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Targeted Renal Therapy

A novel device holds promise in preventing and treating renal insufficiency.

BY DAVID E. ALLIE, MD; BARRY S. WEINSTOCK, MD; AND PAUL TEIRSTEIN, MD

In 1998, the National Kidney Foundation task force on cardiovascular disease recommended that patients with renal insufficiency should be considered at the highest risk category for cardiovascular events, and that contrast-induced nephropathy (CIN) should be reduced due to an increase in cardiovascular death and all-cause mortality even in patients with mild renal insufficiency.[1] With the burgeoning revolution of catheter-based therapies requiring contrast imaging now reaching every cardiovascular territory, the potential clinical impact of CIN looms large. The definition of CIN varies; in clinical trials, CIN was defined as an increase in serum creatinine (Cr) >0.5 mg/dL or >25% of baseline at between 24 to 120 hours after contrast exposure, with the peak level reported between 3 to 5 days.[2-4]

The pathogenesis of CIN likewise remains incompletely defined. Potential etiologies include a direct renal cellular cytotoxic effect with an increase in toxic oxygen-free radicals; intense renal medullary vasoconstriction mediated by multiple vasoconstrictors, including adenosine, vasopressin, endohelin, and prostaglandin E2;[5,6] acute increase in renal osmolality requiring an increase in renal cellular oxygen consumption; acute reduction of renal blood flow with ensuing endothelial dysfunction; and decreased nitric oxide and prostacyclin production resulting in renal medullary hypercoagulability, hyperviscosity, and worsening ischemia.

The clinical impact of CIN was described by McCullough et al in 1997, but only recently have cardiovascular interventionists realized the significant increase in morbidity and mortality associated with CIN.[7] CIN is the third leading cause of hospital-acquired acute renal failure. McCullough et al reported a 14% incidence of CIN in 1,826 percutaneous coronary intervention (PCI) patients, with a 7.1% in-hospital mortality in patients who developed CIN but did not require dialysis and 35.7% if the patient required dialysis (P <.001), with <20% 2-year survival.[7] The in-hospital mortality was 0.7% without CIN. Gruberg et al reported a 37% incidence of CIN (7.3% requiring dialysis) in 440 PCI patients with baseline renal insufficiency (Cr ≥1.8 mg/dL), with three times higher in-hospital mortality (14.9% vs 4.9%) and two times higher 1-year mortality (37.7% vs 19.4%) in patients with CIN.[8] Clearly, the clinical impact of CIN in PCI is significant and has been unappreciated.

TARGETED RENAL THERAPY IN PERIPHERAL VASCULAR DISEASE

The incidence and impact of CIN in percutaneous peripheral intervention (PPI) remains almost totally unknown and unexplored but may be of greater clinical importance than in PCI because all predictors of CIN in PCI occur—and are magnified—in PPI. Mehran et al identified CIN predictors in PCI, including diabetes, age >75 years, female gender, contrast volume, Cr clearance, congestive heart failure, hypotension, preprocedure renal insufficiency and anemia, and validated a CIN risk score prediction model.[9] The incidence of these CIN predictors is likely greater in the commonly decade-older PPI versus PCI population. The individual incidences of diabetes and preprocedural renal insufficiency in large PCI trials was approximately 20%, but both have been reported at a much higher incidence (50% to 80%) in the PPI population, especially in patients requiring infrainguinal PPI for critical limb ischemia (CLI).[10] This is especially significant when considering the combination of diabetes and preprocedure renal insufficiency was shown by Parfey et al to increase the incidence of CIN during PCI to approximately 50%.[11]

Several other clinical differences in PPI versus PCI likely frequently increase the PPI patient's risk for CIN and worsening renal insufficiency, including complex, longer case duration with higher contrast use; higher rates of secondary reinterventions, repeat contrast exposures, and multiple procedures required; overall higher hemorrhagic and ischemic complication rates in PPI; more frequent multichannel CTA use, therefore increasing contrast exposure; and higher renal

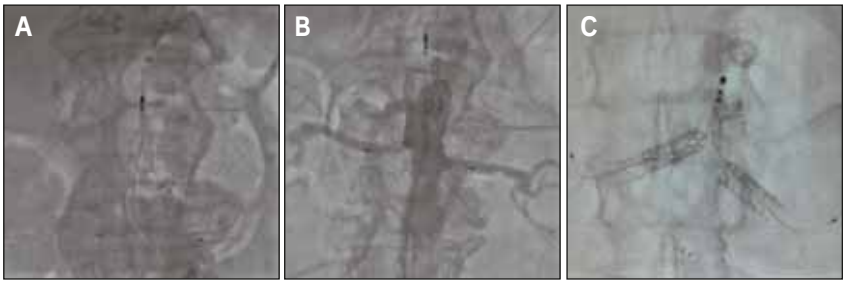

Figure 1. Be*neph*it PV Infusion System (FlowMedica, Inc., Fremont, CA) placement through a brachial approach (A) demonstrates positioning in native renal arteries (B) and in a patient with renal insufficiency and bilateral renal stents (C).

Figure 2. The Be*neph*it CV Infusion System.

atheroembolic risk (incidence of renal artery stenosis [RAS], perirenal aortic catheter manipulations, etc). A typical PVD patient presenting today would be a frail 81-year-old woman weighing 90 pounds, with bilateral ischemic diabetic foot ulcers, CLI with a hematocrit of 30.2%, and serum Cr of 1.9 mg/dL. This patient is certainly at extreme risk of CIN, and strategies to prevent CIN are not only warranted in PCI, but are essential in treating PVD and many of our aging cardiovascular patients.

RENAL INSUFFICIENCY IN SURGERY

Acute renal failure remains a major morbidity factor after cardiac surgery, with a reported incidence of 1%-2% to 30% in the high-risk patient population, with mortalities of 7%-38% to 60%-100% if hemodialysis is required.[12-15] Etiologies of renal insufficiency associated with cardiac surgery include age, diabetes, preoperative serum Cr, hypotension, hypothermia, perioperative low cardiac output, high-dose ionotrope use, RAS, congestive heart failure, emergency-urgent cardiac surgery, intra-aortic balloon pump, cardiopulmonary bypass versus off-pump bypass, anemia and oliguria during cardiopulmonary bypass, bypass duration, and multiple exogenous and endogenous endotoxins (drugs, contrast, cardiopulmonary bypass by-products, etc.).[12-15] Interestingly, contrast administration <48 hours prior to surgery is an independent preoperative predictor of worsening renal insufficiency, but no guidelines exist for optimal renal protection in cardiac surgery within 72 hours of angiography. In fact, the association of CIN and renal insufficiency after cardiac surgery is unknown, underestimated, and is likely to be at least a major contributing factor to a significant number of patients with acute renal failure and significant renal insufficiency after cardiac surgery yearly.

Avoiding worsening renal insufficiency after cardiac surgery is imperative when considering short- and long-term morbidity and mortality outcomes are associated with even mild degrees of renal dysfunction (serum Cr 1.5 to 1.8 mg/dL).[16] In a prospective analysis of 26,506 CABG patients from the Ontario, Canada Cardiac Case Network Database, Lok et al reported the overall in-hospital, 30-day, and 1-year mortalities to be associated with renal insufficiency. The 1-year mortality for moderate-to-severe renal insufficiency was found to be 29.3%, 11.1% for mild renal insufficiency, and 3.8% for no renal insufficiency (P <.0001).[17] The clinical and economic implications are tremendous when considering that approximately 18% of the US population (>50 million people) has some degree of renal insufficiency, and 14% of the approximately 700,000 patients undergoing cardiac surgery have preoperative renal insufficiency and are therefore at risk for perioperative acute renal failure.[15,17,18]

The incidence of renal insufficiency after open and catheter-based EVAR is also associated with preoperative renal insufficiency and postprocedure high mortality.[19,20] Renal insufficiency is reported in 2% to 6% of infrarenal open abdominal aortic aneurysm repairs and is significantly higher in thoracic artery aneurysms. Interestingly, renal insufficiency after EVAR is the third most commonly experienced morbidity, and few reports exist implicating CIN as a prevalent etiology, with most reports concentrating on technique-related etiologies (atheroembolism, RAS, and suprarenal fixation struts).[19-22] Renal insufficiency after EVAR has been reported from 6% to 39%.[19-21] Carpenter et al reported a 20% incidence of preoperative renal dysfunction in 98 EVAR cases, with an average volume of intraoperative contrast use of 152 mL (35 to 420 mL) underscoring the potential for intraoperative-induced CIN.[23] Permanent renal insufficiency was reported at 16% in this series despite liberal use of MRA and gadolinium for preprocedure planning. With the rapid adoption of multichannel CTA for the diagnosis, planning, and follow-up of patients with thoracic and abdominal aortic aneurysms and peripheral vascular disease, the additional 75-mL to 125-mL contrast volume load will further mandate physicians to deploy strategies to minimize CIN.

Fenoldopam (FEN) is a short-acting selective dopamine-1 agonist and vasodilator that is the only agent shown to increase both renal cortical and medullary blood flow.[24] The initial favorable clinical reports of systemic intravenous fenoldopam administration in reducing CIN in PCI were not duplicated in the randomized CONTRAST trial.[25] Unfortunately, fenoldopam has a first-pass renal metabolism and can cause hypotension at mild-to-moderate systemic doses, and it can be theorized that the CONTRAST trial results were secondary to an inability to deliver therapeutic doses directly to the renal medulla. Direct, high-dose intrarenal infusion of fenoldopam, in concept, has the potential to deliver selective renal vasodilatation and increased medullary blood flow with the potential to reduce CIN in both the cath/endovascular lab and the endovascular or operative suite. When considering the multiple etiologies and impact of renal insufficiency and acute renal failure during cardiac surgery, targeted renal therapy is particularly appealing. Few data exist investigating fenoldopam in cardiac surgery. Ranucci et al reported a significant reduction (from 22% to 11%; P = .028) in post-cardiac surgery acute renal failure and lower mortality rate (6.5% vs 15.7%; P = .03), with a 24-hour systemic fenoldopam infusion in 108 cardiac surgery patients by uni-

variate analysis.[26] Due to the small sample size, this could not be confirmed by multivariable analysis, but fenoldopam was an independent protective factor in the low-cardiac-output subset. Targeted renal therapy has been successfully utilized at the Cardiovascular Institute of the South during high-risk open abdominal aortic aneurysm, EVAR, and CABG procedures. The FDA has granted 510(k) approval to the B*enephi*t PV Infusion System, which is now commercially available in 40-cm, 105-cm, and 140-cm lengths (Figure 1). This infusion system is currently being investigated for targeted renal therapy in a series of clinical registries and trials.

CLINICAL TRIALS

Several clinical trials at various stages of completion are being conducted to study targeted renal therapy using the B*enephi*t Infusion System.

FEN-01

The completed FEN-01 study validated the feasibility, safety, and efficacy of intrarenal (IR) drug delivery and validated several key hypotheses about IR fenoldopam (IR-FEN).[27] Thirty-three patients with mild renal insufficiency were randomized 2:1 to receive treatment first with intravenous fenoldopam (IV-FEN), then IR-FEN versus placebo.

ONE CENTER'S EXPERIENCE

By Paul Teirstein, MD

At Scripps Clinic, direct intrarenal drug infusion has become part of our everyday management of patients at risk for CIN. Along with low osmolar contrast agents and N-acetylcystine, we consider local infusion of renal vasodilators for all patients with significant renal dysfunction undergoing coronary angiography. The B*enephi*t Infusion catheter is now FDA approved, and our physicians, nurses, and technologists have become comfortable using it on a routine basis. As a practical matter, patients with a serum Cr of 1.5 mg/dL or higher are usually selected for treatment, particularly diabetics and patients with complex anatomy who we know will consume more than a minor quantity of contrast (ie, *ad hoc* percutaneous coronary intervention, bifurcations, multiple lesions, and diffuse disease).

Our initial study using direct drug infusion into the renal arteries measured changes in glomerular filtration rate (GFR) in at-risk patients undergoing coronary angiography and/or percutaneous coronary intervention. We compared GFR changes in patients receiving a direct intrarenal infusion of fenoldopam (a dopamine agonist that increases blood flow in the renal medulla) to patients receiving placebo. This was a small study, but the results were dramatic. During the procedure, while fenoldopam was being infused, we found a 24% increase in GFR, compared to a much smaller 10% GFR increase in placebo patients. Even more exciting were our findings after the procedure. Two hours after the last contrast injection and discontinuation of intrarenal fenoldopam, we found GFR was maintained at 25% above baseline in treated patients, whereas GFR was reduced by 14% in patients who received placebo. This decrease in GFR 2 hours after the procedure is consistent with the well-known experience of renal shut-down several hours after contrast exposure in patients who develop CIN.

Inserting the FlowMedica catheter has become a very routine procedure. We first obtain an aortogram using 7 mL to 10 mL of contrast hand-injected through a pigtail catheter, which identifies the location of the renal arteries and uncovers any previously unsuspected renal artery stenoses. The B*enephi*t catheter is easy to use. For most patients, we are able to intubate both renal arteries with less than 60 seconds of manipulation. Our nurses have both the sidearm saline infusion and fenoldopam infusion premixed and tubing de-bubbled so the additional time needed to deploy the device and initiate therapy is minimal.

The B*enephi*t catheter's infusion arms are low profile and have atraumatic leading edges, and we have not encountered device-related complications. In fact, the most common reason we abort a renal protection procedure is the discovery of previously undiagnosed significant renal artery stenosis. This is one of the "hidden benefits" of offering our patients intrarenal drug infusion. Because these patients have renal dysfunction, it is a pleasant surprise to encounter renal artery disease because this gives us the opportunity to implant renal stents, which may improve the disease process. If renal artery stenosis is encountered, we abort the coronary procedure and deploy stents into the renal arteries, if appropriate. The patient is then brought back at a later date for the coronary procedure, along with direct intrarenal drug infusion. The presence of renal stents facilitates deployment of the B*enephi*t infusion catheter because the renal artery ostia are wide open and the target is now visible without contrast injection.

Our enthusiasm for direct intrarenal drug infusion at Scripps Clinic is founded primarily on the clinical success we have observed. Our experience is that in almost every at-risk patient we treat, the creatinine is lower the morning after the procedure. During the past year, this very consistent finding has moved us to depend on the FlowMedica infusion catheter, particularly in high-risk patients who require difficult, complex intervention. This new technology has given us increased confidence in our ability to avoid worsening renal function in this challenging patient population.

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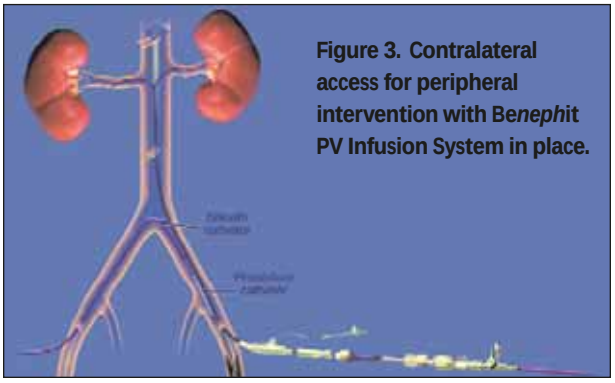

Figure 3. Contralateral access for peripheral intervention with Be*neph*it PV Infusion System in place.

Inulin was used to measure the glomerular filtration rate (GFR) and serum FEN levels were evaluated. A Be*neph*it CV Introducer Sheath was used so that the coronary catheters could be advanced through one port, with the Be*neph*it CV Infusion Catheter advanced through the second port (Figure 2). IR-FEN infusion maximized the favorable hemodynamic benefits of FEN by direct targeted infusion of the medication into the renal arteries. Systemic FEN levels were lower with IR-FEN compared to IV-FEN due to first-pass renal metabolism and excretion of FEN. Administration of IR-FEN compared to IV-FEN (0.2 µg/kg per minute) resulted in 30% lower serum levels of FEN. The mean serum level of IR-FEN at the 0.2 µg/kg per minute dose was almost identical to the mean serum level of IV-FEN 0.1 µg/kg per minute. Additionally, there was 45% less reduction in systemic blood pressure with IR-FEN compared to IV-FEN (12±3 mm Hg vs 23±3 mm Hg; *P*<.001). Importantly, GFR was not significantly altered by IV-FEN but was significantly increased by 24% during IR-FEN (*P*<.0001 compared to baseline pre-FEN GFR). The increase in GFR after IR-FEN was significantly greater than the increase seen with IV-FEN (25% vs 5%; *P*<.001). GFR measured 2 hours after the procedure remained significantly elevated (25% increase) in IR-FEN patients, whereas GFR in patients who were taking placebo declined by 14%.

TIFFANY

The randomized TIFFANY study (Targeted Infusion of Fenoldopam For Avoidance of NephropathY) examines IR-FEN in coronary intervention patients at very high risk for radiocontrast nephropathy diabetic patients with serum Cr >2 mg/dL or Cr clearance <35 mL/min. This dose escalation study will compare IR-FEN at doses of 0.2, 0.4, and 0.8 µg/kg per minute versus placebo. Completion of TIFFANY is expected in the near future.

BE-RITE REGISTRY

Additional nonrandomized clinical data are being accumulated in high-risk patients in the ongoing Be*neph*it System Renal Infusion ThErapy Registry (Be-RITe) Registry.[28] Thus far, mean baseline serum Cr is 2.3, with 26% of patients having baseline serum Cr >2.5. Targeted renal therapy was performed primarily with fenoldopam. Two-thirds (67%) of patients experienced no increase in serum Cr, whereas 28% actually showed a decrease in serum Cr. Therefore, only 5% of these high-risk patients developed an increase in serum Cr.

PATRICIA

Patients undergoing peripheral vascular intervention are frequently diabetic and have chronic renal insufficiency, which results in a high risk for radiocontrast nephropathy. One recent study reported significant renal impairment in 46% of patients undergoing peripheral vascular intervention.[29] The recently started PATRICIA Trial (Peripheral Angiographers' Targeted Renal Infusion for Contrast Injury Avoidance Trial) evaluates the use of targeted renal therapy with the Be*neph*it PV Infusion System to deliver IR-FEN (0.4 µg/kg per minute) in patients at high risk for radiocontrast nephropathy (serum Cr >2 mg/dL or Cr clearance <45 mL/min) undergoing peripheral vascular intervention. In this 50-patient pilot trial, both the treatment and control-arm patients will receive iodixanol contrast, intravenous saline hydration, intravenous sodium bicarbonate, and oral N-acetyl-cysteine. Serum Cr and Cr clearance will be evaluated at 24 and 72 hours to determine the incidence of radiocontrast nephropathy.

ADDITIONAL TRIALS

A variety of clinical trials with the Be*neph*it Infusion systems are underway. One center is initiating a randomized pilot study to evaluate the influence of IR sodium bicarbonate instead of fenoldopam on the incidence of radiocontrast nephropathy compared to standard of care approaches in high-risk patients undergoing percutaneous coronary or peripheral vascular intervention. Another center is evaluating IR-FEN in patients with chronic renal insufficiency who are undergoing CABG and/or valve surgery, or abdominal aortic aneurysm repair, often using a brachial approach to place the Be*neph*it Infusion System. In view of the high mortality associated with postoperative renal failure, there is tremendous potential clinical benefit from intraoperative and postoperative IR-FEN. The Be*neph*it Infusion System is also being used to deliver different therapeutic agents for disease processes other than nephropathy. As an example, trials are evaluating the use of IR nesiritide for treating patients with congestive heart failure. Similar to fenoldopam, use of therapeutically effective doses of nesiritide is often limited by hypotension, which may be overcome by direct renal infusion with first-pass excretion.

PERIPHERAL INTERVENTION CASE STUDY

A 69-year-old man with hypertension, diabetes, previous CABG, an implantable cardiodefibrillator, chronic obstructive pulmonary disease, and dyslipidemia presented with severe, lifestyle-limiting left leg claudication. Duplex exami-

nation demonstrated severe stenosis of the distal left superficial femoral artery with peak systolic velocity of 382 cm/s. Ankle-brachial index at rest was reduced to 0.7, and monophasic flow was noted distal to the stenosis. The patient's serum Cr was elevated at 1.7, with estimated Cr clearance of 46 mL/min. The risk stratification scoring system developed and validated by Mehran et al[30] identified a 57.3% risk of contrast nephropathy from a procedure using approximately 200 mL of contrast. Because of the high risk of radiocontrast nephropathy and the increased mortality associated with this adverse outcome, this patient was treated with intraprocedural IR-FEN. A 7-F contralateral sheath was placed via the right common femoral artery, and a B*enephit* PV Infusion System was placed retrograde in the left common femoral artery (Figure 3). The renal arteries were cannulated easily, and IR-FEN 0.4 µg/kg per minute was infused for the duration of the procedure (39 minutes). Plaque excision with the SilverHawk (FoxHollow Technologies, Redwood City, CA) device reduced distal superficial femoral artery stenosis (80% to 90%) to 10% without complication. Despite a total contrast load of 195 mL of iodixanol, serum Cr was 1.7 at 24 hours and only 1.9 at 72 hours, significantly less than the accepted criteria for radiocontrast nephropathy of a 0.5-mg/dL increase or a 25% increase in serum Cr. Cr clearance declined only slightly from 46 mL/min to 41 mL/min.

DISCUSSION

This case demonstrates a novel technique for delivering a therapeutic dose of FEN directly to the kidneys to prevent radiocontrast nephropathy. Targeted renal therapy expands the therapeutic window for renally excreted medications due to first-pass metabolism and excretion. IR-FEN has been demonstrated (FEN-01) to increase the GFR while limiting systemic hypotension in contrast to IV-FEN. The B*enephit* PV Infusion Catheter may be easily and safely advanced into the renal arteries by positioning a dedicated 5-F B*enephit* Introducer Sheath just inferior to the origin of the renal arteries. Even minimally experienced operators can typically place the system in 1 to 2 minutes. With the B*enephit* CV Infusion System, an 8-F introducer sheath allows placement of a coronary guide catheter and a B*enephit* Infusion Catheter through the same sheath during percutaneous coronary intervention (Figure 4). However, this approach is not technically feasible for peripheral procedures, particularly those involving contralateral arterial access. In this patient, it was possible to accomplish superficial femoral artery intervention and targeted renal therapy by placing a contralateral introducer sheath retrograde from the right common femoral artery, while simultaneously placing the 5-F B*enephit* PV Introducer Sheath retrograde from the left common femoral artery such that the two introducer sheaths pass through the same artery (left iliac), but in opposite directions (Figure 3).

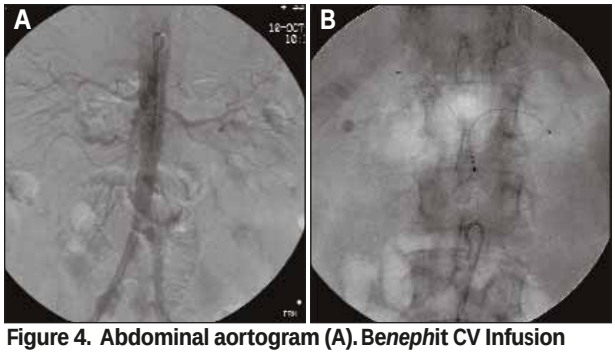

Figure 4. Abdominal aortogram (A). B*enephit* CV Infusion Catheter placed intrarenally (B).

Despite the estimated risk of radiocontrast nephropathy >50% associated with this patient, a complete bilateral diagnostic angiogram and left superficial femoral artery plaque excision utilizing nearly
200 mL of contrast material was successfully completed with no clinically significant change in serum Cr or Cr clearance.

CONCLUSION

Targeted renal therapy is a promising approach for preventing radiocontrast nephropathy in high-risk patients, particularly those patients with peripheral vascular disease. The B*enephit* Infusion Catheter systems offer the interventionist ease of use as well as a highly favorable safety profile and potentially provides enhanced clinical efficacy in a variety of high-risk clinical settings. In addition to radiocontrast nephropathy prevention, IR fenoldopam is currently being evaluated for prevention of postoperative renal failure after coronary bypass surgery (and/or valve surgery) and following abdominal and thoracic aortic aneurysm repair. Additional studies are examining treatment of severe congestive heart failure using IR nesiritide. The B*enephit* Infusion Catheter provides a vehicle for targeted renal therapy using a variety of cardiovascular and renovascular medications. Clinical indications will be determined by the results of the previously mentioned studies. ■

References for this article are available at www.evtoday.com.

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