Editorial

Contrast-Induced Acute Renal Failure

Acute oliguric renal failure is an uncommon, but recognized complication of the use of iodinated radiographic contrast media, and renewed attention has been given to this problem with a succession of papers in major medical journals [1-6]. These reports should remind radiologists that, although modern contrast agents are well tolerated by large numbers of patients, they are not completely innocuous substances. Indeed, they may induce occult renal injury with greater frequency than is commonly appreciated and this injury may be permanent. How does this happen?

Although the exact pathogenetic mechanisms involved in contrast-induced renal failure remain obscure, theories invoking a wide variety of factors have been proposed. Killen and Lance [7] attributed the nephrotoxicity of commonly used angiographic contrast media to a direct effect on tubular epithelium. All gradations of injury, from cloudy swelling to cellular dissolution, were noted in tubular cells. However, the glomeruli were spared.

Postlethwaite and Kelley [8] noted the considerable uricosuric effect of iodinated contrast materials, especially cholecystographic agents, and postulated that acute uric acid nephropathy could account for occasional cases of renal failure after their administration. The uricosuric effect of these agents seemed to be caused by enhancement of uric acid secretion by proximal and distal convoluted tubular cells. The theory is supported by the observation that this effect is completely inhibited by prior administration of pyrizinamide, a drug believed to specifically and completely block the tubular secretion of urate. The uricosuria produced by contrast agents may be accompanied by precipitation of urate in the tubular lumen, causing obstruction to the flow of urine and possibly cellular injury.

Berdon et al. [9] suggested that contrast exposure could induce precipitation of Tamm-Horsfall protein, a natural constituent of urine, in normal patients. They proposed that this mucoprotein is capable of forming a viscid gel that can partially or totally block urine flow through the tubules in the proper setting of dehydration, relative oliguria, and specific urine protein and electrolyte concentration. Further investigation of this, and other contrast-protein interactions, is needed to assess its importance in the pathogenesis of transient renal failure.

The hemodynamic changes following intravascular administration of iodinated contrast media are of particular interest. In peripheral vascular beds, a drop in peripheral resistance and an effective increase in blood flow are observed. These phenomena are in large part related to the osmolarity of the injected material [10, 11]. Sodium content and pH of the contrast do not seem to be significant in this regard. In the kidney, however, iodinated contrast agents have consistently been shown to decrease total renal blood flow in experimental animals [12-14]. Some investigators [15, 16] have observed crenation, spherocyte formation, and decreased pliability of red blood cells in the presence of various contrast materials and have related these phenomena to the hypertonicity of these agents. They proposed that the nonpliable erythrocytes, unable to pass through capillary beds, cause sludging and therefore decreased flow in the renal microcirculation. Studying the microcirculation of the bat's wing, Wiedeman [16] noted abnormal platelet clumping and adherence of white blood cells to vessel walls, and implied that direct endothelial damage was also a significant factor.

One must of course consider the unique features of renal circulation in any discussion of hemodynamic changes induced by hyperosmolar substances such as iodinated contrast media. Talner and Davidson [13] found a decrease in renal extraction of *p*-aminohippuric acid accompanied by a transient fall in renal blood flow, after the administration of various contrast agents, hypertonic saline, and mannitol directly into the renal artery of dogs. Aortic and renal artery pressure did not change significantly, and they suggested intrarenal vasoconstriction as a possible explanation for these effects. It would be attractive to implicate the macula densa and juxtaglomerular apparatus here, since the juxtaglomerular apparatus is thought to play a major role in the autoregulation of renal blood flow. It has been shown that sodium content and osmolarity of tubular fluid can influence glomerular filtration, presumably mediated by macula densa cells. Whether a similar type of feedback mechanism regulates renal blood flow after arteriography remains to be determined.

The decrease in renal blood flow might alternatively reflect a change in the complex system of regional blood flow in the kidney. Four regions, each with different flow characteristics, have been identified in acute experiments by autoradiography. These are (1) cortex, (2) outer medulla–inner cortex, (3) inner medulla, and (4) perirenal and hilar fat. The rate of flow is most rapid in the cortical compartment, which receives about 88% of the total nutrient blood flow in the normal kidney [17]. Rerouting of blood from the cortex to the medulla (Trueta shunting) may occur in the end stages of such renal disorders as collagen vascular diseases, malignant nephrosclerosis,

chronic glomerulonephritis, and also in transplant rejection. This is thought to indicate high resistance in the renal cortex, leading to decreased perfusion in this region with respect to the remainder of the kidney. Recently, Tadavarthy et al. [18] reported temporary Trueta shunting in normal kidneys during renal angiography. The mechanism of this phenomenon and its relevance to contrast-induced renal failure are unknown and may warrant further investigation in connection with the other hemodynamic effects of contrast agents.

One might question how this theoretical information applies to the clinical situation. Specifically, can the high risk patient be identified, and what prophylactic measures might be instituted to decrease the incidence of acute oliguric renal failure after contrast studies? The clinical profiles of patients who develop acute renal failure following the administration of iodinated contrast material would suggest that vascular factors are more significant than any tubular cytotoxic effects. Diabetics are at increased risk to develop acute oliguric renal failure after receiving radiocontrast agents, especially in the presence of dehydration and azotemia [6, 19, 20]. In this regard, it should be mentioned that while dehydration could accentuate any of the previously described effects of contrast, adequate hydration does not seem to necessarily protect against renal failure [2, 21, 22].

All of the patients described by Diaz-Buxo et al. [23] had been diabetic for a minimum of 6 years, and all had clinical evidence of diabetic retinopathy, neuropathy, and nephropathy. Harkonen and Kjellstrand [24] studied 29 diabetic patients in whom excretory urography was performed as a routine investigation of renal status and not because of sudden changes in renal function. Exacerbation of preexisting renal insufficiency after pyelography was noted in 76% of these patients, and in nine patients there was irreversible deterioration of renal function. The main risk factors seemed to be early-onset diabetes and more severe degrees of renal insufficiency before the study.

More recently, Van Zee et al. [4] noted an incidence of acute oliguric renal failure of about 5% after excretory urography, in a group of high risk patients which included diabetics and nondiabetics. This is to be compared with an overall incidence of less than 1% in unselected populations. Of the nondiabetic group, 14 of 15 had recognized renal disease due to hypertension (five patients), glomerulonephritis (three), hydronephrosis (three), and gouty nephropathy, polycystic disease, and mild transplant rejection (one patient each). It is noteworthy that all but two patients were well hydrated at the time of urography. These findings support an impression that small vessel disease may significantly predispose to contrast-induced renal failure. Tubular epithelial cell toxicity in such compromised kidneys may be a secondary and additive phenomenon rather than an initiating event in renal failure in this setting. Although intratubular contrast concentrations may actually be less than normal, the period of exposure is prolonged and each nephron handles a larger fraction of the administered dose. Direct tubular damage may therefore occur. Urate nephropathy may also play some role, since many patients are hyperuricemic due to underlying renal insufficiency. This nevertheless does not seem to be the major determinant of contrast-induced renal failure, since not all patients who develop this complication have elevated serum uric acid prior to study.

The high incidence of acute renal failure in susceptible groups of patients may be partially explained by the relatively large doses of contrast used for drip infusion urography and some angiographic examinations. Gruskin et al. [12] observed that hematuria did not occur in infants undergoing cardiac catheterization when the dose of contrast did not exceed 3 ml/kg. Other investigators [4, 21] have also postulated a dose-related effect, but consistent dose-response relationships have not been demonstrated to date either clinically or experimentally [3]. Further study of this question is needed, but from the available data it is not unreasonable to conclude that the maximum safe dose of contrast is probably less than 5 ml/kg, and undoubtedly much less in patients with underlying renovascular disease and/or hyperuricemia.

In summary, clinical and experimental data seem to identify the patient at high risk to develop contrast-induced acute renal failure as having either or both of the following: (1) small vessel renal disease, diabetic or otherwise, and (2) hyperuricemia, either primary or secondary to underlying renal insufficiency. If possible, alternatives to contrast examinations should be found for such patients. However, if necessary diagnostic information cannot be obtained other than by contrast examination, then doses of iodinated contrast media should be kept to a minimum, and an adequate state of hydration should be maintained. The benefits of preserving renal blood flow and controlling serum and urine uric acid have yet to be ascertained by controlled clinical trials.

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