Nephrogenic Systemic Fibrosis: Considerations for the Cardiologist*

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The manuscript by Schietinger et al. (1) in this issue of JACC (JACC: Cardiovascular Imaging) assesses patterns of late gadolinium enhancement (LGE) in the myocardium of chronic hemodialysis patients. The observation that the majority of LGE was not infarct related but was tied to the degree of left ventricular hypertrophy, particularly in dysfunctional segments, led the authors to suggest that LGE patterns within the myocardium may be able to serve as a clinical marker, perhaps for sudden death.

However, the prospect for investigating such potential has been quelled by the new reality of nephrogenic systemic fibrosis (NSF). During the course of the Schietinger et al. (1) study, an emerging awareness of NSF, particularly in this highest-risk chronic hemodialysis population, and the identification of a new NSF case within their cohort forced its premature termination.

Nephrogenic systemic fibrosis is a systemic fibrosing disorder strongly associated with the administration of gadolinium-based contrast agents (GBCAs) in patients with substantial renal disease (2–4). The available data suggest a 3% to 7% prevalence in the vulnerable population (4,5), although prevalence determination is problematic (5).

First reported in 2000 by Cowper et al. (6) as a unique fibrosing disorder that was recognized among patients undergoing renal dialysis, an early term ascribed to the condition, nephrogenic fibrosing dermopathy, emanated from its dermal manifestations.

The recognition of systemic involvement prompted a change in the name of the disorder to NSF (7). The clinical manifestations of NSF are highly variable spanning from a tiny plaque on the lower extremities to severe contractures and death. Not until 2006 was it first suggested that some of the GBCAs may trigger the development of NSF (2,3). The functional consequences of NSF are often debilitating and may be fatal. Treatment is multidisciplinary, predominantly supportive, and largely ineffective.

Nephrogenic systemic fibrosis is most commonly observed in patients with at least stage 4 chronic kidney disease (CKD), when the estimated glomerular filtration rate (eGFR) is <30 ml/min per 1.73 m², with a clear majority noted in dialysis patients. While NSF has not been documented in CKD patients having an eGFR >30 ml/min per 1.73 m², it has been seen in acute renal failure patients with higher eGFR values, particularly with concurrent pro-inflammatory processes (4,8).

To highlight the risk posed to patients with kidney problems, a black box warning on the product labels of all 5 of the GBCAs approved in the U.S. has been added in response to a request by the U.S. Food and Drug Administration. A summary of some of the important observations regarding NSF follows. Most of the epidemiological data have been gathered using the unreliable strategy of self-reporting. Published studies are chiefly retrospective reviews of relatively small populations (each typically <40 individuals). The documentation of the type and dose of GBCA has been poor. The largest number of cases is associated with exposure to the GBCA, gadodiamide. The association between NSF and GBCA use is preponderant but not universal (9). The onset of noticeable disease is unpredictable with respect to the time of...
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patients with an eGFR the macrocyclic agents, since they are far less likely available Gd-chelates with strong kinetic stabilities, considerations support the use of a subset of the are relatively sparse, the chemical and physical perspectives (14). Nevertheless, the macrocyclic agent (gadoteridol) supports this per- hemodialysis patients after administration of the recent report showing no cases of NSF in long-term exposure, and there are relatively low numbers of reported cases given the historical prolific use of GBCAs in renal insufficiency patients.

The predominant mechanistic hypothesis for NSF involves the liberation of free gadolinium (Gd) from its binding molecule, thought to trigger an inflammatory response. Support for this hypothesis resides in data demonstrating gadolinium in skin biopsy specimens of NSF patients (8) and in experimental studies in both humans (10) and animals (11). However, an as yet unidentified cofactor may be operative.

Gadolinium belongs to the lanthanide series, a set of chemically related elements with atomic numbers from 57 to 71 that have unpaired electrons. The interactions between the unpaired electrons of the gadolinium ion and the hydrogen nuclei of water molecules in tissues augment image contrast. However, the bare gadolinium metal ion is highly toxic. Therefore, it is essential that it be bonded to an organic moiety or ligand to provide a metal chelate complex (e.g., Gd-DTPA, Gd-BOPTA, Gd-DOTA, and so on) for altering image contrast.

The variable risk of NSF among the different GBCAs may be attributable to differences in the chemical stability of agents, a reflection of the propensity with which they are likely to dissociate and release free Gd\(^{3+}\) in vivo. The physical parameter that is most compelling to guide clinical practice from a chemistry perspective is the kinetic stability of an agent (12). The greater the kinetic stability, the less likely it is for an agent to dissociate. The biological relevance of the kinetic properties of several contrast agents was reported in a study showing strong correlation between the dissociation rates of chelates in acid and the long-term deposition of Gd\(^{3+}\) in rat tissues (11).

Given that the clinical and epidemiological data are relatively sparse, the chemical and physical considerations support the use of a subset of the available Gd-chelates with strong kinetic stabilities, the macrocyclic agents, since they are far less likely to dissociate (12,13). This is particularly the case for patients with an eGFR <30 ml/min/1.73 m\(^2\). A recent report showing no cases of NSF in long-term hemodialysis patients after administration of the macrocyclic agent (gadoteridol) supports this perspective (14).

Institutional policies and procedures are evolving to address the exposure to GBCAs in patients at risk for NSF. A variety of screening procedures to identify patients with low eGFR rates, increased attention to the types and doses of contrast agent administered, alterations in imaging strategies, and education at all levels of the medical community are important components to such initiatives. The use of screening forms and routine venous sampling for serum creatinine values before Gd-enhanced magnetic resonance imaging are becoming pervasive. These procedures help address the limited awareness of kidney disease in patients with stage 4 and 5 CKD who are not yet on dialysis. However, circumstances in which a high-risk individual requires a GBCA to facilitate their management will arise. In this scenario, an informed consent process specifically addressing the risk for NSF should be applied.

For myocardial scar and fibrosis imaging inversion recovery sequences with an inversion time structured to null the normal myocardium are used to optimize the contrast between the tissue retaining gadolinium (scar) and the healthy or viable myocardium (15). Options to alter the time between contrast administration and imaging, to adjust inversion times, to use agents with high relaxivity (T1 “brightening” capability), and to image at high field strength offer opportunities for dose reduction with potential to reduce NSF risk (16,17). Such optimization, coupled with the use of macrocyclic agents, could broaden the opportunities for efficacious imaging in patients at risk for NSF. The increased imperative for contrast media-independent techniques capable of demonstrating myocardial viability will revive important lines of research in diffusion, phosphorus, and sodium-based magnetic resonance evaluations (18–20).

Prospective registries that have recently been initiated or are soon to be, as mandated of the manufacturers by the U.S. Food and Drug Administration, will likely generate more reliable data regarding the incidence, prevalence, potential co-factors, and the degrees of severity of this disorder. It is hoped that from such data refined strategies will emerge to guide the best risk: benefit selections for patients requiring GBCAs for their care.

Thus, the provocative data from Schietinger et al. (1) cannot be further validated or advanced until issues related to NSF in this population are adequately addressed. Knowledge regarding the risks of NSF in this vulnerable group will help to minimize this potentially devastating iatrogenic disorder.

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REFERENCES


Key Words: nephrogenic systemic fibrosis • gadolinium • safety • renal insufficiency • contrast media.