Coronary Artery Disease

Exaggeration of Nonculprit Stenosis Severity During Acute Myocardial Infarction: Implications for Immediate Multivessel Revascularization

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OBJECTIVES
This study was designed to assess the prevalence and clinical significance of exaggerated nonculprit lesion stenosis in the setting of acute (<12 h) myocardial infarction (AMI).

BACKGROUND
Although microvascular spasm may reduce nonculprit artery flow during AMI, it is unknown whether increased tone may exaggerate nonculprit lesion severity.

METHODS
In patients with additional angiography within nine months of AMI, and significant nonculprit lesions imaged in matching views, stenosis severity was compared between studies in a random blinded fashion using validated quantitative coronary angiography software. Baseline demographics, medications, hemodynamics at each study, and clinical status at follow-up (infarct/unstable angina/stable angina) were used to determine the independent influence of the infarct presentation on stenosis exaggeration.

RESULTS
From 548 patients with AMI (1/99 to 6/01, 321 with multivessel disease), 112 had additional angiography; of these 48 had 59 lesions suitable for analysis. Between infarct and noninfarct angiograms there was a significant change in minimal lumen diameter (1.53 ± 0.51 mm vs. 1.78 ± 0.65 mm, p < 0.001) and percentage stenosis (49.3 ± 14.5% vs. 40.4 ± 16.6%, p < 0.0001) of the nonculprit lesion without significant change in reference segment diameter, which was not predicted by changes in medication or hemodynamics. Twenty-one percent of patients had lesions >50% at AMI that were <50% at non-AMI angiography. Infarct versus noninfarct setting was the only significant independent predictor of change in nonculprit stenosis.

CONCLUSIONS
Significant exaggeration of nonculprit lesion stenosis severity occurs at infarct angiography, which may affect revascularization decision making in an appreciable number of patients. (J Am Coll Cardiol 2002;40:911–6) © 2002 by the American College of Cardiology Foundation

Percutaneous coronary intervention (PCI) has evolved substantially over the past quarter century since Andreas Gruntzig's first report of coronary angioplasty (1). Complete revascularization of multivessel disease with PCI is not only feasible, but is associated with less morbidity and similar mortality to bypass surgery even in high-risk patients (2). Improved stent technology and antiplatelet therapy has made it safer such that multivessel PCI in stable patients is commonly being achieved with only one procedure and excellent results (3).

The growing availability of coronary angiographic facilities has meant that PCI is increasingly being used for reperfusion in acute myocardial infarction (AMI), either as the primary modality or as a backup if thrombolysis fails. Around 30% to 60% of patients presenting with AMI have multivessel disease (4–6), and management of nonculprit lesions is controversial (that is, immediate PCI, deferred PCI, or deferred coronary artery bypass grafting [CABG]). The most common approach is to defer nonculprit revascularization away from the unfavorable hemodynamic and metabolic milieu of acute infarction, although in the setting of cardiogenic shock, there appears to be a consensus that ischemia should be relieved not only in the infarct-related artery (IRA) but also in the non-IRA territories (7). Recent evidence suggests that complete revascularization at the time of infarction may be advantageous, even in the absence of cardiogenic shock. First, slow flow in the non-IRA territories is worse with >50% epicardial stenosis, is proportional to percent of stenosis in this range (8), and is associated with reduced non-IRA territory wall thickening, which rapidly improves when flow is returned to normal (9). Second, coronary plaque instability is frequently a multifocal process: multiple complex plaques are often seen at infarct PCI (10) and are associated with a significantly increased risk of recurrent acute coronary syndromes that might be prevented by multivessel PCI (11). Last, simultaneous multivessel PCI at the time of infarction should limit vascular access and anticoagulant-related bleeding compli-
Abbreviations and Acronyms

AMI = acute myocardial infarction
CABG = coronary artery bypass grafting
IRA = infarct related artery
MLD = minimal luminal diameter
PCI = percutaneous coronary intervention
PP = primary PCI
QCA = quantitative coronary angiography
RCA = right coronary artery
RP = rescue PCI

To further complicate the conundrum, it has been our clinical impression that nonculprit lesion severity was often exaggerated at the time of infarction, and that this may have significant effect on clinical decision making regarding further revascularization. Although there is extensive literature on increased microvascular tone at the time of AMI, change in macrovascular tone has never been recognized as a significant source of nonculprit lesion severity exaggeration. We performed a retrospective analysis of all patients who had coronary angiography at the time of AMI, and another coronary angiogram within nine months, to examine the extent and clinical significance of variation in the severity of lesions in the nonculprit artery.

METHODS

We examined our infarct PCI database for all patients who had coronary angiography at the time of confirmed infarction (within 12 h of pain with a view to primary or rescue coronary angioplasty) between January 1999 and June 2001 and had a second coronary angiogram within nine months (before January 1999 images were recorded on video, preventing analysis using digital quantitative coronary angiography [QCA]). Myocardial infarction was confirmed in each patient by a greater than threefold rise in serum creatine kinase-myocardial band or a troponin T elevation above 0.1 ng/ml. Telephone follow-up (95% complete) was used to find all patients who had had another coronary angiogram at another institution. All infarct angiograms were then reviewed by two experienced operators to find those patients who had a lesion in the nonculprit artery of agreed severity >50% (by visual estimation). The culprit was identified as the site of acute occlusion or impaired (< TIMI [Thrombolysis In Myocardial Infarction] 3) flow. If there was normal flow in all vessels, a site with complex plaque was inferred as the culprit by an associated wall motion defect on left ventriculogram. Nonculprit lesions were defined as lesions in an artery other than the infarct-related artery with smooth angiographic borders and no associated thrombus. We then assessed the additional angiograms to ensure that images were obtained in matching projections (they were excluded for >5° difference in any plane). Patients were excluded if nonculprit lesions were revascularized before the second angiogram either by PCI (multivessel PCI at the time of infarction was only performed in patients with cardiogenic shock or multiple culprit lesions) or CABG. End-diastolic images in the least foreshortened view were used to measure lesion severity using the QCA-CMS system (Medis, Leiden, The Netherlands), as previously described (12). First angiographic images from both studies were used (before any intracoronary nitrates were administered). Analysis was performed by two experienced operators who were blinded to the sequence of the angiograms. Patient characteristics recorded included age, gender, Killip class on presentation, medications, atherosclerotic risk factors (smoking history, hypertension, hyperlipidemia, diabetes mellitus, and family history of premature vascular disease), history of coronary artery disease (past angina, AMI, PCI, or CABG), hemodynamics (blood pressure and heart rate at the start of each procedure), and clinical setting of the second angiogram (stable vs. unstable coronary syndrome).

Comparisons of hemodynamic and angiographic data between the two studies were made using paired t tests. Multiple logistic regression was used to adjust for the effects of baseline demographics, changes in medications, changes in hemodynamics, and clinical setting on changes in nonculprit vessel reference diameter and lesion severity. Continuous variables were compared between patient groups using Student t test. Mann-Whitney rank-sum test was used when the data did not fit a normal distribution. Categorical variables were compared between patient groups using chi-square or Fisher exact test where appropriate.

RESULTS

Between January 1999 and June 2001, 548 patients had coronary angiography at time of AMI: 304 for primary PCI (PP, presented with MI to our hospital) and 244 for rescue PCI (RP, presented to a hospital without angiographic facilities and either failed to reperfuse with thrombolysis or were thrombolysis-ineligible). There were 321 patients with operator-reported multivessel disease (176 [58%] from the PP group, 145 [59%] from the RP group). A total of 112 patients (84 PP, 28 RP) had additional coronary angiography within nine months: 14 for assessment of restenosis (asymptomatic), 19 before planned PCI of a nonculprit lesion, 17 before planned CABG, three before noncardiac surgery, and 62 for assessment of recurrent chest pain or anginal equivalent. Of these, 64 had either no significant lesion in a nonculprit vessel (n = 41), had coronary artery grafting of the nonculprit lesion (n = 5), or a matching angiographic view was not available (n = 18). This left 48 patients with 59 nonculprit lesions, and this constitutes our study group.

Patient demographics are shown in Table 1 from the total group, PP, multivessel disease, and the study group. At time of AMI, 45 patients (94%) underwent PCI of the culprit lesion, two (4%) were managed medically and one (2%) had
CABG. A median of 73 days (interquartile range 13 to 135 days) elapsed between angiograms. The additional angiogram was for stable symptoms in 37 patients (77%) and unstable symptoms in 11 patients (23%). 17 were before PCI, seven before CABG, four for restenosis, one before noncardiac surgery, and 19 for assessment of chest pain. No patient was on vasopressor agents at MI or follow-up.

Between infarct and noninfarct angiograms there was a significant change in minimal lumen diameter (MLD) (1.53 ± 0.51 mm vs. 1.78 ± 0.65 mm, p < 0.001) and percentage stenosis (49.3% ± 14.5% vs. 40.4% ± 16.6%, p < 0.0001) of the nonculprit lesion. The nonculprit vessel reference diameter was not significantly different between study dates (3.1 ± 0.8 mm vs. 3.0 ± 0.8 mm, p = 0.3). The differences in hemodynamics and medications between study dates are shown in Tables 2 and 3 respectively. The groups were then divided into right coronary artery (RCA) IRA or non-RCA IRA (Table 2). Diastolic blood pressure was significantly higher in the non-RCA IRA group and heart rate in the non-RCA IRA group at time of the infarct angiogram compared to the RCA IRA group and the noninfarct angiogram. There was no association on multiple logistic regression between the difference in hemodynamics or medication and the change in nonculprit lesion MLD or percentage stenosis (all p > 0.30).

Ten lesions (17%) in ten patients (21%) had nonculprit lesions of >50% stenosis at time of AMI that were < 50% stenosis at time of non-AMI angiogram. In this group there was a marked improvement in MLD (1.15 ± 0.35 mm vs. 1.70 ± 0.68 mm, p < 0.05) and percentage stenosis (60.2 ± 9.2 vs. 39.0 ± 6.6, p < 0.001), but no significant change in reference diameter (3.0 ± 0.8 vs. 2.8 ± 1.0). If infarct angiography were used to determine revascularization strategy in these patients, they would be unnecessarily subject to the risks of that strategy, be that PCI or CABG. This group could not be predicted on the basis of infarct heart rate (71.2 ± 12.7 vs. 74.2 ± 15.1, p = 0.58), systolic blood pressure (129.5 ± 28.2 vs. 124.3 ± 22.3, p = 0.61), or Killip class 1/2/3 (41/5/2 vs. 10/0/0 p = 0.41).

**DISCUSSION**

This study shows that severity of stenosis in moderately obstructive nonculprit lesions is frequently exaggerated at the time of myocardial infarction. These observations have
important implications for decision making on complete revascularization strategy in patients with multivessel disease. Potential causes for the dynamic component of nonculprit stenosis include vasoconstriction, thrombus, plaque regression at follow-up, or changes in reference segment vessel tone, although vasoconstriction would appear the most likely. In light of these findings, immediate PCI of nonculprit lesions may expose the patient to unnecessary risks of both acute complications and restenosis. If deferred nonculprit revascularization is the chosen strategy, repeat angiography may help prevent unnecessary procedures in these patients.

This study is the first to systematically assess the severity and clinical importance of nonculprit lesion exaggeration during myocardial infarction. A previous case report of significant vasospasm of a nonculprit lesion at the time of myocardial infarction (13) might easily have originated from a patient in whom myocardial infarction resulted from extreme vasospasm rather than plaque rupture and thrombosis, making its general applicability unknown. This study shows that exaggeration of nonculprit lesions is common and, if immediate revascularization were to be attempted on all lesions of >50% stenosis, would prompt unnecessary PCI in one in five patients with multivessel disease.

**Potential sources of nonculprit lesion exaggeration.** The reasons why nonculprit lesions become less stenotic at follow-up include vasoconstriction of the lesion, relative vasodilation of the angiographically normal reference segment or thrombus at the lesion site during AMI, regression of nonculprit lesions with lipid-lowering therapy, and change in medication and hemodynamics, although vasoconstriction at the time of infarction would seem the most likely. It is unlikely that our findings could be explained by relative vasodilation of the reference segment during AMI, as the reference segment diameters were similar between study dates. Changes in medication between the study dates had no effect on stenosis severity by univariate or multivariate analysis. Although angiotensin-converting enzyme inhibitor and statin therapy became more frequent, intravenous nitrate therapy was less frequent at follow-up, and the association of these opposing changes may have helped to conceal any specific effect. Many patients had statin therapy initiated at the time of infarction; regression in angiographic stenosis, which would be expected with such therapy over this time period (14), is far less than we observed. Only angiographically smooth nonculprit lesions were included in this study, so thrombus dissipation is unlikely to be responsible. Furthermore, if the nonculprit lesions had unidentified plaque rupture and thrombus, available evidence from angiographic follow-up of unstable lesions suggests they would get more rather than less stenotic (15).

Thus, vasoconstriction would seem the most likely cause of nonculprit lesion exaggeration. Circulating catecholamine levels are increased during AMI and significantly enhance microvascular coronary resistance reducing non-IRA flow (8,9). In an attempt to evaluate whether variation in sympathetic tone could be responsible, we correlated changes in heart rate and blood pressure with changes in stenosis severity and found no significant association. However, RCA-related infarction may reduce heart rate and blood pressure through conduction system and right ventricular ischemia, respectively. In patients with non-RCA AMI, diastolic blood pressure was significantly higher and there was a trend toward higher systolic blood pressure,
providing some evidence of increased sympathetic drive. However, even in the non-RCA group these changes in hemodynamics between studies did not correlate with changes in nonculprit stenosis. Bioactivity of several other important coronary vasoconstrictors, including serotonin, endothelin, angiotensin, and thromboxane, is also increased during myocardial infarction (16,17), whereas oxidant stress reduces the vasodilatory effects of nitric oxide, adenosine, and prostacyclin (18,19). However, as this was a retrospective study, we could not obtain direct evidence of the relative contribution of each of these biochemical abnormalities. An accurate assessment of the relative importance of specific vasoconstrictors would require further study with sequential administration of selectively targeted intracoronary vasoconstrictors and may enable exclusion of nonculprit coronary stenosis reversibility.

**Study limitations.** This study has several limitations. First, it is a retrospective study where the study group may be subject to selection bias; those patients who were subject to repeat angiography may be not totally representative of all patients undergoing infarct PCI. The most obvious factor that reduced the chance of repeat angiography was whether the patient was having primary or rescue PCI. This most likely relates to understandable differences in practice in centers with and those without angiographic facilities. Demographics were very similar in the whole group and the PP group (and thus by subtraction the RP group), suggesting that the findings in PP are likely to be similar in those RP patients who did not have repeat angiography. Second, although off-line QCA analysis methods were standard, acquisition was not uniform. In our lab most angulation and tower heights are standard with a constant source to patient length and minimal tower height for each view, creating some reproducibility: only 18 of a possible 66 patients were excluded because of variation in views. Last, because of the almost uniform therapy with nitrates at AMI and angiotensin-converting enzyme inhibitors and statins at follow-up, the ability of multiple logistic regression to discern the importance of these therapy differences in reduced nonculprit lesion stenosis is limited.

**Clinical implications.** Nonculprit PCI at the time of AMI may be associated with increased risk of acute closure and restenosis due to high circulating levels of procoagulants and growth factors respectively. However, evidence has lately been accumulating in favor of nonculprit PCI. Recent angiographic evidence suggests that plaque instability is a multifocal process and that unstable lesions in the non-infarct-related artery predispose to recurrent acute coronary syndromes (11). Serologic evidence shows that markers of arterial wall inflammation are often persistently elevated after infarction and predict further acute coronary syndromes (20). In addition, flow in nonculprit arteries is significantly impaired at the time of infarction, and restoration of normal flow in the non-IRA territory appears to aid recovery of left ventricular function after myocardial infarction (9). The only published data on this controversy is a retrospective case-control study comparing multivessel PCI at the time of infarction with a staged approach (21). Immediate nonculprit PCI had a 96% success rate, a figure that would seem to argue for immediate nonculprit PCI rather than against it, but was associated with an excess of death and stroke, despite matching for age and Killip class. Randomized data would help clarify this apparent contradiction.

Amidst this confusion, our data would suggest that some nonculprit interventions may be avoidable in such an unfriendly and uncertain milieu. If vasoconstriction is the main cause, it would be useful to develop a safe and effective protocol to identify those patients in whom nonculprit PCI is unnecessary to improve the risk-benefit ratio of immediate PCI, or to accurately identify those lesions that should be revascularized when the dust has settled.

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