Nitrates and viability: a durable affair.

INVITED COMMENTARY

Nitrates and Viability: A Durable Affair

The relationship between nitrate administration and viability detection dates back many years. Already in the 1970s, various groups had demonstrated that an improvement in regional left ventricular function produced by the acute administration of nitrates was related to a subsequent favorable response after coronary bypass surgery (*1,2*). In particular, Helfant et al. (*1*) showed that 15 of 18 asynergic segments with improvement after sublingual nitroglycerin had a similar improvement after bypass grafting, whereas the 2 segments with persistent dysfunction after nitroglycerin were unchanged even after bypass surgery. Similarly, Chesebro et al. (*2*) observed a good correlation between the changes in wall thickening produced by sublingual nitroglycerin and those registered several months after bypass surgery. Giving a histologic substrate to these clinical observations, Bodenheimer et al. (*3*) detected a lower degree of fibrosis in the nitrate-responsive segments than in the other asynergic segments. To explain these data, various mechanisms of action were suggested. Certainly, nitrates positively affect the relationship between myocardial oxygen supply and demand, mainly through the reduction in preload and afterload of the ventricles (*4*). However, it was also suggested that at least part of this effect was caused by a direct action on coronary circulation, either by vasodilatation of stenoses or by redistribution of flow to the ischemic areas, particularly through collateral vessels (*5,6*). The role of collateral circulation was confirmed in animal experiments by Hisano et al., who demonstrated that the improvement in regional function under isosorbide dinitrate was related to the degree of development of collaterals (*7*). In humans, Fujita et al. (*8*) observed that in patients in whom the territory of a completely occluded left ventricular descending artery was supplied by a good collateral circulation, both global and regional function improved significantly after sublingual nitroglycerin, whereas no change was registered in the remaining patients with occlusion but without collaterals. In all the above studies, attention was given mainly to the functional changes induced by nitrate administration. However, in good agreement with the hypothesis of a direct action on coronary collateral circulation, Aoki et al. demonstrated that in collateral-dependent noninfarcted myocardium the acute administration of nitroglycerin reduced the extent and severity of the ^{201}Tl myocardial perfusion defect induced by exercise (*9*).

In the second half of the 1980s, the concept of hibernating myocardium, that is, chronic regional asynergia of ischemic origin with reversible dysfunction after successful revascularization, was introduced and deeply modified the diagnostic approach to heart failure in patients with coronary artery disease (*10*). Perfusion/metabolism imaging with PET emerged as the most accurate test to detect viable hibernating myocardium and was found to be more reliable than stress-redistribution ^{201}Tl myocardial perfusion scintigraphy (*11*). To overcome the limitations of stress-redistribution scans and because of the need to evaluate large numbers of patients, modifications of the standard ^{201}Tl imaging protocol were proposed. Delayed redistribution (*12*), rest-reinjection (*13*), and rest-redistribution (*14*) were tested and had good results for viability detection. The possibility of using the acute effects of nitrate on coronary blood flow to improve the detection of viable hibernating myocardium was examined for the first time by He et al., who demonstrated the increase in ^{201}Tl defect reversibility if the tracer was reinjected after isosorbide dinitrate administration (*15*). However, because all of the various protocols proposed for viability detection were effective, nitrate-enhanced imaging was not considered essential if ^{201}Tl was chosen as the perfusion agent. In the case of ^{99m}Tc-labeled perfusion tracers, several early reports suggested an underestimation of myocardial viability in the standard resting images obtained using these agents (*16,17*). The imaging protocol modifications used for ^{201}Tl imaging were hardly feasible with the ^{99m}Tc-labeled perfusion tracers, although resting ^{99m}Tc-sestamibi quantitative SPECT (*18*) and redistribution images (*19*) were reported to achieve quite good results. In contrast, the experimental data clearly showed that all ^{99m}Tc-labeled agents available for clinical use (^{99m}Tc-sestamibi, ^{99m}Tc-teboroxime, and ^{99m}Tc-tetrofosmin) were not just pure flow tracers but also required myocyte viability to be retained within the myocardium (*20–22*). Therefore, the use of nitrate enhancement appeared an attractive approach to improve their ability to recognize viable myocardium. Bisi et al. observed that stress defect reversibility in resting ^{99m}Tc-teboroxime images was greater after nitrate enhancement, with a closer agreement to ^{201}Tl reinjection data (*23*). In patients with previous myocardial infarction, Galli et al. found a sizable decrease in resting ^{99m}Tc-sestamibi uptake defects after nitroglycerin administration in 20 of 36 subjects and correlated it with indexes of likely preserved viability (*24*). Finally, Bisi et al., using ^{99m}Tc-sestamibi SPECT, demonstrated for the first time a direct relationship be-

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tween nitrate-induced improvement in myocardial perfusion and regional functional recovery after coronary revascularization (*25*). In a patient population with left ventricular dysfunction and coronary artery disease that underwent successful revascularization, 7 patients showed significant functional recovery in at least 1 dysfunctional coronary territory and 11 showed an unchanged wall motion pattern in all asynergic territories: In the first group a decrease in the extent of the baseline perfusion defect was observed after isosorbide dinitrate infusion ($-37.4\% \pm 21.6\%$), whereas in the second group no change in perfusion defect extent was registered in nitrate-enhanced imaging ($+5.8\% \pm 8.4\%$, $P < 0.0005$ vs. the first group). Since then, several articles have confirmed the reliability of nitrate ^{99m}Tc-sestamibi scintigraphy for the recognition of viable myocardium within dysfunctional segments and the prediction of regional functional recovery (*26–29*). Similarly, nitrate administration increased the rate of defect reversibility in ^{99m}Tc-tetrofosmin scintigraphy and improved its agreement with ^{201}Tl (*30*,*31*). Even the use of ^{201}Tl nitrate-enhanced imaging was confirmed to be helpful for viability detection (*32*).

Despite the general agreement that the results of nitrate-enhanced perfusion imaging for predicting regional improvement compare well with other established methods (*33*), a clear-cut demonstration of the effects of nitrate administration on coronary circulation in the setting of viable dysfunctional myocardium was still lacking. Using PET and $^{13}NH_3$, Fallen et al. had demonstrated that the topical application of nitroglycerin produced a preferential increase in tracer retention in ischemic versus nonischemic segments (*34*). Their patient population, however, did not include patients with left ventricular dysfunction, and the segment characterization was based on a stress-induced ^{201}Tl defect; thus, there was no clear relationship between a preferential nitrate-induced increase in coronary blood flow and myocardial viability. The study by Tadamura et al. (*35*) that appears in this issue of *The Journal of Nuclear Medicine* tries to fill this gap, examining the changes induced by the acute administration of nitroglycerin on coronary blood flow in different groups of myocardial segments classified on the basis of one of the currently used techniques for viability detection, that is, ^{201}Tl rest-redistribution SPECT. The authors identify 4 groups of regions: segments with normal uptake, segments with reversible defect (ischemic), segments with mild-to-moderate fixed defect (viable), and segments with severe fixed defect (nonviable). Measuring the absolute myocardial blood flow with ^{15}O-water, the authors observed a preserved myocardial blood flow in front of a decrease in systemic arterial pressure in the segments classified as either ischemic or viable; this result was produced by a selective decrease in coronary vascular resistance in these 2 groups of segments (from 141 ± 50 to 114 ± 29 mm Hg/[mL/min/g], $P = 0.004$, and from 165 ± 64 to 149 ± 60 mm Hg/[mL/min/g], $P = 0.003$, in the ischemic and in the viable segments, respectively). Conversely, both the normal segments and those with a persistent severe reduction in ^{201}Tl uptake showed a decrease in myocardial blood flow after nitrate administration because the drop in arterial pressure was not compensated for by a reduction in coronary vascular resistance. These results are interesting because they are the first direct demonstration that the effects of acute nitrate administration on coronary blood flow are not only selective but also remarkably favorable for the detection of ischemic viable myocardium. Thus, Tadamura et al. give a physiopathologic support to the above-mentioned clinical studies reporting the accuracy of nitrate-enhanced imaging protocols for the issue of viability detection. However, various problems still remain.

First, and as recognized by the authors, the limitations of the study must be considered. The patient population is not one for which the issue of viability is of major clinical relevance because most patients had a normal or near-normal left ventricular function and only 9 of 23 patients had a left ventricular ejection fraction $\leq 40\%$. Also, the reference method used by Tadamura et al. (*35*) to define the viability status of the myocardial segments is not optimal. Although widely used in clinical practice, ^{201}Tl rest-redistribution cannot be considered the ultimate standard of myocardial viability. In particular, the specificity of this technique is well known to be relatively low (*33*). It is reasonable to assume that at least part of the segments considered viable according to the rest-redistribution scan result were not liable to functionally improve after revascularization and were hence nonviable according to the prevailing notion. Furthermore, no functional correlates of ^{201}Tl uptake have been examined, so that it is impossible to understand whether there is a relationship between degree of functional impairment and nitrate-induced changes in coronary vascular resistance. Certainly, these limitations in patient selection and study protocol do not cancel the value of the report by Tadamura et al. but require that further studies be performed in which myocardial blood flow measurement under nitrate is examined while taking into account both baseline regional function and its evolution after revascularization.

Other problems are related to the more general issue of the role of baseline resting hypoperfusion in determining reversible dysfunction of the myocardium. The demonstration that nitrates induce a decrease in coronary vascular resistance in viable segments agrees with the classic concept that reversible dysfunction is caused by a status of chronic hypoperfusion (*10*). This concept, however, is not unanimously accepted, and the possibility that reversible dysfunction is caused by a status of repeated stunning in the presence of a severe reduction in coronary reserve, but with preserved resting perfusion, must be considered (*36*). Most probably, there is a continuous spectrum of conditions ranging from true hibernation to minimal-threshold

ischemia with repetitive stunning (*37*). It is reasonable to hypothesize that the role of nitrate imaging could be slightly different under these conditions. Particularly with ^{99m}Tc-labeled perfusion tracers, and so excluding the effects of redistribution, resting uptake should usually be preserved in the case of chronic stunning, similarly to what has been already demonstrated after acute myocardial infarction treated by effective reperfusion (*38*), whereas nitrate administration would be necessary to allow a recognizable uptake in segments with true hibernation. If this hypothesis were true, nitrate imaging could be useful not only to overcome the imaging limitations of nonredistributing ^{99m}Tc-labeled perfusion tracers but also to differentiate between the 2 different conditions of reversible ischemic dysfunction. This problem could have important clinical implications. For instance, a different time course of functional recovery after revascularization in hibernating versus stunned myocardium has been observed (*39*). Furthermore, it cannot be excluded that hibernation and chronic stunning have different prognostic implications.

Another point to be clarified is whether the response to nitrate administration could be helpful to differentiate between viable myocardium liable to functionally improve after revascularization versus partially preserved viability in the instance of nontransmural necrosis, which could be valuable to prevent ventricular remodeling but should not be expected to recover after revascularization (*40*). In other words, nitrate imaging could play a role in improvement of the specificity of myocardial perfusion SPECT for the issue of viability detection, at least in terms of recognition of reversible dysfunction.

In conclusion, the study by Tadamura et al. (*35*) gives important support to the use of nitrate-enhanced imaging for the detection of viable myocardium. At the same time, it also justifies the need for further studies to improve our knowledge of the different physiopathologic conditions that subtend the presence of ischemic and possibly reversible myocardial dysfunction. Nitrate-enhanced imaging could play an interesting role in this kind of study about myocardial viability. The story of this durable affair goes on.

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