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Modulation of Left Ventricular Diastolic Distensibility by Collateral Flow Recruitment During Balloon Coronary Occlusion

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OBJECTIVES The goals of this study were to elucidate the scaffolding effect of blood-filled coronary vasculature and to determine the functional role of recruited collateral flow in modulating left ventricular (LV) distensibility during balloon coronary occlusion (BCO).

BACKGROUND Although LV distensibility is an important factor affecting acute dilation after myocardial infarction, the response of LV diastolic pressure–volume (P-V) relations to coronary occlusion is inconsistent in humans.

METHODS Micromanometer and conductance derived LV P-V loops were serially obtained from 16 patients undergoing percutaneous transluminal coronary angioplasty. Coronary collateral flow recruitment was angiographically evaluated by contralateral and ipsilateral contrast injection during BCO.

RESULTS In the group with poor collateral flow (grades 0–I; n = 8), BCO resulted in a downward and rightward shift of the diastolic P-V relations, where end-diastolic volume (EDV) increased by 13% ($p < 0.05$) without appreciable change in end-diastolic pressure (EDP; 18 ± 6 to 18 ± 8 mm Hg). In contrast, BCO in the group with good collateral flow (grades II–III; n = 8) shifted the diastolic P-V relations upward to the right with a concomitant increase in minimal pressure (min-P; 6 ± 4 to 10 ± 5 mm Hg, $p < 0.05$), EDP (15 ± 7 to 21 ± 9 mm Hg, $p < 0.05$) and EDV (+10%, $p < 0.05$). Reactive hyperemia after balloon deflation caused a rapid and parallel upward shift of the diastolic P-V relations with a marked increase in min-P and EDP, especially in the group with poor collateral flow, before any improvement in LV contraction or relaxation abnormalities.

CONCLUSIONS Grades of coronary filling, either retrograde or anterograde, abruptly modulate LV distensibility through the rapid scaffolding effect of coronary vascular turgor. (J Am Coll Cardiol 1999;34:500–6) © 1999 by the American College of Cardiology

Left ventricular (LV) dilation after acute myocardial infarction, leading to congestive heart failure, proved to be favorably modified by good collateral flow recruitment or successful recanalization of the infarct-related artery, even when achieved beyond the time window for myocardial salvage (1–3). Animal experiments strongly support the direct erectile effect of coronary vasculature to reduce LV diastolic distensibility and subsequent LV dilation, whereas a loss of coronary vascular turgor substantially increases LV distensibility (4–7). Despite these experimental observations, the mechanical effects of blood-filled vasculature on LV distensibility are still a subject of controversy in clinical settings. Previous clinical studies demonstrated that balloon coronary occlusion (BCO) is accompanied by increased, decreased or unaltered diastolic distensibility (8–10). One of the possible explanations for these inconsistent responses could be related to different grades of coronary collateral flow recruited during BCO. Collateral flow affects LV diastolic function not only by changing the extent and severity of ischemia, but also by augmenting coronary vascular turgor and washout of accumulated ischemic metabolites. However, previous studies did not take the effect of recruited collateral flow on LV distensibility during BCO into account.

Accordingly, we conducted the present study to evaluate the functional role of recruited coronary collateral flow in relation to LV distensibility. Conductance-derived LV volumes were used to serially evaluate diastolic pressure–volume (P-V) relations. To elucidate the mechanical effect

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Abbreviations and Acronyms

BCO = balloon coronary occlusion
ECG = electrocardiographic or electrocardiogram
EDP = end-diastolic pressure
EDV = end-diastolic volume
EF = ejection fraction
ESV = end-systolic volume
LV = left ventricle or ventricular
Min-P = minimal pressure
P-V = pressure–volume

of blood-filled coronary vasculature on LV distensibility, we examined the changes in the diastolic P-V relations immediately after balloon deflation. At this point, the rapid mechanical effect of coronary filling could be evaluated independently of myocardial metabolic conditions.

METHODS

Patient group. The study group consisted of 16 patients (11 men and 5 women; mean age 59 years) (Table 1). All patients had anginal pain and electrocardiographic (ECG) evidence of myocardial ischemia during an exercise stress test. Three patients had prior myocardial infarction (two transmural, one nontransmural). Coronary angioplasty was performed for 18 target legions (9 left anterior descending coronary arteries, 5 left circumflex coronary arteries, 3 right coronary arteries and 1 large first diagonal branch). All patients gave written informed consent, and the protocol was approved by our institute's Committee on Clinical Investigation. All procedures were successfully performed, and no complications were encountered.

Assessment of hypoperfused area of LV. Exercise thallium-201 scintigraphy was used for the quantitative assessment of the size of the abnormally perfused bed supplied by the target vessel. Computed tomographic polar maps were divided into 24 segments, and the average counts of each segment were determined as a quantitative variable and normalized by the segment with the highest value. Abnormally perfused segments were defined by thallium counts less than the mean value +2 SD determined in 12 normal subjects.

Left ventricular P-V measurements. Contrast left ventriculography is limited to a single beat volume measurement during BCO and could mask the actual changes in chamber distensibility by extra-volume loading to the heart (11). Conductance volumetry has conquered these problems, allowing serial evaluation of the physiologic alteration of LV distensibility (12). Therefore, we advanced an 8F conductance catheter (Sentron, Roden, The Netherlands) and a 2F micromanometer-tipped catheter fully extended within its lumen (Millar instruments, Houston, Texas) to the LV apex from the left femoral artery. The 12-electrode catheter was connected to a Sigma-5/DF signal conditioner processor (Leycom Cardiodynamics Inc., Zoetermeer, The Netherlands) that used a dual excitation algorithm. Catheter

Table 1. Study Group

	Patient Initials	Age (yr)	Gender	CCS	MI	Target Lesion	BCO Collateral
Good collateral flow group	ST	49	M	II	−	LAD	III
	SS	64	M	I	−	LAD	III
	TM	55	M	II	−	LAD	III
	TT	59	M	II	−	LAD	II
	ON	61	M	II	−	LAD	III
						D1	II
	KT	62	F	III	+	LAD	II
						LCx	II
	YS	65	F	II	−	LCx	III
	IY	59	M	I	NQW	LCx	III
Poor collateral flow group	MS	80	M	I	−	LAD	0
	EN	43	F	II	−	RCA	0
	HK	36	M	II	−	RCA	I
	SN	72	M	I	+	LAD	I
	IY	60	M	I	−	LCx	0
	SY	74	F	III	−	LAD	I
	NE	56	F	III	−	RCA	I
	OT	61	M	II	−	LCx	0

BCO collateral = collateral grade evaluated during balloon coronary occlusion; CCS = Canadian Cardiovascular Society functional class; D1 = first diagonal branch; F = female; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; M = male; MI = myocardial infarction; + = previous myocardial infarction; − = no previous myocardial infarction; NQW = non–Q-wave myocardial infarction; and RCA = right coronary artery.

sensing length was identified by checking each segment's P-V loop so that the most proximal sense electrode was just above the aortic valve. Segmental volumes were summed to yield total conductance volume, which was calibrated using actual volume derived from the LV angiogram. Accuracy and reproducibility of the conductance method have been confirmed, and conductance-derived volume has been correlated linearly with angiographic volumes over a wide range of loading and contraction modes (13–15). The relative insensitivity of parallel conductance to acute ischemia has been previously reported by Kass et al. (16). Therefore, this method has a great advantage in comparing LV P-V relations during emergency interventions in a single subject.

Study protocol. After baseline hemodynamic recordings, coronary angioplasty was performed in 18 target lesions using conventional technique through the right femoral sheath. Serial recordings of P-V loops began just before the balloon crossed the lesion, thereafter every 15 s during BCO and after deflation. After the third inflation, the conductance catheter was replaced by an angiographic catheter where contralateral and ipsilateral coronary angiography was performed during the subsequent inflation. Coronary collateral flow recruited during BCO was graded according to Rentrop's criteria (17,18): grade 0 = no filling of any collateral channels; grade I = collateral channel filling but no contrast agent seen in the epicardial segment of the dilated vessel; grade II = partial filling of the epicardial segment of the dilated vessel; and grade III = complete filling of the dilated vessel by collateral channels. Accordingly, patients were divided into two groups: poor collateral flow group consisting of eight patients with grade 0–I collateral channels; and good collateral flow group consisting of eight patients with grade II–III collateral channels recruited during BCO. Distal coronary flow was recorded during the entire procedure in two patients using a Doppler guide wire (Flowire, Endosonics, Cordova, California). Retrograde collateral flow signals were defined as an inverted flow signal detected only during BCO. A 12-lead ECG was recorded throughout the entire procedure.

Data acquisition and analysis. Micromanometer pressure and conductance-derived volume were digitized by an online analog-to-digital converter (ANA-LOG-PRO I, Canopus, Kobe, Japan) at 333 Hz and stored using a PC system (PC-98note ns/R, NEC, Tokyo, Japan). Instantaneous P-V loops were recorded on a beat-to-beat basis, and steady-state measurements obtained during expiration were averaged over a 12-s recording period that spanned multiple respiratory cycles. Hemodynamic variables derived from digital P-V relations were analyzed with software developed in our laboratory (19). The time constant of isovolumic pressure decay was calculated by the derivative method of Raff and Glantz (20). Data obtained at the early phase of inflation (15 to 30 s), at the end of BCO and over 10 s immediately after balloon deflation were compared with the baseline value by an examiner who had no knowledge of the state of collateral flow. Loops obtained during the first balloon inflation were excluded from the analysis.

Statistical analysis. Results are presented as the mean value ± SD, unless otherwise specified. Analysis of variance for repeated measures and the Bonferroni multiple comparison test were applied to assess significant changes in hemodynamic indexes throughout the procedure. Changes in hemodynamic variables from baseline were compared between the groups using the unpaired Student *t* test. $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics for each group are listed in Table 1. There were no differences in age, prevalence of previous myocardial infarction and Canadian Cardiovascular Society functional class between the groups. Despite relatively high incidence of right coronary lesion in the poor collateral flow group, there was no difference in the number of the hypoperfused segment (5.0 ± 2.0 in poor collateral flow group vs. 6.7 ± 3.0 in good collateral flow group), as assessed by exercise thallium-201 scintigraphy.

Left ventricular hemodynamic data. No differences were seen in baseline cardiac function between the two groups (Table 2). During the early phase of BCO, end-systolic volume (ESV) and end-diastolic volume (EDV) significantly increased and ejection fraction (EF) fell in both groups. The changes in ESV and EF tended to be greater in the poor collateral flow group compared with the good collateral flow group (ESV +43% vs. +32%; EF −13% vs. −10%). Left ventricular relaxation was also impaired, as evidenced by prolongation of isovolumic pressure decay by 26% in the good collateral flow group ($p < 0.05$) and 16% in the poor collateral flow group ($p < 0.05$). The most distinct difference during the early phase of BCO was the response of minimal pressure (min-P) and end-diastolic pressure (EDP), which rose substantially in the good collateral flow group, whereas it remained relatively unchanged in the poor collateral flow group. Serial hemodynamic recordings throughout BCO showed a gradual increase in LV volumes and diastolic pressures in the poor collateral flow group. Within 10 s after deflation, min-P and EDP rose significantly in the poor collateral flow group, whereas LV volumes and relaxation indexes remained unchanged (Table 2). Absolute deviations of the ST segment after deflation were similar to those recorded before deflation (2.0 ± 0.9 vs. 1.7 ± 0.9 mm in the good collateral flow group; 1.8 ± 0.7 vs. 1.5 ± 0.6 mm in the poor collateral flow group).

Left ventricular P-V relation. In the good collateral flow group (Fig. 1), 7 of 10 loops obtained during BCO from eight patients had an upward shift of the diastolic P-V relations and two showed a rightward shift along a similar diastolic P-V relation. No change in the whole P-V loop was observed in the remaining one patient who had no

Table 2. Hemodynamic Changes During Angioplasty

	Good Collateral Flow	Poor Collateral Flow	p Value‡
HR (beats/min)			
Baseline	72 ± 15	76 ± 15	NS
Early inflation	74 ± 26	75 ± 13	NS
Late inflation	70 ± 18	74 ± 20	NS
Deflation	73 ± 23	75 ± 13	NS
ESVI (ml/m^2)			
Baseline	33 ± 13	22 ± 8	NS
Early inflation	41 ± 12*	32 ± 9*	NS
Late inflation	41 ± 13*	34 ± 11*	NS
Deflation	42 ± 13*	33 ± 9*	NS
EDVI (ml/m^2)			
Baseline	75 ± 17	68 ± 11	NS
Early inflation	82 ± 16*	77 ± 14*	NS
Late inflation	81 ± 17*	79 ± 12*	NS
Deflation	85 ± 20*	75 ± 13*	NS
EF (%)			
Baseline	56 ± 13	67 ± 10	NS
Early inflation	50 ± 12*	58 ± 10*	NS
Late inflation	49 ± 12*	58 ± 11*	NS
Deflation	51 ± 10*	57 ± 9*	NS
LVPSP (mm Hg)			
Baseline	135 ± 14	145 ± 22	NS
Early inflation	135 ± 17	142 ± 21	NS
Late inflation	134 ± 21	138 ± 23	NS
Deflation	138 ± 1	147 ± 22	NS
Min-P (mm Hg)			
Baseline	6 ± 4	7 ± 4	NS
Early inflation	10 ± 5*	6 ± 4	NS
Late inflation	11 ± 5*	7 ± 5	NS
Deflation	12 ± 5*	10 ± 5†	NS
EDP (mm Hg)			
Baseline	15 ± 7	18 ± 6	NS
Early inflation	21 ± 9*	18 ± 8	NS
Late inflation	22 ± 3*	19 ± 8	NS
Deflation	22 ± 7*	23 ± 8*†	NS
+dP/dt (mm Hg/s)			
Baseline	1,829 ± 346	2,057 ± 322	NS
Early inflation	1,691 ± 345*	1,894 ± 252*	NS
Late inflation	1,710 ± 352*	1,889 ± 267*	NS
Deflation	1,768 ± 365	1,965 ± 257	NS
−dP/dt (mm Hg/s)			
Baseline	−1,818 ± 254	−1,942 ± 325	NS
Early inflation	−1,571 ± 337*	−1,734 ± 237	NS
Late inflation	−1,571 ± 337*	−1,782 ± 263	NS
Deflation	−1,606 ± 300*	−1,912 ± 313	< 0.05
Td (ms)			
Baseline	39 ± 4	33 ± 10	NS
Early inflation	49 ± 7*	38 ± 13*	NS
Late inflation	51 ± 8*	41 ± 14*	NS
Deflation	48 ± 8*	38 ± 13*	NS

*$p < 0.05$ vs. baseline. †$p < 0.05$ vs. inflation. ‡Good vs. poor collateral flow.

Deflation = over 10 s immediately after deflation; −dP/dt and +dP/dt = rate of fall and rise, respectively, in left ventricular pressure; EDP = end-diastolic pressure; EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; HR = heart rate; LVPSP = left ventricular peak systolic pressure; Min-P = minimal pressure; NS = not significant; Td = time constant of left ventricular pressure decay by non-zero asymptote; early inflation = 30 s of inflation; late inflation = end of inflation.

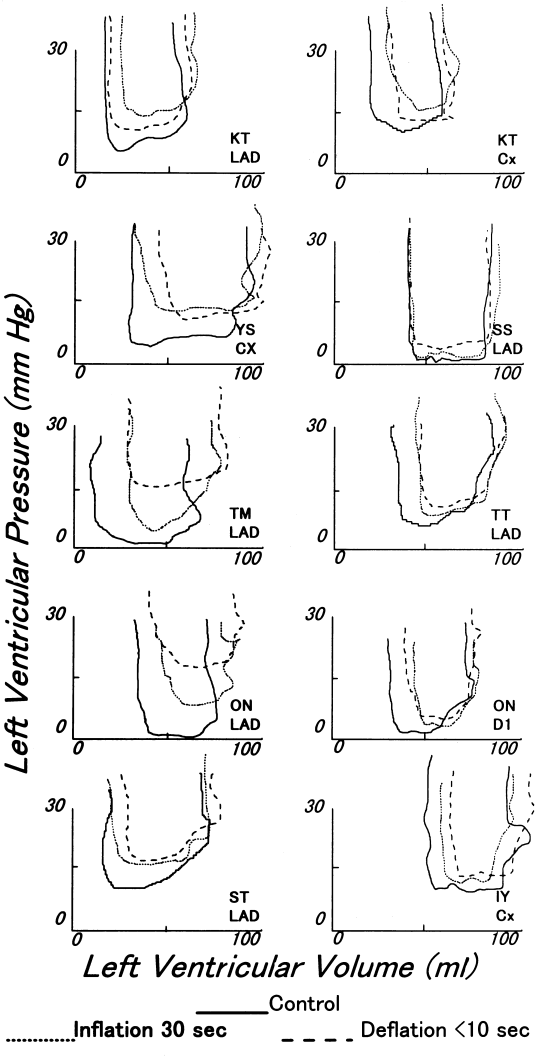

Figure 1. Individual diastolic P-V relations of the good collateral flow group. Seven of 10 loops obtained during BCO had an upward shift of the diastolic P-V relation, and two loops (patients TT, LAD and ON, D1 [patient initials are followed by target lesion]) showed a rightward shift along a similar diastolic P-V relation. No change in the entire P-V loop was observed in the remaining one patient (SS, LAD), who had no evidence of myocardial ischemia during BCO. With reactive hyperemia after balloon deflation all but two patients (KT, LAD and Cx and YS, Cx) showed a further upward shift of the diastolic P-V relation. Continuous line = control; dotted line = early inflation; interrupted line = immediately after deflation; D1 = first diagonal branch; Cx = left circumflex coronary artery; LAD = left anterior descending coronary artery.

evidence of myocardial ischemia. In contrast, no upward shift of the diastolic P-V relations was seen in the poor collateral flow group during BCO (Fig. 2). Four patients in this group demonstrated a clear downward shift of the diastolic P-V relations, and the remaining four patients showed a slight rightward shift along a similar diastolic P-V relation during BCO.

Within 10 s after balloon deflation, diastolic P-V rela-

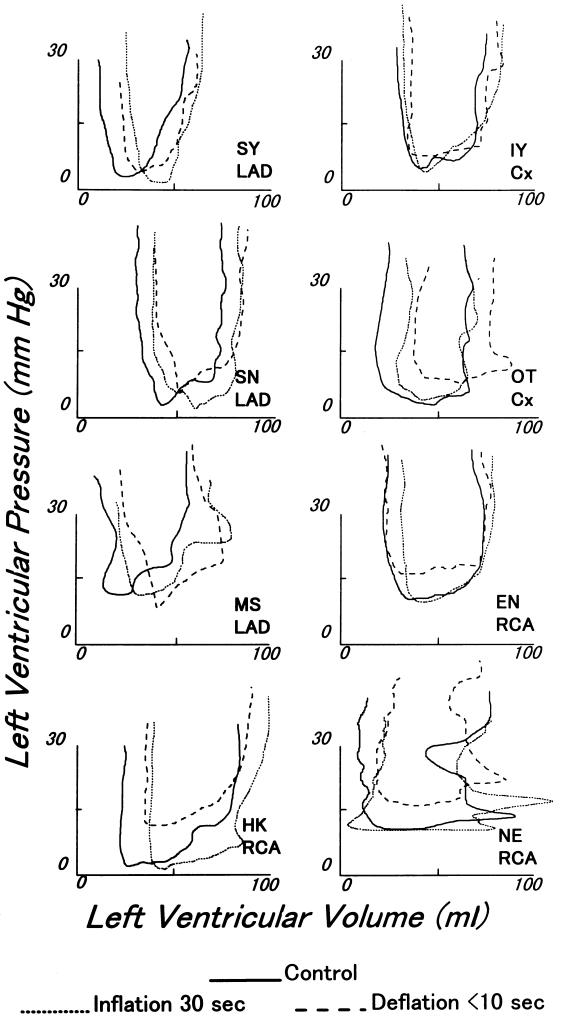

Figure 2. Individual diastolic P-V relations of the poor collateral flow group. Four patients showed a downward shift of the diastolic P-V relation (SY, LAD; SN, LAD; MS, LAD; and HK, RCA [patient initials are followed by target lesion]) during BCO, while the remaining four patients demonstrated a rightward shift along a similar diastolic P-V relation. After balloon deflation all but one patient (MS, LAD) had a parallel upward shift of the diastolic P-V relation. RCA = right coronary artery; other abbreviations as in Figure 1.

tions shifted upward above the level of BCO in seven patients with poor collateral flow and in six patients (seven loops) with good collateral flow. To examine the effects of the ischemic extent on LV distensibility, changes in min-P were plotted against those of ESV, which was used as an indirect measure of ischemic extent during BCO (Fig. 3). Despite a comparable increase in ESV, min-P remained lower in the poor collateral flow group compared with the good collateral flow group.

Doppler coronary flow simultaneously obtained with diastolic P-V relations (Fig. 4) allowed a unique observation of the direct relation between coronary filling and LV diastolic property. In a patient with angiographically good

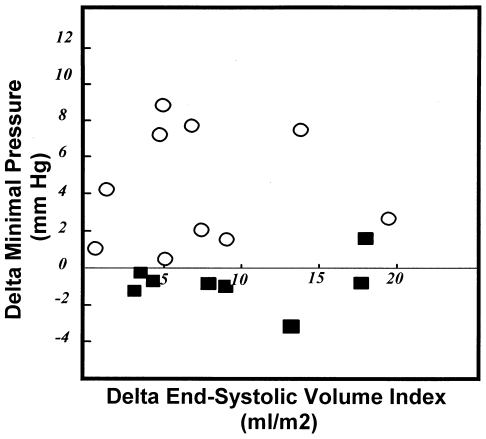

Figure 3. Changes in LV filling pressure and extent of ischemia. For a comparable increase in the LV ESV index, min-P remained lower in the poor collateral flow group **(solid squares)** compared with the good collateral flow group **(open circles).**

collateral channels, a retrograde Doppler flow appeared distal to the occlusion site, along with an upward shift of the diastolic P-V relation. In the other patient with no angiographically detected collateral channels, neither distal coronary flow nor diastolic P-V relation shift was recorded during BCO. After balloon deflation the anterograde coronary flow dramatically increased with a concomitant parallel upward shift of the LV diastolic P-V relation in both patients.

DISCUSSION

The good collateral flow recruited during BCO made the heart less distensible, as reflected by a parallel upward shift of the diastolic P-V relations and increased filling pressures. This contrasted strikingly with the downward shift seen with poor collateral recruitment, suggesting a functional role for collateral flow in modulating LV distensibility. After balloon deflation, hyperemic coronary filling shifted the diastolic P-V relations rapidly upward, while myocardial ischemia remained unchanged, as reflected by a depressed LV relaxation rate, unchanged LV volumes and ischemic ECG changes. Therefore, the rapid decrease in LV distensibility could be largely attributed to the scaffolding effect of blood-filled coronary vasculature rather than the changes in myocardial metabolic conditions.

Diastolic distensibility during coronary occlusion. Left ventricular diastolic P-V relations are determined by the interaction of multiple factors, including intrinsic myocardial elastic properties, ventricular relaxation, external restraint and coronary vascular turgor (21–23). A clear downward shift of diastolic pressure–segment length relations was experimentally documented during coronary occlusion and contrasted sharply with the upward shift of this relation in tachycardia-induced ischemia (7,24). This disparate phenomenon was elegantly analyzed by Kihara et al. (25), who

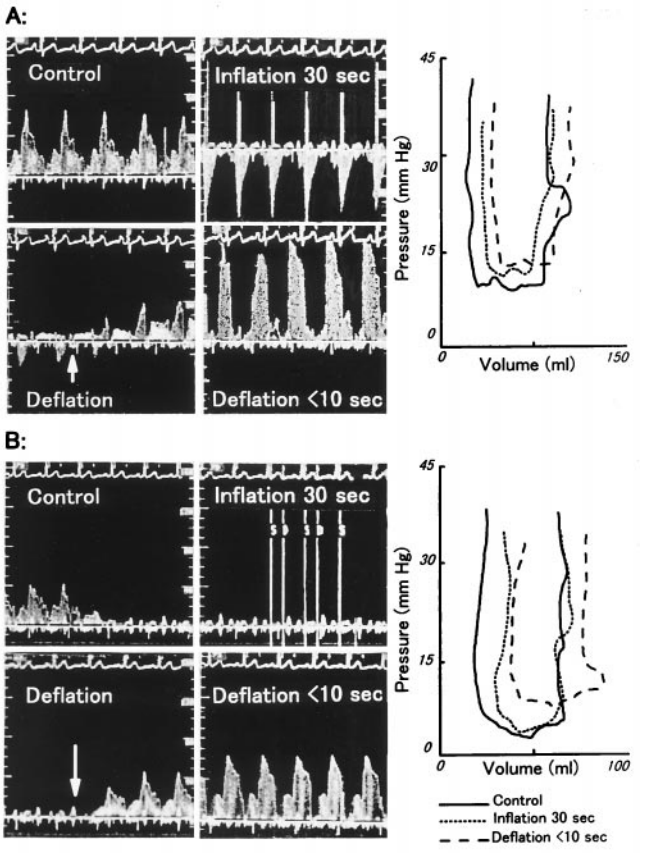

Figure 4. Simultaneous recording of Doppler coronary flow and diastolic P-V relations. **A,** This patient has grade III angiographic collateral recruitment during BCO. With the appearance of retrograde Doppler flow distal to the occlusion site (inflation 30 s), the diastolic P-V relation shifted upward **(dotted line). B,** This patient has grade 0 angiographic collateral recruitment during BCO. There was neither distal coronary Doppler flow (inflation 30 s) nor a diastolic P-V relation shift during BCO. After balloon deflation, hyperemic flow was recorded (deflation <10 s) with a concomitant parallel upward shift of diastolic P-V relations in both patients **(interrupted line).**

observed LV diastolic pressure and intracellular calcium transient ($[Ca^{2+}]_i$) during hypoxia and ischemia in isolated ferret hearts. They concluded that the force needed to decrease LV distensibility, caused by the ischemia-induced increase in diastolic $[Ca^{2+}]_i$, has been overwhelmed by other factors that increase LV distensibility, such as rapid loss of coronary turgor and decreased Ca^{2+} sensitivity of myofilaments by accumulation of metabolites.

In clinical settings, however, the effect of coronary occlusion on LV distensibility is still a subject of controversy because it results in variable influences on LV diastolic property (8–10). The present study revealed that the grade of collateral recruitment during BCO is one of the important factors affecting LV distensibility. The upward shift of diastolic P-V relations and dramatically increased EDP were predominantly observed in the good collateral flow group with grade III collateral recruitment during BCO. However, two patients with grade II collateral recruitment had a dominant rightward shift along a similar diastolic P-V relation that could be explained by less turgor. Meanwhile, the downward shift was only seen in the poor collateral flow group during the early phase of BCO. These findings suggest that the loss of coronary vascular turgor could play an important role in the increased LV distensibility in this group and could offset any rise in EDP caused by enhanced atrial contribution during myocardial ischemia. The significance of coronary vascular filling with regard to LV distensibility was also documented by De Bruyne et al. (26), who maintained coronary vascular turgor by saline perfusion distal to BCO site.

Retrograde collateral flow, if lower than baseline anterograde flow, could exert less turgor. Nevertheless, with the appearance of retrograde coronary flow (Fig. 4A), LV distensibility dramatically decreased compared with the control state. Although not clearly understood, a possible mechanism for this response is the opening of an extensive collateral network that could increase LV wall thickness, and thus decrease LV distensibility (27). This could be exaggerated by provocation of ischemia, as Vogel et al. (4) have shown experimentally that the ischemic heart is more sensitive than the normal heart to the turgor effect of coronary blood flow.

Study limitations. First, because of the small number of patients we included intermediate grade of collateral flow recruited during BCO (grade II) in the good collateral flow group. This could be responsible for the similarity in LV functional depression noticed in both groups during the early phase of BCO. However, during the progression of occlusion, LV function in the good collateral flow group did not deteriorate further, whereas that in the poor collateral flow group continued to worsen until the end of BCO. Second, angiographic grading of collateral flow and LV diastolic P-V relations were evaluated separately in two consecutive BCOs. This may generate a degree of bias in the relation between LV distensibility and collateral recruitment during BCO. To overcome this limitation, we simultaneously recorded diastolic P-V relations and distal Doppler coronary flow and found that the presence of retrograde coronary flow plays an important role in LV distensibility response to BCO. Finally, a change in pericardial restraint and interventricular interaction could influence the upward shift of diastolic P-V relations seen in the good collateral flow group. We could not determine the relative contribution of external constraint and vascular turgor to LV distensibility because of a lack of inferior vena caval occlusion and right atrial pressure measurement. In the present study, the poor collateral flow group is likely to be subjected to more external constraint because this group has relatively larger EDV during BCO and a higher incidence of right coronary lesion that might provoke right ventricular ischemia and dilation. However, no upward shift of the diastolic P-V relations was seen in the latter poor collateral flow

group, suggesting that the grade of collateral recruitment would be more important in modulating LV distensibility under these conditions. In addition, the starting position on the intrinsic diastolic P-V curves could affect the magnitude of change in LV pressure during myocardial ischemia. This mechanism is less likely to be applied in the present study because there was no significant difference in the baseline LV filling pressure and LV volumes between the study groups.

Clinical implications. Infarct expansion leads to ventricular dilation and remodeling, which are associated with a poor prognosis. Modulation of these processes might crucially influence the subsequent development of heart failure and eventually prognosis. In acutely compromised LV contractile function caused by myocardial hypoperfusion, the resultant loss of vascular turgor could increase LV distensibility and help to maintain stroke volume through the Frank-Starling mechanism. In the long term, however, the poorly perfused myocardium could not cope with the increased wall stress and could fail to maintain ventricular shape. Several clinical and experimental studies have documented that delayed restoration of coronary filling limits LV dilation and improves survival, even if only little myocardial salvage occurs. These findings have given rise to what is known as the "open-artery hypothesis." Among the proposed mechanisms, mechanical scaffolding of the blood-filled coronary bed has been suspected to support the infarct-related area and limit infarct expansion. A clear relation between LV distensibility and extent of coronary filling presented in this study could provide the rational basis for the importance of this scaffolding effect of the open-artery hypothesis. Further study is warranted to elucidate whether the reduced LV distensibility caused by coronary vasculature filling favorably modifies the ventricular remodeling process in the long-term follow-up.

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