Nuclear Cardiology After Angioplasty and Stent Placement: Beyond Sensitivity and Specificity*

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Despite excellent immediate clinical results and anatomic improvement of critical coronary artery stenosis, functional abnormalities have been noted to persist for several days or weeks after successful percutaneous transluminal coronary artery balloon angioplasty (PTCA) (1–13). Even without eventual angiographic restenosis, persistent abnormalities of wall motion (1,2), myocardial perfusion (3–8) and coronary blood flow dynamics (9–13) have been reported early after successful PTCA. The clinical and pathophysiologic significance of these persistent functional abnormalities have remained elusive since they were first described more than 15 years ago. Is there light at the end of the tunnel? We will briefly summarize the extensive nuclear cardiology data as it relates to the functional abnormalities present early after PTCA and stent placement, including the study of Kosa et al. (14) published in this issue of the Journal of the American College of Cardiology.

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The past. Successful PTCA results in marked anatomic, physiologic and clinical improvement. Thus, minimal lumen coronary artery stenosis, stress-induced myocardial perfusion and wall motion abnormalities and coronary blood flow reserve (CFR) all improve significantly with successful PTCA. In contrast to the immediate clinical improvement, with resolution of symptoms when complete revascularization is achieved, abnormalities of coronary flow, perfusion and function resolve more gradually in a substantial proportion of patients (1–13). Using rest and exercise radionuclide ventriculography, persistent wall motion abnormalities in the vascular territory of the culprit lesion were reported to persist one day to one month after successful PTCA (1,2). Regional wall motion abnormalities during exercise were noted in 12 (29%) of 41 patients studied by DePuey et al. (1) and in 31 (65%) of 48 patients studied by O’Keefe et al. (2); yet most patients with persistent early wall motion abnormalities had widely patent vessels during follow-up coronary angiography four to 18 months after PTCA. What are the mechanism(s) of the delayed resolution of wall motion abnormalities after successful PTCA? Could they relate to restenosis? Let us examine further the results from the pooled data of these two studies (1,2). Of the 43 patients with an abnormal early rest–exercise radionuclide ventriculogram, 19 patients (44%) developed late angiographic restenosis. In contrast, of the 46 patients with a normal early radionuclide ventriculogram, only 2 (4%) developed late restenosis. Although data derived from radionuclide ventriculography do not offer direct coronary anatomic insights, they raise the possibility of common mechanisms being responsible for both the wall motion abnormalities early after PTCA and late restenosis.

Using stress myocardial perfusion imaging, several investigators have documented persistently abnormal scans 12 h to six weeks after successful PTCA in a significant number of patients without evidence of restenosis during clinical and angiographic follow-up (3–8). Pooled data of four studies with adequate angiographic follow-up (3–6) show that although myocardial perfusion in the territory of the dilated coronary vessel improved from the pre–PTCA studies, it remained abnormal in 99 (41%) of 242 patients in studies performed early after PTCA. During sequential myocardial perfusion studies (3,7), approximately one-half of patients with an abnormal scan early after balloon angioplasty had normal studies at three to 10 months after PTCA. What are the mechanism(s) for an abnormal stress perfusion scan very early after successful PTCA? Could they relate to those of restenosis? Analysis of the pooled data shows that 53 (53%) of the 99 patients with an “abnormal” early perfusion scan developed angiographic restenosis during late follow-up at six to 18 months after PTCA. More remarkably, only 17 (12%) of the 143 patients with a normal early myocardial perfusion scan subsequently developed angiographic restenosis (3–6). Such results led Wijns, Hardoff and Jain and colleagues (4–6) to conclude that an abnormal early post–PTCA perfusion scan was useful in separating groups with high versus low risk for late restenosis. These data do not offer pathophysiologic insights but suggest that the mechanisms for restenosis may be the same as those responsible for the slow resolution of perfusion abnormalities after PTCA.

Similar observations have been made during measurements of CFR before and after PTCA. The CFR improves immediately after successful and seemingly uneventful PTCA, but in a significant number of patients it remains below normal levels (9–13). Again, most patients with abnormal CFR early after PTCA do not develop clinical or angiographic restenosis, and in these patients, CFR im-

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proves further with time and normalizes by 3 to 12 months after PTCA (9,10). What are the mechanisms for subnormal CFR immediately after PTCA? It seems clear that there is a significant relation between post-PTCA CFR values and measures of procedural vessel injury such as residual cross-sectional areas and residual pressure gradients (10,12). Does abnormal CFR early after PTCA predict the development of later restenosis? Although a large proportion of patients (40% to 100% in individual studies) have abnormal CFR soon after PTCA, only ~50% of such patients develop late restenosis.

The present. A variety of local factors of anatomic and functional integrity, such as intimal tears, intimal flaps, plaque rupture, endothelial hemorrhage, mural thrombus, deposition of fibrin (15) as well as inflammation, recoil and local spasm (16,17), leading to residual stenosis, may be the main determinants of the early abnormalities of function, perfusion and flow after PTCA (10–12,18). The subsequent disposition of these local factors as vascular remodeling unfolds may determine late restenosis after PTCA (18,19). Standard visual angiographic assessment of lumen diameter narrowing is an imprecise and inaccurate method of quantifying the actual cross-sectional area of a stenosed vessel; this approach may be even less accurate immediately after PTCA. However, the residual cross-sectional area, measured using intravascular ultrasound (19) or digital quantitative analysis of coronary angiograms (18) immediately to 24 h after PTCA, appear to predict late restenosis. Alternatively, other nonlocal factors, such as abnormal vascular reactivity and autoregulation, cell dysfunction due to prolonged or repetitive ischemia, reperfusion injury, diffuse atherosclerosis of large epicardial coronary arteries and microvascular disease, could modulate the early abnormalities after PTCA (1,3,12). The findings of Kosa et al. (14) suggest that local factors may be the key players involved in the pathophysiology of the early functional, perfusion and flow abnormalities noted soon after balloon angioplasty. These investigators used state-of-the-art positron emission tomographic (PET) techniques, with 13N-ammonia, to measure coronary blood flow at baseline and at maximal vasodilation. They found that CFR improved immediately after stent placement to levels comparable to other reference regions. The use of stents, as opposed to balloon angioplasty alone, is associated with larger residual cross-sectional areas, owing in part to wall wrapping of intimal flaps. In addition, stents reduce the tendency for vascular spasm and recoil. The different response of CFR to these two forms of revascularization suggests that local vascular abnormalities incurred at the time of mechanical intervention are the determinants of the early post-PTCA functional, perfusion and blood flow abnormalities.

The results of the study of Kosa et al. (14) need interpretation in the context of the patient group chosen and the study design used. Ideally, the effects of stent placement on CFR should be studied in patients with single-vessel coronary artery disease. If adjacent regions are to be used for control purposes for measurements of blood flow, they must be supplied by angiographically normal coronary arteries. Significant coronary artery lesions detected by vascular ultrasound or at autopsy may appear mild on angiography (18,19). The greater CFR Kosa et al. (14) found in regions where stents were placed may be explained by their inclusion of patients with mild disease in coronary arteries of reference regions. Their reported levels of CFR are low in both stented and remote vessel areas, in agreement with previous studies (20). In addition, considering previous studies before and after PTCA, serial measurements of CFR would have been useful to understand the time-related changes that follow placement of coronary stents. Despite these limitations, their results agree with the findings of Haude et al. (21). These investigators measured myocardial perfusion reserve (MPR), using digital subtraction coronary angiography, in 25 patients with single-vessel coronary artery disease involving the left anterior descending coronary artery and no previous myocardial infarction. Measurements of MPR were made consecutively during a single session at baseline, after PTCA and again after stent placement. They found that although MPR improved, it remained subnormal after PTCA but normalized immediately after stent placement. The progressive increase of MPR at baseline, after PTCA and after stent placement correlated with a progressively larger vascular lumen and a more pronounced inhibition of elastic recoil after stent placement (21).

The future. Before accepting CFR measurements as a useful tool for the detection of restenosis soon after stent placement, more information is needed regarding the normal values of CFR, the individual variability of repeated measurements, the time course of CFR after stenting and its relation with other measures of coronary anatomy and function. Routine stress–rest myocardial perfusion studies, exercise radionuclide ventriculography and measurements of CFR soon after coronary interventions have no place in the care of the individual asymptomatic patient in an attempt to predict restenosis. In contrast, noninvasive cardiac studies, including 13N-ammonia PET measurements of CFR, are useful tools to detect restenosis in symptomatic or asymptomatic patients when used three months or longer after coronary interventions. Studies performed one day to eight weeks after PTCA (and possibly stent placement [see later discussion]) are of dubious clinical relevance, because abnormalities may indicate that restenosis is already present or they may reflect a dilated vessel still undergoing remodeling and scarring, which ultimately may or may not restenose. Nevertheless, a normal study in a symptomatic patient is reassuring even when performed early after coronary interventions.

Until the problem of restenosis after PTCA and stent placement is solved, early detection of patients at high risk
for restenosis is important. In the quest for a solution to this problem, there continues to be a large number of trials testing methods to prevent restenosis. The use of myocardial perfusion, wall motion or CFR measurements early after coronary interventions as surrogate end points for restenosis in these study groups is an intriguing possibility that needs to be tested.

Kosa et al. (14) suggest that, unlike the post-PTCA situation, common noninvasive imaging methods to detect myocardial ischemia may be useful to detect restenosis early after stent placement. Before accepting this suggestion, further studies are necessary to see if early abnormalities of systolic function and perfusion, similar to those present early after PTCA, are also present after placement of stents. The time sequences of wall motion, myocardial perfusion and coronary blood flow abnormalities after stent placement and their correlation with other variables of coronary anatomy and function and with the eventual development of restenosis are some of the specific areas that need to be investigated. By further defining the similarities and differences between the vascular and myocardial responses elicited by balloon angioplasty and stent placement, our understanding of these two popular and widespread methods for revascularization will increase.

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