/s); non-occlusive flow velocity ($V_{Ø\text{-}occl}$, cm/s) was recorded sequentially. This patient belonged to the group with insufficient collateral flow; ECG ST-segment elevations in lead II and aVL represent signs of ischemia. Pressure-derived collateral flow index (CFI_p, no unit) is calculated as mean coronary occlusive pressure (P_{occl}) minus central venous pressure (CVP = 7 mmHg) divided by mean aortic pressure (P_{ao}) minus CVP. CFI_p overestimates CFI_v which is probably due to high LVEDP.

Data analysis

Intra-individual analysis

The following parameters were determined before [LV end-diastolic pressure (LVEDP) mmHg, as the LV pressure at the onset of the ECG QRS complex] and every 10 s (from 20 s on) during coronary occlusion (LVEDP, CFI_v, and CFI_p). The intra-individual change of these variables was analysed.

Inter-individual analysis

From occlusive coronary measurements, the following coronary vascular resistance indices (R, mmHg s/cm) obtained at the end of the first 60 s occlusion were calculated and related to simultaneous LVEDP:

$$R_{coll} = (P_{ao} - P_{occl})/V_{occl};\ R_{periph} = (P_{occl} - CVP)/V_{occl}).^{9,10}$$

Statistical analysis

Using a two-group study design (insufficient and sufficient coronary collaterals) and a two-sided unpaired Student's *t*-test at a significance level of <0.05, an absolute difference between CFI_p and CFI_v of 0.05 [standard deviation (SD) = 0.10] at 60 s of occlusion could be detected with a sample size of 40 patients. This power analysis was performed based on the hypothesis that the resistance to collateral flow is influenced by LVEDP (i.e. CFI_p exceeds CFI_v at a certain level of LVEDP).

Inter-group comparisons of continuous demographic, haemodynamic, angiographic, collateral flow, and coronary resistance data were performed by a two-sided unpaired Student's *t*-test. A χ^2-test (2×2 table) was used for comparison of categorical variables among the study groups. A two-way ANOVA test for repeated measures was used for intra-individual changes of parameters before and during occlusion. Possible correlations between different timepoints were taken into account by adjusting the significance level according to a Bonferroni correction ($P < 0.01$). Linear regression analysis with Bonferroni correction for significance determination ($P < 0.025$, as two analyses were performed) was used for the inter-individual relationship between LVEDP and coronary resistance indices at 60 s of occlusion. Mean values $\pm$ SD are given unless otherwise indicated.

Results

Patient characteristics

There were no statistically significant differences between the two study groups regarding gender, age, body mass index, the frequency of recent non-Q wave myocardial infarction, angina pectoris class, duration of angina pectoris, LV hypertrophy, cardiovascular risk factors, the use of vasoactive substances, and serum lipids (*Table 1*).

Coronary angiographic data

The following parameters obtained during coronary angiography were not statistically different between the study groups (*Table 2*): number of vessels with CAD, the coronary artery, and the location of the stenotic lesion within the vessel undergoing collateral assessment and PCI, lesion severity of the stenosis undergoing PCI and AR. Fluoroscopy time tended to be shorter in patients

Table 1 Clinical characteristics

	ECG signs of ischaemia during coronary occlusion[a] ($n = 33$)	No ECG signs of ischaemia during coronary occlusion[a] ($n = 17$)	*P*
Men, *n* (%)	24 (73)	12 (71)	0.92
Age (years)	62 ± 9	64 ± 12	0.55
Body mass index (kg/m^2)	28 ± 2	27 ± 4	0.62
Recent non-Q wave myocardial infarction, *n* (%)	10 (30)	4 (24)	0.75
Angina pectoris CCS class	2.2 ± 0.9	1.9 ± 0.9	0.29
Duration of symptoms (months)	14 ± 30	18 ± 33	0.71
Left ventricular hypertrophy on ECG, *n* (%)	17 (52)	7 (41)	0.33
Cardiovascular risk factors, *n* (%)			
Diabetes mellitus	5 (15)	3 (20)	0.78
Systemic hypertension	21 (64)	7 (41)	0.15
Smoking	15 (45)	10 (59)	0.31
Obesity	16 (48)	8 (47)	0.77
Hypercholesterolaemia	23 (70)	11 (65)	0.45
Family history of CAD	11 (33)	7 (41)	0.53
Cardiovascular medication, *n* (%)			
Acetylsalicylic acid	26 (79)	11 (65)	0.33
Beta-blockers	16 (48)	8 (47)	0.91
Nitrates	13 (39)	9 (53)	0.31
Cholesterol lowering drugs	14 (42)	9 (53)	0.41
Angiotensin-converting enzyme inhibitors	14 (42)	4 (24)	0.21
Calcium antagonists	3 (9)	2 (12)	0.74
Diuretics	6 (18)	0 (0)	0.06
Serum lipids			
Cholesterol (mmol/L)	5.41 ± 1.0	5.38 ± 1.1	0.74
High density lipoprotein cholesterol (mmol/L)	1.31 ± 0.4	1.26 ± 0.4	0.65
Total cholesterol/high density lipoprotein cholesterol	4.40 ± 1.4	4.37 ± 1.4	0.89
Triglycerides (mmol/L)	1.81 ± 1.8	1.69 ± 1.0	0.52

CCS, Canadian Cardiac Society.
[a]Obtained at 1 min of occlusion.

with, as compared with those without, ECG signs of ischaemia during occlusion.

Haemodynamic variables and collateral circulation data

The following haemodynamic variables obtained before coronary occlusion did not differ between the groups: heart rate, LV ejection fraction, systemic blood pressure, LVEDP, and coronary average peak flow velocity measured after PCI ($V_{Ø\text{-}occl}$) (*Table 3*).

Parameters obtained during coronary occlusion and collateral circulation data: heart rate, mean aortic blood pressure, and central venous pressure were not statistically different between the groups (*Table 3*). LVEDP was higher and mean coronary occlusive pressure (P_{occl}) and velocity (V_{occl}) were lower in patients with, rather than without, ECG signs of ischaemia (i.e. insufficient versus sufficient collateral vessels; *Table 3*). Patients with ECG signs of ischaemia more often had angina pectoris during coronary balloon occlusion than those without ECG signs of ischaemia. Velocity- and pressure-derived CFI was significantly different between the groups. Collateral resistance index (R_{coll}) was higher in the group with, rather than without, ECG signs of ischaemia during occlusion, but coronary peripheral resistance index (R_{periph}) was similar among the groups.

Figure 3 documents the recording in one of the patients with insufficient collateral flow and severely elevated LVEDP illustrating a discrepancy between velocity- and pressure-derived CFI. Overall, this divergence tended to be different between the groups (*Table 3*), although the general agreement between CFI_v and CFI_p was good ($CFI_v = 0.07 + 0.66\ CFI_p$; $r = 0.74$, $P < 0.0001$, standard error of estimate = 0.077). Mean difference CFI_p minus $CFI_v = 0.009 \pm 0.90$; number of values ≥ 0.909: eight, all in the group with ECG signs of ischaemia during occlusion. Intra-individual changes during occlusion of LVEDP and CFI revealed the following: a steady LVEDP increase in patients with but also without ECG signs of ischaemia, a decrease and increase, respectively in CFI_v and CFI_p, respectively, among patients with insufficient collateral flow, but no change in CFI in those with sufficient collaterals (*Figure 4*). R_{periph} and R_{coll} showed a direct association with simultaneous LVEDP in patients with insufficient collaterals (i.e. ECG signs of ischaemia), but not in those with sufficient collaterals (no ECG signs of ischaemia; *Figure 5*). This relationship was not present in the range of LVEDP up to 27 mmHg. Non-occlusive LVEDP correlated directly with occlusive LVEDP (occlusive LVEDP = 10 + 0.77, non-occlusive LVEDP; $r = 0.66$,

Table 2 Coronary angiographic data

	ECG signs of ischaemia during coronary occlusion[a] ($n = 33$)	No ECG signs of ischaemia during coronary occlusion[a] ($n = 17$)	P
Number of vessels diseased, *n* (%)			0.11
1	17 (52)	10 (59)	
2	15 (45)	4 (24)	
3	1 (3)	3 (18)	
Vessel undergoing PCI and CFI measurement, *n* (%)			0.48
Left anterior descending coronary artery	18 (55)	8 (47)	
Left circumflex coronary artery	7 (21)	2 (12)	
Right coronary artery	8 (24)	7 (41)	
Site of stenosis and CFI measurement, *n* (%)			0.38
Proximal segment	16 (48)	12 (71)	
Mid segment	14 (42)	4 (24)	
Distal segment	3 (9)	1 (6)	
Percentage diameter stenosis	90 ± 12	90 ± 13	0.44
Myocardial area at risk for ischaemia ()	46 ± 23	52 ± 23	0.48
Fluoroscopy time (min)	16 ± 8	22 ± 11	0.06

[a]Obtained at 1 min of occlusion.

$P < 0.0001$); a non-occlusive LVEDP of $\geq$18 mmHg predicted occlusive LVEDP of $\geq$25 mmHg with 100% sensitivity and 85% specificity.

Discussion

This study in humans with CAD undergoing brief arterial occlusions illustrates for the first time that the collateral circulation is reciprocally tied to LV filling pressure. If poorly developed, it influences LVEDP directly via the extent of myocardial ischaemia. If it is well developed, LV filling pressure still increases gradually during coronary occlusion despite the absence of ischaemia suggesting transmission of coronary collateral perfusion pressure to the LV. In the presence of low but not high collateral flow, vascular resistance to collateral as well as coronary peripheral flow is related to LV filling pressure in the high range of the scale (*Figure 1*).

Extent of ischaemia and LV filling pressure

The present investigation is not unprecedented in documenting, but was designed to demonstrate, that low collateral flow to a blocked coronary artery directly influences LV filling pressure via the extent of myocardial ischaemia. The methodology of the study had to be set up this way, because all the elements theoretically influencing the relationship between LV filling pressure and the collateral circulation during coronary occlusion had to be accounted for: degree of ischaemia, size of ischaemic area at risk, LVEDP, precisely measured collateral flow, and vascular resistance indices. The question of under which conditions LV filling pressure is influenced by collateral flow and/or vice versa can be answered only by confirming that more extensive myocardial ischaemia (due to less collateral flow) leads to more severely elevated filling pressure when compared with the situation with absent ischaemia (*Table 3* and *Figure 4A*). The duration of vascular occlusion was identical and the angiographically determined ischaemic area at risk for infarction was similar between the two groups with different collateral degrees, thus leaving the following variables as determinants for the extent of ischaemia and hence LV filling pressure during occlusion: number of episodes of ischaemic preconditioning, myocardial oxygen consumption at the time of occlusion, LV volume during occlusion, and collateral supply to the area at risk.[11] It is very likely that the difference in filling pressures between present and absent myocardial ischaemia observed during 60 s (*Figure 4A*) was exclusively due to variable collateral supply, since the following variables were not different between the groups: duration of angina pectoris and the product of heart rate and aortic blood pressure at 60 s of occlusion. That LV volume had relevantly changed during a 60 s coronary occlusion seems unlikely.

The question may be raised of whether the intraindividually observed decrease in CFI_v over the course of the occlusion (*Figure 4B*) can also be used as an argument for the causal effect of low collateral flow with extended ischaemia, consequent LV systolic dysfunction, and increased LV filling pressure. Rather not, because there was only a trend to decrease in CFI_v, and the pressure-derived CFI in this group with low collateral flow was going up at the same time, the fact of which could be taken as a sign for the influence of LV filling pressure on the collateral circulation instead of the opposite (see below). However, the undoubtedly primary event in the group with insufficient collaterals was the initiation of ischaemia by vascular occlusion and not the elevation of LV filling pressure, leaving its observed difference between the groups as the consequence of variable degrees of ischaemia.

Sufficient collateral flow and LV filling pressure

If, in the group with insufficient collaterals, dispersing ischaemia during occlusion with ensuing systolic LV

Table 3 Haemodynamic variables and coronary collateral circulation data

	ECG signs of ischaemia during coronary occlusion[a] ($n = 33$)	No ECG signs of ischaemia during coronary occlusion[a] ($n = 17$)	*P*
Haemodynamic parameters[b]			
Heart rate (beats/min)	68 ± 10	67 ± 12	0.62
Left ventricular ejection fraction (%)	62 ± 11	65 ± 6	0.36
Systolic blood pressure (mmHg)	125 ± 20	123 ± 16	0.73
Diastolic blood pressure (mmHg)	75 ± 10	72 ± 9	0.36
Left ventricular end-diastolic pressure (mmHg)	14 ± 7	13 ± 5	0.79
Non-occlusive distal coronary flow velocity, $V_{Ø\text{-}occl}$ (cm/s)	22 ± 8	19 ± 6	0.66
Parameters obtained during coronary artery occlusion			
Heart rate at 60 s (beats/min)	74 ± 12	67 ± 12	0.20
LVEDP at 60 s (mmHg)	23 ± 8	18 ± 7	0.04
Mean aortic blood pressure at 60 s, P_{ao} (mmHg)	101 ± 16	97 ± 11	0.48
Mean coronary occlusive pressure at 60 s, P_{occl} (mmHg)	23 ± 10	35 ± 13	0.0006
Coronary occlusive flow velocity at 60 s, V_{occl} (cm/s)	3.1 ± 1.3	6.5 ± 2.3	<0.0001
Central venous pressure during occlusion (mmHg)	7.1 ± 2.3	7.7 ± 4.5	0.55
Collateral and coronary resistance assessment			
No angina pectoris during occlusion, *n* (%)	0 (0)	13 (76)	<0.0001
CFI_v at 60 s occlusion (no unit)	0.146 ± 0.055	0.336 ± 0.099	<0.0001
CFI_p at 60 s occlusion (no unit)	0.168 ± 0.102	0.321 ± 0.120	<0.0001
CFI_p-CFI_v at 60 s occlusion (no unit)	+0.022 ± 0.094	−0.026 ± 0.072	0.04
Collateral resistance index, R_{coll} (mmHg s/cm)	31.1 ± 19.0	11.4 ± 6.9	0.0001
Coronary peripheral resistance index, R_{periph} (mmHg s/cm)	6.0 ± 4.8	4.8 ± 2.0	0.34

[a]Obtained at 1 min of occlusion.
[b]Obtained during coronary artery patency; distal coronary flow velocity measured after completed intervention and after cessation of hyperaemia.

dysfunction is taken as the cause of rising filling pressure, why then is LVEDP also rising in the group with collaterals sufficient to prevent ECG signs of ischaemia (*Figure 4A* and *C*)? Theoretically, it may be due to the fact that absent ECG signs of ischaemia do not exclude myocardial ischaemia with LV dysfunction. Based on the results of a previous study in a sufficiently comparable population, the occurrence of regional systolic or diastolic LV dysfunction undetected by ECG with subsequently elevated filling pressure in the presence of well-grown collaterals appears unlikely, since the mentioned work has not documented it by tissue Doppler imaging in the myocardial region undergoing coronary occlusion.[12] More likely (although not proven) is that the recruitment of well-developed collaterals with augmenting perfusion pressure during the first (unobserved) 20 s of coronary occlusion was conveyed transmyocardially to the LV, thus suggesting an effect of the well-developed collateral circulation on LV filling pressure identically directed but differently caused compared with that of the poorly developed via ischaemia. In this situation, elevated LVEDP signifies reduced LV distensibility (i.e. enhanced LV diastolic pressure per filling volume; *Figure 1*) with diastolic ventricular dysfunction, and not extensive ischaemia with primary systolic dysfunction. Compared with the numerous reports documenting reduced ischaemia with well-developed collaterals, there has been only one so far with similar results to ours indicating modulation of LV distensibility through the scaffolding effect of coronary collateral turgor in patients with high versus low angiographic collateral degree.[4] Aside from the very inaccurate method of collateral assessment by angiographic grading, the number of patients included in the study was low ($n = 16$), the duration of coronary occlusion was not indicated, and co-factors influencing myocardial ischaemia such as AR were not estimated, rendering the conclusion of the investigation debatable.

LV filling pressure and occlusive coronary resistances

Whether LV filling pressure influences collateral flow has not been investigated in patients to date. It has as much clinical relevance as the ability of abundant collaterals to salvage myocardium, or their capacity to withhold remodelling of an infarcted ventricle, because it could advance pre-existing ischaemia, in the sense of a vicious cycle, by further reducing collateral flow after an initiating event of ischaemia with an increase in filling pressure. As indicated above, our intra-individual data analysis in patients with insufficient collaterals is in favour of the existence of such a relationship, because CFI_v tended to decrease and CFI_p increased significantly during the 60 s occlusion (*Figure 4B*). This 'cross-over' pattern of the simultaneously measured collateral flow values can only be explained by a scenario in which there is 'outward' transmission of pressure (steady increase in CFI_p) with reduced collateral flow (CFI_v). The

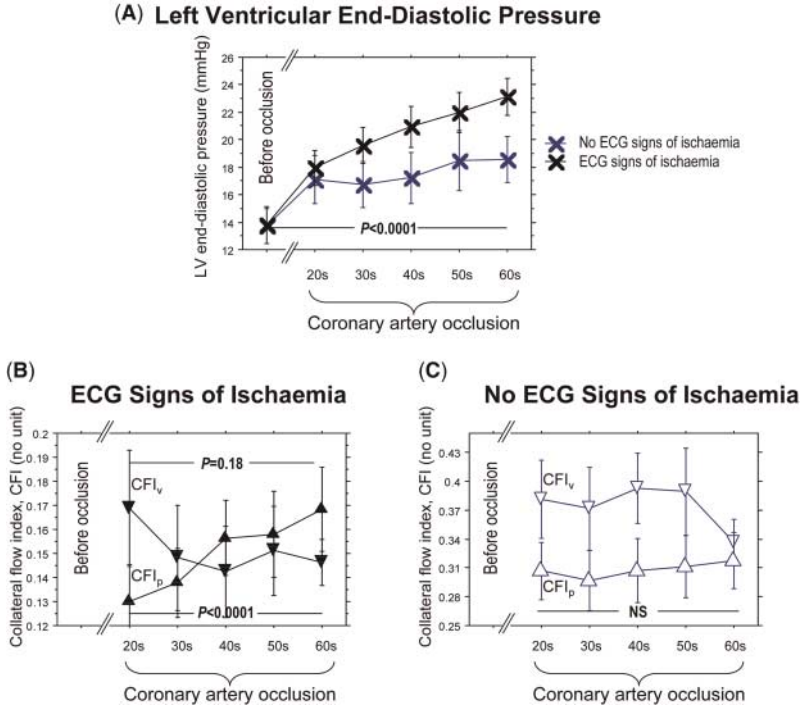

Figure 4 Intra-individual changes before and during the first 60 s coronary balloon occlusion over time (horizontal axis). (*A*) shows changes in LVEDP in patients with insufficient ($CFI_v < 0.25$, black symbols) and sufficient collaterals ($CFI_v \geq 0.25$, blue symbols); the *P*-value is identical for both groups. (*B*) illustrates the temporal changes of pressure-derived (CFI_p, upright triangles; lower P-value) and velocity-derived collateral flow index (CFI_v, reversed triangles) in patients with insufficient collateral flow. (*C*) depicts the respective values in patients with sufficient collaterals (significance level 'NS: not significant' is given for both CFIs). Error bars: standard error. All *P*-values are given for the repeated measures comparison.

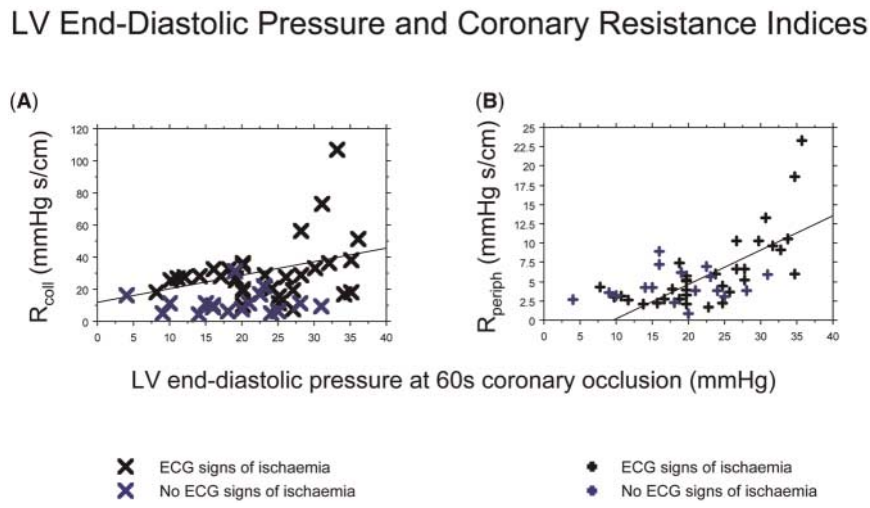

Figure 5 Correlation between LVEDP (horizontal axis) and simultaneously obtained coronary collateral resistance index (R_{coll}; left *A*) and coronary peripheral resistance index (R_{periph}; right *B*) at 60 s of occlusion. Black symbols: insufficient collaterals; blue symbols: sufficient collaterals. $R_{coll} = 0.90$ LVEDP $- 5.24$, $r = 37$, $P = 0.008$; $R_{periph} = 0.32$ LVEDP $- 1.35$, $r = 61$, $P < 0.0001$. There was no association between the respective parameters in patients with sufficient collaterals.

clinically burning question is under which conditions of LV filling pressure and collateral supply such a vicious cycle starts to revolve. Simultaneously measured occlusive aortic, coronary, and central venous pressure, as well as coronary flow velocity, represent the essential parameters to answer this question, since they provide resistance indices to coronary flow which can be searched for a steep increase at a certain LVEDP.

Kattus and Gregg[13] have reported an inhibition of collateral blood flow by distension of the left ventricle in the open-chest dog. Later, the reduction in collateral flow with increased LV pre-load has been found to be

mediated by elongation of the collateral vessels as the ventricular size increases, and by augmented extravascular pressure tending to collapse the collaterals, a phenomenon called vascular waterfall mechanism.[5] The latter describes that the collective back pressure- to-vascular flow relationship remains constant over a certain range of back pressures and, at the 'waterfall pressure' ($\sim$24–30 mmHg for the collateral circulation)[5] experiences a break beyond which flow depends inversely on back pressure.[14] Our inter-individual data analysis documents that there is a sharp increase in the resistance to coronary flow (R_{coll} and R_{periph}) beyond an LV filling pressure of 25–27 mmHg (*Figure 4*). This observation could only be made in patients with collaterals insufficient to prevent ECG signs of ischaemia during occlusion. Whilst the mentioned relationship could be caused either way, our finding within the patients with insufficient collaterals of a concurrent reduction in CFI_v with increasing CFI_p over the duration of coronary occlusion speaks for an 'outward' transmission of LV filling pressure.

Since both coronary resistance indices are, in part, calculated on the basis of coronary occlusive pressure and flow velocity, the rise in R_{coll} and R_{periph} beyond a certain LV filling pressure also points to it as a source of variability among pressure- and velocity-derived CFI, the amount of which has been found in other studies (including this one) to be around 0.08 in absolute terms (standard error of estimate).[7] Thus, the influence of LV filling pressure on resistance to occlusive coronary flow can also be expressed as a difference between CFI_p and CFI_v. Similar to R_{coll} and R_{periph}, CFI_p begins to overestimate CFI_v relevantly only beyond an LVEDP of 27 mmHg. Patients developing such a level of LV filling pressure during coronary occlusion can be predicted quite accurately on the basis of a non-occlusive LVEDP of $\geq$18 mmHg. This implies that velocity-derived CFI should be used instead of CFI_p at non-occlusive LVEDP $\geq$ 18 mmHg, despite the fact that pressure-derived measurements are much more robust and easier to get than velocity-derived measurements.

Study limitations

As indicated above, alterations of LV volume during the 60 s coronary occlusion have not been accounted for by obtaining pressure–volume curves. Thus, actual values of LV distensibility instead of LV filling pressure could have been determined.

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