Molecular Cardiology

Intracoronary Growth Factor and Myocardial Perfusion

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The treatment of patients with severe and extensive coronary artery disease (CAD) is problematic and often frustrating. While we are able to help many more patients than ever before because of the continuing evolution of revascularization procedures, many patients who are either incapacitated or at high risk remain untreatable. These patients constitute the greatest "growth market" for cardiology. This group includes those with severe left ventricular dysfunction or refractory angina who are not candidates for coronary artery bypass surgery (CABS) or percutaneous transluminal coronary angioplasty. Among the exciting new developments for the treatment of these patients is the application of molecular cardiology techniques. The use of therapeutic angiogenesis—the induction of growth of new vessels triggered by growth factors such as recombinant human vascular endothelial growth factor (rhVEGF)—has been reported in a number of studies. Preliminary results claim enhanced collaterals (demonstrated by catheterization) and improvement in symptom status.

Effect of Intracoronary Recombinant Human Vascular Endothelial Growth Factor on Myocardial Perfusion: Evidence for a Dose-Dependent Effect

Hendel RC, Henry TD, Rocha-Singh K, et al.
Circulation. 2000;101:118-121.

Hendel and colleagues from Northwestern University reported the results of serial imaging with stress myocardial perfusion single-photon emission CT (SPECT) in a cohort of patients undergoing intracoronary administration of rhVEGF as part of a phase 1 trial.

In this study, 14 patients with known severe CAD that was not amenable to revascularization with conventional approaches were identified. Exclusion criteria included recent myocardial infarction or CABS, diabetes, and cancer within the past 5 years, thus limiting the study to stable patients. Those in the study received 4 doses of rhVEGF, either low-dose (between 0.005 and 0.017 µg/kg) or high- dose (0.05 and 0.167 µg/kg) via selective intracoronary injection. Patients underwent either exercise or dobutamine infusion or received dipyridamole to induce stress and had stress and rest SPECT imaging performed at baseline (pretreatment) and at 30 and 60 days post-treatment. The SPECT images were interpreted both quantitatively and semiquantitatively, the latter by using a 5-point, 20-segment scoring system.

No difference was present after treatment with respect to the extent and severity of perfusion defects on the stress images. Improvements were present in the rest SPECT images, which are thought to reflect resting myocardial blood flow. Using quantitative software, investigators found that rest perfusion improved at 30 days, only to worsen at 60 days. By semiquantitative methods, the number of abnormal segments on the rest images significantly decreased with treatment. Importantly, when patients were subgrouped by the dose of rhVEGF received, a significant reduction in semiquantitative scores for the rest images was present at 60 days, although no difference was present in the stress scores. Interestingly, of the 7 patients who underwent serial catheterization, the 4 who received high-dose rhVEGF had a statistically significant improvement in collateral count density.

The cardiology community eagerly awaits further data on the results of these exciting new agents. The current study is important in that although no change in the stress images were found by SPECT, rest flow appears to improve in certain patients.

If the mechanism of action of VEGF and other similar agents is the growth of new collateral vessels, the results reported by Hendel and colleagues should not be surprising. Among patients routinely referred for stress SPECT evaluation who have complete occlusion of a coronary artery with angiographically demonstrated collaterals, several patterns of stress and rest perfusion can be seen. If no infarction has occurred and rest flow through the collaterals is sufficient, then the rest images are normal; the stress images, however, may be either normal (collaterals have sufficient reserve to achieve a 3- to 4-fold increase in flow reserve) or abnormal (collaterals can achieve adequate rest flow, but insufficient reserve is present to achieve higher flow levels). Collateral flow, in certain instances, may be insufficient to achieve adequate rest flow, and resting defects may be present as well (whether these defects represent hibernation or infarction can be determined by a viability study). It remains to be seen whether other factors—new agents, different vectors,

more time after treatment to permit therapeutic benefit, patient selection, adjunctive treatments, etc—may modify the presence and impact of these collaterals.

Unfortunately, certain particulars have been omitted from the report. The difference between the areas of abnormality on the stress and rest images equals the amount of stress-induced ischemia. In the current study, if the overall defect size did not change and the rest defects got smaller, did the amount of inducible ischemia increase? After all, if the growth of collaterals enhanced rest flow and resolved resting defects, paradoxically, the amount of stress-induced ischemia may increase. In the current study, the ischemic variables were not included.

Also, there is no mention of which isotopes were used for the rest and stress images and whether all patients received the same protocol. It is difficult to interpret these results without knowledge of the agent used for the studies. If these were stress-redistribution thallium protocols, then the rest images would identify hypoperfused but viable myocardium, and these findings would suggest that the treatment yielded normal flow to previously hibernating regions. If the rest agent was a technetium Tc 99m sestamibi (^{99m}Tc sestamibi), the amount of improvement detected may be decreased, since many would claim that a 4-hour redistribution thallium image would detect more viability than a resting ^{99m}Tc sestamibi study.

Finally, it must be said that investigators who have participated in the various ongoing VEGF studies are unsure about the optimal agent and protocol for assessing this new treatment. Given these early, promising results and the important potential benefits of this treatment, we can be certain to see further studies.

Nuclear Cardiology

Incorporation of Electron Beam CT into Routine Testing Algorithms: Do We "Just Do It?"

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Two distinct phenomena have marked the medical landscape during the past decade. On one hand, a plethora of new technology has emerged, as evidenced both by the dramatic acceleration of the technology of the testing we currently use and by the development of new and exciting technology that may be added to our noninvasive testing armamentarium. On the other hand, the need to contain the costs of medical care has infiltrated our health care system and has shifted the process by which we evaluate technology. Thus, we now attempt to evaluate new technology by means of "evidence-based medicine." Simply put, we must now subject each new modality to strict criteria when evaluating its performance characteristics prior to its clinical acceptance (ie, reimbursement).

Among these criteria are the need for evidence that the new modality in question will be able to yield added or incremental value over that provided by the tests ordinarily performed prior to the new test. For stress imaging modalities, this is shown by demonstrating with an appropriate analysis that stress nuclear CT or echocardiography adds incremental value toward a defined diagnostic or prognostic end point after adjusting for clinical, historical, and treadmill testing information. The newest noninvasive testing modality, electron beam CT (EBCT), used to detect and quantify the extent of coronary artery calcification, is now the target of heated debate as to whether it adds incremental value over other sources of clinical information.

Identification of Patients at Increased Risk of First Unheralded Acute Myocardial Infarction by Electron Beam Computed Tomography

Raggi P, Callister TQ, Cooil B, et al.
Circulation. 2000;101:850-855.

Raggi and colleagues, from one of the premier EBCT centers in the country, reported on the use of EBCT to predict the occurrence of myocardial infarction (MI) in patients referred for evaluation with this test because of cardiac risk factors. The authors studied 2 cohorts: the first consisted of 172 patients whose MIs were their initial manifestation of coronary artery disease (CAD) and who underwent EBCT scanning shortly thereafter (3 to 60 days; mean, 31 days); the second consisted of 632 patients with no CAD history who underwent EBCT for evaluation of cardiac risk factors and were followed for occurrence of cardiac death or MI for a mean of 32 months. The goal of the authors was to compare the value of absolute calcium scores (a measurement of coronary artery calcification) in these patients with the calcium score percentile (from a large cohort previously tested) as predictors of adverse outcomes.