Renal Effect of Low-Dose Dopamine in High-Risk Patients Undergoing Coronary Angiography

Gare et al. (1) report no advantage of dopamine over “adequate hydration” in patients with mild to moderate renal insufficiency undergoing coronary angiography. The absence of a clinically important effect is no surprise, for dopamine (2 mg/kg/min) would not be a sufficient vasodilator to counteract such a potent renal afferent arteriolar vasoconstrictor as intrarenal adenosine. The kidney responds to contrast media-induced osmotic stress with afferent arteriolar vasoconstriction. This tubuloglomerular feedback response is largely mediated by adenosine, a mechanism that has been confirmed by both animal and clinical studies (2–5). In our randomized and blinded studies, the magnitude of adenosine release and depression of creatinine clearance was proportional to the osmolality of the contrast agent, essentially a dose-response relation (2). It is attenuated by the adenosine receptor blocker theophylline (3–5).

When pretreated with long-acting theophylline in addition to hydration with D5W or half-normal saline, patients with moderate renal dysfunction (creatinine ≤2.0 mg/dl) are reliably protected from the nephrotoxic effects of contrast media (3–5). We currently prescribe Theodur (3 mg/kg) orally the night before and b.i.d. the day of angiography. It is critical that theophylline be administered before contrast injection, but prolonged treatment after angiography is unnecessary.

Theophylline prophylaxis to attenuate contrast-media nephrotoxicity has not been adopted by cardiologists, perhaps because the studies appeared in journals they do not normally read. Theophylline prophylaxis is effective, safe, and inexpensive. In view of the magnitude of the clinical problem of contrast-media nephrotoxicity, we wish to bring this therapeutic strategy to the attention of the readers of JACC.

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REFERENCES

REPLY
Thank you for your interest in our article on the renal effect of low-dose dopamine in high-risk patients undergoing coronary angiography (1). We found no important renal protective effect of dopamine in patients at high risk for contrast nephropathy (CN) undergoing coronary angiography. We agree that the vasodilator effect of low-dose dopamine may be too small to counteract the afferent arteriolar vasoconstriction induced by the contrast medium. Higher doses of dopamine, however, may contribute to even more severe vasoconstriction.

We have also been interested in the adenosine receptor blocking effect of theophylline. We found that the acute renal failure induced by indomethacin and contrast medium in rats with diabetes mellitus (DM) was mediated by adenosine via suppression of renal and/or systemic NO2/NO3 production and that theophylline reversed NO2/NO3 secretion to levels similar to those of DM rats (2). The role of theophylline as a means of reducing CN in the clinical setting, however, is not well defined. Although Katholi (3) and Kolonko (4) have found some beneficial effect of theophylline, more recent studies focusing on higher-risk patients failed to demonstrate such effect. Abizaid et al. (5) found that neither aminophylline nor dopamine reduced the incidence of CN compared with saline hydration alone, in patients with serum creatinine ≥1.5 mg/dl. Erley et al. (whose previous study was cited by Katholi and Taylor in their present Letter to the Editor) randomized 80 patients with serum creatinine ≥1.5 mg/dl to either 810 mg of theophylline daily or placebo (6). They found that hydration alone was sufficient to preserve glomerular filtration and that theophylline had no additional benefit; they suggested that theophylline might be beneficial in patients for whom sufficient hydration is difficult, such as patients with severe congestive heart failure (6). Such patients, however, are usually treated with multiple medications, and adding theophylline at a sufficient dose may be accompanied by intolerable side effects.

Therefore, it seems to us that the advantages of theophylline in reducing the detrimental effect of contrast media, especially in high-risk patients, have yet to be proven. The prevention of CN in patients receiving contrast media should be based, at the present time, on adequate hydration accompanied by diuresis when needed.

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Extraction Efficiency of Extracellular MRI Contrast Agents and Its Model-Dependent Effects on Estimates of Myocardial Blood Flow

In their recent study, Cullen et al. (1) report on the highly relevant determination of a perfusion reserve index with magnetic resonance imaging (MRI) in patients with coronary artery disease. Without wanting to detract from the fact that theirs is a valuable study, we take issue with the negative appraisal of first-pass imaging with rapid bolus injections.

Based on numerous studies with extravascular and intravascular MRI contrast agents it has been shown that the best sensitivity to changes in myocardial blood flow is observed with a rapid bolus injection and imaging during the initial wash-in of contrast agent (2). The investigators suggest that a slower injection and a correspondingly lower temporal resolution (the authors report acquisition of an image every six heart beats) are of practical advantage. In fact, this forces them to determine blood flow indirectly with the Kety model by measuring the product of extraction efficiency (E) and myocardial blood flow (F) and to assume that the extraction efficiency is unchanged for different pathologies. The Kety model is most suitable for modeling the kinetics of freely diffusable tracers because the extraction efficiency can then be set to unity. For extracellular MRI contrast agents such as Gd-DTPA, which are barrier-limited, the assumption that the extraction remains constant is controversial. Several investigators have shown that E varies with flow, and between normal and ischemic/reperfused myocardium by as much as 100% (3,4). Data by Watson et al. (5) comparing the FE product with blood flows measured by positron emission tomography (PET) show that at low flows the FE product is rather insensitive to changes in flow. Furthermore, E is generally not constant during distribution of a tracer, and the choice of an E value is by no means unambiguous. The fact that the reported values of the perfusion reserve index, calculated with the assumption of a constant E, agree in normal healthy volunteers with previous PET studies is not sufficient to validate the application of the Kety model in patients.

Although Cullen et al. (1) describe their MRI measurements as first-pass studies, this does not seem to be appropriate when images are acquired every six heart beats. In fact, the Kety model may not fit well with data acquired in a true first-pass study owing to the initially low extraction of contrast agent during wash-in. The authors’ criticism (p. 1391) of previous first-pass studies (6) because of use of a fast bolus injection is misleading. The perfusion reserve estimate obtained in patients with microvascular dysfunction with such MRI first-pass studies was validated by comparison to the coronary flow reserve (6). It remains to be shown that a perfusion reserve index derived with the Kety model corresponds under different pathophysiological conditions to the myocardial blood flow reserve. In our opinion the first-pass technique is preferred to determine myocardial blood flow and the myocardial blood flow reserve.

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REPLY

I would like to respond to several issues raised by the letter of Jerosch-Herold et al. First, I do not purport that a lower temporal resolution of an image every six heart beats used in our study (1) confers an advantage. This is a clear compromise between having more slices and less data points on the first-pass transit curves, which was necessitated by the hardware constraints we had at the inception of this study. Although the use of an inversion-recovery sequence results in relatively prolonged image acquisition times even with the fastest magnetic resonance imaging (MRI) scanners, the images are stable and of good quality for analysis. This is in contrast to the saturation-recovery sequences used by Jerosch-Herold (2), which may allow more of the heart to be imaged in less time but in which the images are often of poor quality and subject to artefacts. However, the slower injection technique used in our study is an advantage over the power injections into the right subclavian vein reported in other studies (2); this is because a relatively invasive subclavian line is needed, which is less attractive for patient and operator. Also, a power injector is required, which is safe with magnetic fields and correspondingly expensive, whereas our technique can be administered manually through a peripheral vein.

Second, the question of whether the extraction efficiency (E) remains constant or varies with myocardial flow (F) is controversial and as yet remains a subject for further research. In support of using the EF product (K1) for estimating flow, a recent study by Vallee et al. (3) in a canine occluded coronary artery model demonstrated that F measured with microspheres had a linear fit to K1 for Gd-DTPA, (r = 0.88). However, as the behavior of E is uncertain at differing flow rates, the term “myocardial perfusion