

Renal insufficiency after cardiac surgery: a challenging clinical problem^{*}

Philippe Kolh

University of Liège Hospital (CHU ULg), B 35 Sart Tilman, Liège 4000, Belgium

This editorial refers to 'Efficacy of N-acetylcysteine in preventing renal injury after heart surgery: a systematic review of randomized trials'[†], by A.S. Adabag *et al.*, on page 1910

Acute renal insufficiency (ARI) after cardiac surgery is a complex and frequent clinical problem. It increases short- and long-term mortality, the incidence of post-operative complications such as respiratory infections, sepsis, and gastrointestinal bleeding, and intensive care unit (ICU) and hospital lengths of stay.^{1,2} Identified risk factors for post-operative ARI in cardiac surgical patients include pre-operative renal insufficiency, advanced age, history of congestive heart failure, diabetes mellitus, recent exposure to nephrotoxic agents such as contrast dye, intra-aortic balloon pump, emergency operation, prolonged cardiopulmonary bypass (CPB) time, low urinary output during CPB, and need for deep hypothermic circulatory arrest (*Figure 1*).^{2,3}

Analysing the pre-operative risk factor trends in cardiac surgery during the 1990-1999 decade in the large, voluntary, nationwide STS database, Ferguson *et al.* showed that the incidence of pre-operative renal insufficiency increased from 3.0 to 4.6%. Recently, Swaminathan *et al.*⁴ showed that, among coronary artery bypass grafting (CABG) patients, the incidence of acute renal failure increased significantly from 1.1 to 4.1%. While the proportion of a diagnosis of acute renal failure cases requiring haemodialysis decreased from 15.8 to 8.7%, the percentage of survivors with post-operative special care requirements increased from 35.5 to 64.5%.⁵

Over the last few years, the prognostic importance of mildly elevated pre-operative serum creatinine levels or small increases in post-operative creatinine values became apparent, leading to a shift in our understanding of the importance of even small degrees of acute kidney injury. Antunes *et al.*⁶ reported, among 2122 patients with pre-operative creatinine serum levels <2.0 mg/dL having CABG and an uncomplicated post-operative course, a mean increase of 0.3 mg/dL between pre-operative (1.0 mg/dL) and maximal post-operative (1.3 mg/dL) serum creatinine levels, and a mean reduction of 20 mL/min in the estimated creatinine clearance, from 82 to 62 mL/min. When compared with pre-operative creatinine levels <1.3 mg/dL, levels of 1.3-1.6 mg/dL and of >1.7 mg/dL increased the likelihood of developing post-operative renal insufficiency by 5.5 and 14 times, respectively.⁶ A mild elevation (1.3-2.0 mg/dL) of the pre-operative creatinine level significantly increased the probability of peri-operative mortality, low cardiac output, haemodialysis, and prolonged hospital length of stay. In this study,⁶ the duration of CBP increased mortality, morbidity, and incidence of renal dysfunction by a factor of 1.14 for each 10 min of CPB time.

Potential reasons for renal dysfunction include cardiovascular compromise, prolonged CPB time, increased catecholamine level, non-pulsatile flow, hypothermia, renal hypoperfusion, and the induction of inflammatory mediators.⁷ A number of possible strategies aimed at alleviating the development of renal dysfunction during cardiac surgery have been evaluated (*Figure 2*). Techniques that could decrease the incidence of ARI include off-pump CABG, minimally invasive surgery, specialized devices designed to reduce atheromatous embolic load, and changes in bypass temperature management strategies. Several renoprotective drugs, such as dopamine, calcium channel antagonists, loop diuretics, atrial natriuretic peptide, and angiotensin-converting enzyme inhibitors, have also been evaluated but mostly yielded conflicting or even negative results.

Numerous factors may collectively contribute to renal ischaemia and systemic inflammatory responses, resulting in generous formation of reactive oxygen species and depletion of endogenous antioxidants.⁷ Therefore, several antioxidant agents, such as catalase, superoxide dismutase, dimethyl sulfoxide, and allopurinol, have been tested but showed variable effects on renal function, as some improve function whereas others do not.

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The thiol-modifying agent *N*-acetyl-L-cysteine (NAC) has been used in a variety of disease states, such as paracetamol toxicity, pulmonary oxygen toxicity, and human immunodeficiency virus infection.⁸ Recently, NAC has gained renewed interest and wide use because of its role in the minimization of reperfusion injury after acute myocardial infarction and its protective effects on renal function in diabetic patients after contrast dye injection.^{9,10}

The diversity of pharmacological applications of NAC is due to the chemical properties of the cysteinyl thiol group of the NAC molecule. NAC is an antioxidant that reacts best with the hydroxyl radical and hypochlorous acid but poorly with hydrogen peroxide and the superoxide radical. Experimental studies¹¹ in rats showed that NAC, infused at 6 mM/kg 1 h prior to and 1 h following renal ischaemia, significantly reduced the induction of the transcription factors c-fos and c-jun in the post-ischaemic kidney, reduced stress-induced protein kinase activity, mitigated the loss of renal function, and aided recovery in the post-reperfusion-injured kidney (*Figure 3*). NAC-infused animals had a higher glomerular filtration rate at 1 and 7 days after the induction of ischaemia.¹¹

In addition to its antioxidant properties, another mechanism by which NAC might improve renal function is an interaction between NAC and nitric oxide (NO). Lessio *et al.*¹² found that NAC blunts the reduction of inducible NO synthase expression and NO synthesis caused by cyclosporin in rat renal artery vascular smooth muscle cell cultures (*Figure 3*). NO-independent vasodilatation with NAC has also been reported.

Attempting to assess whether or not the use of NAC is beneficial during cardiac surgery, Adabag *et al.*¹³ have reported a systematic review of randomized controlled trials (RCTs) of NAC in adult cardiac surgical patients. Ten RCTs, published between 2005 and 2008, were included. Placebo control was used in all but one study, in which the control group consisted of patients under usual care. In six of the studies, participants were considered to be at high risk for developing ARI. In eight studies, NAC was administered intravenously although there was considerable variation in the dose, duration, and route of administration.

Figure 1 Risk factors for acute renal insufficiency after cardiac surgery.

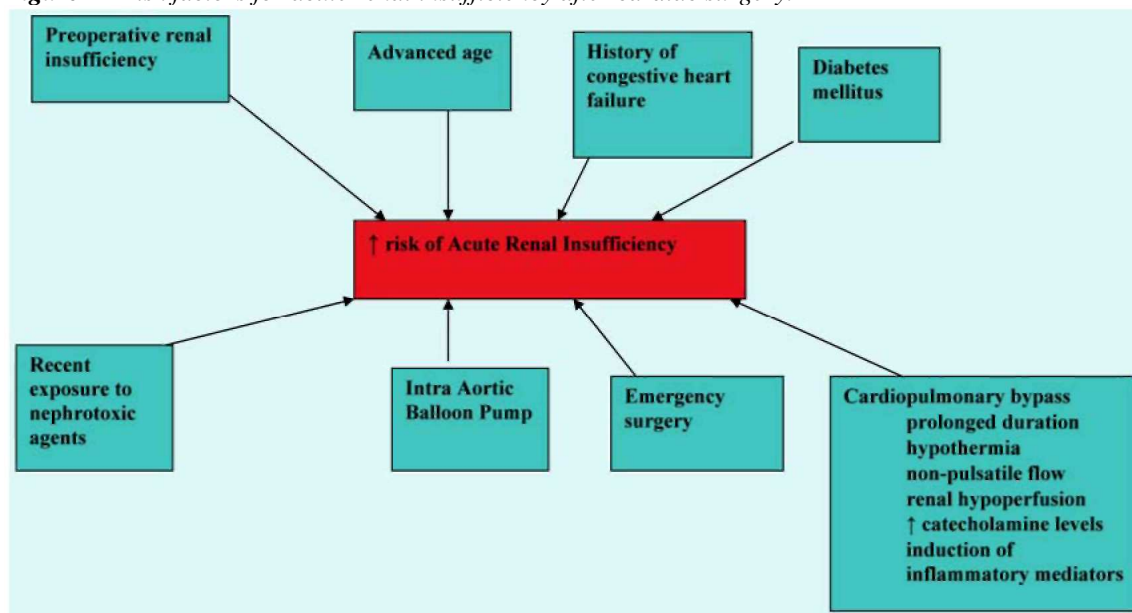


Figure 2 Surgical techniques and pharmaceutical agents used to decrease the incidence of acute renal insufficiency (ARI) after cardiac surgery. CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; ACE, angiotensin-converting enzyme; ANP, atrial natriuretic peptide.

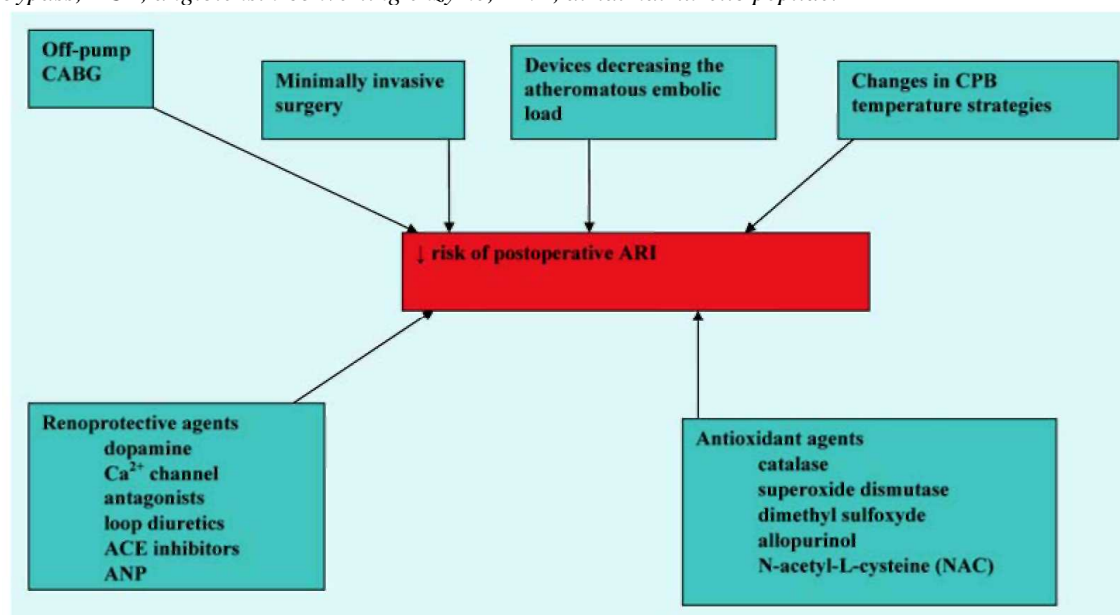
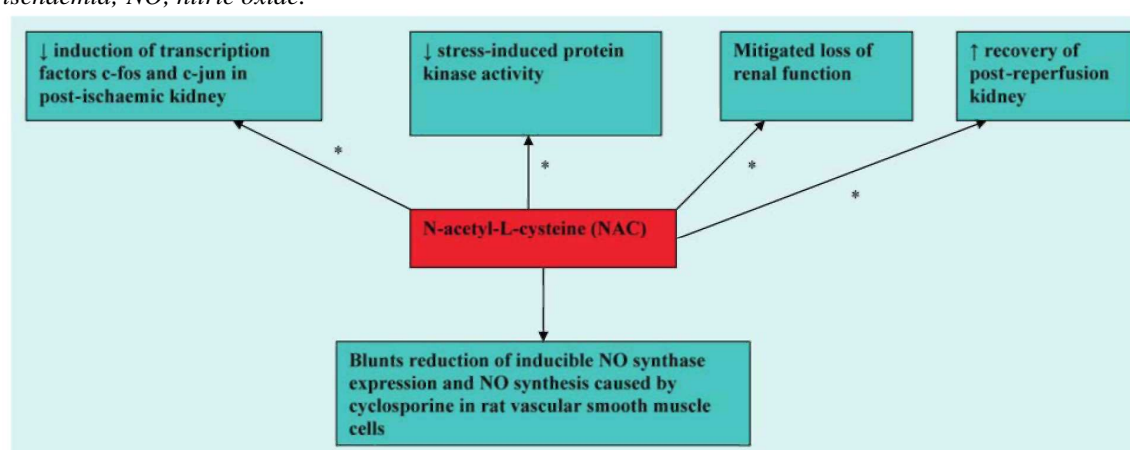


Figure 3 Experimental effects of NAC in rats. *Infused at 6 mM/kg 1 h prior to and 1 h following renal ischaemia; NO, nitric oxide.



The mean age of the 1163 patients included in the meta-analysis was 70 ± 7 years, 71% were males, and 66% underwent CABG alone or combined CABG and valve surgery. Primary outcome was ARI, defined as an absolute increase >0.5 mg/dL or a relative increase $>25\%$ in serum creatinine from baseline within 5 days after surgery. Secondary outcomes were maximum change in serum creatinine from baseline within 5 days of surgery, need for post-operative haemodialysis, all-cause mortality, and lengths of ICU and hospital stays.

Overall, NAC did not reduce ARI incidence (35% NAC vs. 37% placebo), while 3.3% of patients required haemodialysis and 3% died. There was a trend towards reduced ARI incidence among patients with pre-operative chronic kidney disease who received NAC, particularly if it was given intravenously. NAC did not reduce length of ICU or hospital stay, although the lengths of stay varied considerably between studies. Interestingly, in two RCTs, renal function was evaluated 14 and 30 days after surgery, showing similar results between NAC and placebo patients.

Therefore, current evidence does not support the routine use of NAC during cardiac surgery. However, as the authors¹³ correctly pointed out, several limitations of the assessment of the possible role of NAC in post-operative renal function in cardiac surgical patients should be emphasized. First, the serum creatinine level, used

in most studies to measure renal function, is influenced by body square area and body water mass. It often overestimates glomerular filtration rate and misses some subclinical kidney dysfunction. Creatinine clearance testing is more accurate but requires urine volume and urine creatinine. Cystatin C, another glomerular filtration rate marker, is superior to serum creatinine in various selected cases, and proved to be an earlier marker than serum creatinine to reflect ARI. Secondly, doses of NAC used, which varied considerably among trials, may have been inadequate to counteract the ischaemic insults to the renal tubular epithelial cells induced by CPB.

In conclusion, post-operative renal failure in cardiac surgery remains a burden on short- and long-term healthcare resources. The development of techniques or pharmaceutical agents that could significantly protect the kidneys during cardiac surgical procedures is of paramount importance.

Conflict of interest: none declared.

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