Intracoronary Thrombus Formation Causes Focal Vasoconstriction of Epicardial Arteries in Patients With Coronary Artery Disease

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**Background.** Experimental studies have demonstrated that intracoronary platelet aggregation and thrombus formation may induce marked vasoconstriction of epicardial arteries with endothelial injury.

**Methods and Results.** To examine the effects of intracoronary thrombus formation on coronary vasomotor tone of human epicardial arteries in vivo, we studied 15 patients who developed intracoronary thrombi adherent to the guide wire during balloon dilatation. Epicardial artery luminal area was evaluated by quantitative coronary angiography proximal and distal to the site of intracoronary thrombus formation and in a reference vessel before and after thrombus formation as well as after intracoronary injection of 0.2–0.3 mg nitroglycerin. All artery segments distal to the site of thrombus formation showed vasoconstriction with a luminal area reduction of $-27.4\pm17.1\%$ ($p<0.001$), whereas proximal vessel segments and reference vessels not manipulated during percutaneous transluminal coronary angioplasty did not demonstrate any significant luminal area changes during thrombus formation. Angiographic measurements after advancing the guide wire with the adherent thrombus (performed in six of the 15 patients) revealed in all patients that vasoconstriction did develop at a new site distal to the thrombus with persistence of the initial vasoconstriction now residing proximal to the thrombus. Thus, there was a sequential association between thrombus formation and subsequent distal vasoconstriction. Intracoronary injection of nitroglycerin abolished the thrombus-induced vasoconstriction. No significant luminal area changes were observed in 20 patients without angiographic evidence of intracoronary thrombus formation.

**Conclusions.** Intracoronary thrombus formation during percutaneous transluminal coronary angioplasty causes focal vasoconstriction of epicardial arteries in patients with coronary artery disease. Although caution must be advised in the extrapolation of this phenomenon, which was observed in a manipulated artery during coronary angioplasty, the vasoconstrictor response to intracoronary thrombus formation in vivo may play an important role in the dynamic mechanisms of acute coronary heart disease syndromes. *(Circulation 1991;83:1519–1525)*

Acute coronary heart disease syndromes are usually caused by a primary decrease in myocardial oxygen delivery. In particular, there is a growing body of evidence indicating that in most patients, unstable angina is the consequence of platelet aggregation or in situ thrombosis at sites of coronary arterial narrowing and endothelial injury. Recent experimental studies demonstrated that intracoronary platelet aggregation and thrombus formation not only cause mechanical obstruction of large epicardial arteries but also induce marked epicardial vasoconstriction and decreases in coronary blood flow by locally releasing potent vasoconstrictor substances like thromboxane A$_2$ and serotonin. Moreover, the greatly potentiated vasoconstrictor response to activated platelets reported in atherosclerotic animals with dysfunctional endothelium has been implicated in the pathogenesis of coronary vasospasm. However, the response of epicardial arterial vasomotor tone to intracoronary platelet aggregation and thrombus formation has never been assessed in the human intact coronary circulation.

The development of angiographically visible intracoronary thrombus formation during percutaneous transluminal coronary angioplasty (PTCA) provides an ideal model to examine the effects of in situ...
platelet aggregation and thrombus formation with the subsequent release of vasoactive substances in the human intact coronary system.

**Methods**

**Patients**

In 15 patients who underwent PTCA following a standardized protocol between 1988 and 1989 and who had coronary angiograms suitable for quantitative analysis, there was angiographic evidence of intracoronary thrombus formation during the procedure of PTCA (criteria to be described). The control group consisted of 20 prospectively studied consecutive patients who had no angiographic evidence of intracoronary thrombus formation during PTCA. The patient characteristics are summarized in Table 1.

Patients with acute myocardial infarction or angiographic evidence of intracoronary thrombus before PTCA were excluded.

**Angiographic Definition of Thrombus**

Intracoronary thrombus formation was assumed to be present when the angiogram showed an intraluminal filling defect, visible in all projections, remote from the site of PTCA and adherent to the intracoronary guide wire, as evidenced by backward or forward movement of the guide wire under fluoroscopic control.

**PTCA Procedure**

All patients received oral pretreatment with 5 mg isosorbide dinitrate, 10 mg nifedipine, and 330 mg aspirin before PTCA as well as an intravenous injection of 10,000 units heparin at the beginning of the procedure. PTCA was performed by way of the femoral approach using the monorail technique. Balloon sizes were chosen to approximate the diameter of the "normal" coronary segment adjacent to the segment to be dilated. The PTCA procedure followed a standardized protocol, and coronary angiograms were obtained immediately after deflation of the balloon and retraction of the angioplasty catheter into the guiding catheter and also at 5 and 10 minutes after balloon dilatation. If an intraluminal filling defect suggesting the presence of thrombus formation was suspected during the angiogram obtained at 5 or 10 minutes after balloon dilatation, 0.2–0.3 mg nitroglycerin was injected into the coronary system via the guiding catheter, and the angiogram was repeated. In six of the 15 patients, before intracoronary nitroglycerin injection, an additional angiogram suitable for quantitative evaluation was obtained after advancing the guide wire with the adherent thrombus to a more distal position to assess whether vasoconstriction had developed at a new site and to rule out the possibility of passive arterial collapse distal to the thrombus. In the remaining nine patients, the detection of an intraluminal filling defect suggestive of the presence of thrombus formation adherent to the guide wire immediately prompted the intracoronary injection of nitroglycerin to minimize the patient's risk before another coronary angiogram was performed. Thereafter, the PTCA procedure was completed as to obtain an adequate result according to angiographic criteria. In the control patients without angiographic evidence of intracoronary thrombus formation, 0.2–0.3 mg nitroglycerin was injected via the guiding catheter 10 minutes after successful balloon dilatation followed by a final angiogram.

**Quantitative Coronary Angiography**

Coronary angiography was performed using a simultaneous biplane multidirectional isocentric x-ray system (Siemens Bicor, Erlangen, FRG) at a frame rate of 25 frames/sec with projections that best demonstrated the stenosis to be dilated. End-diastolic cine frames were videodigitized, and quantitative measurements were performed by automatic contour detection as previously described. In brief, quantitative coronary angiography was performed by automatic contour detection using a previously validated geometric edge differentiation technique. Calculation of the exact radiological magnification factor of the measured segments was used to scale the data from pixels to millimeters as previously described. The accuracy and precision of this technique as well as the reproducibility of serial measurements under routine clinical conditions have been established in previous studies. To evaluate the variability of quantitative measurements under the conditions of the present investigation, the reproducibility of the measurements (repeated analysis of the cineangiograms by one analyst after 3 months)
was assessed in the present study (intraobserver variability was expressed as coefficient of variation of repeated measurements, \( n=30 \)). Four coronary artery segments were analyzed in patients undergoing PTCA in the left coronary artery system: 1) the segment immediately proximal to the dilated stenosis, 2) the dilated segment, 3) the segment immediately distal to the site of thrombus formation or a segment immediately distal to the dilated segment in the control patients without angiographically visible thrombus formation, and 4) the segment of a coronary artery not manipulated by guide wire or balloon catheter during PTCA (reference vessel).

In patients undergoing PTCA of the right coronary artery, only segments 1–3 could be analyzed, because all potential reference vessels were instrumented during PTCA.

Four- to 6-mm segments of the coronary arteries were analyzed. For the proximal and distal segment as well as for the reference vessel segment, the mean diameter value was measured, and luminal vessel area, which was assumed to be elliptical, was calculated from both views. In three of the 15 patients (20%) with evidence of intracoronary thrombus formation, overlapping of the distal segment with other parts of the coronary tree in one view allowed only single-plane analysis. In these cases, luminal vessel area was assumed to be circular. For the dilated segment, the minimal absolute diameter in either view was used, and stenosis severity was related to the proximal segment and expressed in percent diameter reduction.

The intraobserver variability of the quantitative measurements of the distal segment in the 15 patients with evidence of intracoronary thrombus formation revealed a coefficient of variation of 2.1±1.1% (\( n=30 \) measurements).
FIGURE 2. Graphs showing individual luminal area changes of distal vessel segment. Left panel: Response to intracoronary thrombus (TH) formation and nitroglycerin (NTG) in the 15 patients with evidence of thrombus formation. Right panel: Response 10 minutes after percutaneous transluminal coronary angioplasty (CT2) and after NTG administration in the 20 control patients without thrombus. CTL denotes control angiogram after successful percutaneous transluminal coronary angioplasty. Solid symbols with error bars indicate mean±SD.

Statistical Analysis
All data are expressed as mean±1 SD. Statistical comparisons were made by analysis of variance for repeated measures followed by the Student-Newman-Keuls test. Statistical significance was assumed at p<0.05.

Results
Table 1 illustrates that there were no significant differences between the two groups with respect to the patient and PTCA procedural data. No patient had a stenosis of greater than 50% diameter reduction after PTCA, indicating that no hemodynamically significant flow obstruction was present during assessment of the coronary vasomotor response to intracoronary thrombus formation. Stenosis severity was reduced by a similar amount in both groups.

There were no significant changes in the hemodynamic parameters of heart rate and blood pressure during intracoronary thrombus formation. Intracoronary nitroglycerin reduced mean blood pressure by −6.1±4.7% in both groups (p<0.01).

Coronary Vasomotor Response of Epicardial Arteries
Figure 1 illustrates a representative vasoconstrictor response of an obtuse marginal branch of the left circumflex artery during formation of an intracoronary thrombus adherent to the guide wire. In the group of patients with evidence of thrombus formation, mean luminal area of the vessel segment distal to the thrombus was reduced from 4.80±0.61 to 3.59±0.82 mm² (p<0.01), reflecting a decrease of −27.4±17.1% compared with the prethrombus values (Figure 2). Intracoronary injection of nitroglycerin almost completely reversed this vasoconstriction, and luminal vessel area returned to 4.73±0.93 mm² (p=NS versus prethrombus value) corresponding to a mean increase of 26.5±19.0%. In contrast, in the patients without any evidence of intracoronary thrombus formation, luminal area of the segment distal to the dilated stenosis remained essentially unchanged (−1.3±11.4% compared with control values, p<0.001 versus thrombus group) but increased by 17.8±14.8% in response to nitroglycerin, indicating preserved vasomotor capability of the analyzed segments (Figure 2). The proximal and the reference vessel segments did not demonstrate any significant luminal area changes during intracoronary thrombus formation in the thrombus group or at recontrol 10 minutes after successful PTCA in the nonthrombus group (Figure 3). However, all segments dilated significantly (p<0.01) in response to intracoronary injection of nitroglycerin (Figure 3). There were no significant differences between the analyzed segments and between both groups with respect to the vasodilatory action of intracoronary nitroglycerin.

In the six patients in whom quantitative angiography was available after advancing the guide wire with the adherent thrombus, vasoconstriction developed at a new site, with a luminal area reduction of −21.9±14.1% compared with the first angiogram after thrombus formation. Figure 4 illustrates the development of vasoconstriction at a new site distal to the thrombus with persistence of proximal vasoconstriction after advancement of the guide wire in the left anterior descending artery. Thus, there was a sequential association between thrombus formation and subsequent constriction of arterial segments exposed to the thrombus.

Discussion
The results of the present study demonstrate that intracoronary platelet aggregation and in situ thrombus formation during PTCA may trigger a local vasoconstriction of epicardial arteries in patients with coronary atherosclerosis. This vasoconstriction is maximal immediately distal to the site of thrombus formation, thus suggesting the local re-
lease of potent vasoconstrictor substances. Intracoronary injection of nitroglycerin abolished the thrombus-induced vasoconstriction.

Mechanisms of Thrombus-Induced Vasoconstriction

A recent case-report study in patients with acute ischemic heart disease syndromes demonstrated intense microvascular constriction after angioplasty of the presumably thrombotic coronary arterial lesions, thus suggesting the release of vasoconstrictor substances from the clot disrupted by balloon dilatation. The present study is the first to describe the occurrence of vasoconstriction of large epicardial coronary arteries in response to intracoronary thrombus formation in the intact coronary circulation. Very recently, an experimental study reported similar findings in an in vivo preparation of local platelet activation in large epicardial canine coronary arteries with endothelial injury. In this experimental model, serotonin and thromboxane A2 appeared to be important mediators of the focal coronary vasoconstriction in vivo, since serotonin and thromboxane A2 receptor antagonists both prevented the dynamic vasoconstriction. In the present study, thrombus-induced vasoconstriction occurred despite oral pretreatment with calcium antagonists, aspirin, and nitrates but was completely reversed by the intracoronary injection of nitroglycerin. These findings are in agreement with experimental studies demonstrating the failure of calcium antagonist and aspirin treatment to prevent the vasoconstrictor effects of aggregating platelets as well as the incomplete prevention of vasoconstriction by intravenous nitroglycerin.
In addition, a number of experimental studies have shown that the endothelium plays a critical role in modulating the vessels' response to various vasoactive substances released during thrombus formation like serotonin, thromboxane A₂, ADP, and thrombin, with endothelial dysfunction greatly potentiating the vasoconstrictor responses to activated platelets. Thrombin, in addition to being a potent platelet activator itself, has been shown to induce the release of endothelin, a very potent vasoconstrictor peptide. Endothelial dysfunction of epicardial arteries is well established in patients with atherosclerosis. Impairment of endogenous endothelial vasodilator mechanisms may thus further contribute to the vasoconstrictor response to intracoronary thrombus formation.

Therefore, it is very likely that the dynamic, focal vasoconstriction of atherosclerotic epicardial arteries in response to intracoronary thrombus formation—observed in the intact coronary circulation of the patients in the present study—results from a combination of the local arterial accumulation of thromboxane A₂ and serotonin (and possibly other mediators of vasoconstriction like endothelin) and relative or absolute decreases in local arterial concentrations of endothelium-derived vasodilators, such as endothelium-derived relaxing factors and prostacyclin.

However, it should be kept in mind that the phenomenon of thrombus-induced vasoconstriction was observed in the setting of coronary angioplasty in a manipulated artery. The coronary segment distal to the lesion being dilated may therefore be exposed to minor trauma from guide wire manipulation, which could theoretically induce coronary vasoconstriction due to endothelial injury with secondary platelet aggregation. This mechanism, however, would not adequately explain the development of vasoconstriction at a new site, which was observed in all patients in whom the thrombus was advanced to a more distal part of the vessel. Thus, the demonstration of a sequential association between thrombus formation and subsequent distal vasoconstriction makes it very unlikely that the observed phenomenon reflects vasoconstriction of a traumatized, hyperreactive vessel segment leading subsequently to proximal thrombus formation. However, we cannot totally exclude the possibility that guide wire trauma may have exacerbated the local constrictor responsiveness of the vessel segments exposed to intracoronary thrombus. Therefore, caution must be exerted to extrapolate the findings of the present study to acute ischemic coronary syndromes.

The development of an intraluminal filling defect adherent to the intracoronary guide wire and remote from the site of balloon dilatation provides unequivocal evidence of intracoronary platelet aggregation and in situ thrombus formation. Although the systemic hemodynamic parameters did not change during the assessment of thrombus-induced vasomotion, thrombus formation might have caused a severe mechanical obstruction leading to a fall in distal arterial distending pressure and resulting in a passive collapse of the arterial lumen distal to the thrombus. However, arterial lumen area was never reduced by more than 70% at the site of thrombus formation during the measurements. In addition, the observed vasoconstriction was a focal localized dynamic process and did not comprise the entire distal vasculature. Most importantly, as illustrated in Figures 1 and 4, advancing the guide wire with the adherent thrombus to a more distal portion of the vessel did not immediately reverse vasoconstriction of the vessel segment at the site now residing proximal to the thrombus. If passive arterial collapse had been responsible for the decrease in luminal area, then advancing the thrombus more distally would have resulted in an immediate reversal of the vasoconstriction of this vessel segment, since vasomotion in response to altered distending pressure is regulated on a beat-by-beat basis. Therefore, passive arterial collapse cannot account for the observed thrombus-induced vasoconstriction.

Recent studies proposed that epicardial coronary artery vasoconstriction, possibly mediated by endothelium-derived cyclooxygenase products, routinely occurs after PTCA not only at the site of balloon dilatation but also distal to this site without angiographic evidence of thrombus formation. This angioplasty-induced vasoconstriction could be prevented by intravenous infusion of nitroglycerin. In this regard, it is important to note that nitroglycerin given intravenously at physiological concentrations very effectively reduces platelet deposition after deep arterial injury in addition to its direct smooth muscle relaxant effect. It is very likely that, although angiographically not detectable, balloon dilatation resulted in platelet deposition and possibly thrombus formation at the site of PTCA in the control group, too. However, the lack of a vasoconstrictor response distal to the site of PTCA in the control group suggests that oral pretreatment with nitrates prevented potential angioplasty-induced vasoconstriction and that platelet deposition was not of sufficient magnitude to induce vasoconstriction of the distal vessel segment. Indeed, Lam et al demonstrated a fairly close correlation between the extent of vasoconstriction and the intensity of platelet deposition in damaged porcine arteries after balloon angioplasty.

**Clinical Implications**

Thrombus-induced vasoconstriction developed despite pretreatment with aspirin, indicating that blocking only the thromboxane A₂-dependent pathway of platelet activation completely prevented neither the development of intracoronary thrombi adherent to the guide wire during PTCA nor the thrombus-associated vasoconstriction. Although intracoronary injection of nitroglycerin completely reversed thrombus-associated vasoconstriction, oral pretreatment with nitrates prevented neither the development of intracoronary thrombi nor the thrombus-associated vasoconstriction. Therefore, further studies aiming at a reduction of thrombus-associated vasoconstriction should use more potent, selective inhibitors of plate-
let metabolism and activation. Encouraging experimental results have not only been reported for thromboxane and serotonin receptor antagonists, but also for hirudin, a potent and specific thrombin inhibitor, and for monoclonal antibodies against platelet membrane receptors.

In addition, although caution must be advised in the extrapolation of the findings of the present study, which was limited to patients undergoing coronary angioplasty, the demonstration of focal vasoconstriction of epicardial arteries in response to in situ thrombus formation in the intact coronary circulation may provide further important insights into the dynamic mechanisms of acute coronary heart disease syndromes in humans. Although the degree of arterial luminal area reduction appears to be rather moderate, thrombus-induced vasoconstriction at the site of a coronary arterial lesion may greatly potentiate stenosis severity and may thereby further decrease coronary blood flow and myocardial oxygen delivery.

References

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