N-acetylcysteine for prevention of acute renal failure in patients with chronic renal insufficiency undergoing cardiac surgery: A prospective, randomized, clinical trial*

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Objective: **To assess the preventive effect of the antioxidant *N*-acetylcysteine on postoperative acute renal failure in patients with renal insufficiency undergoing cardiac surgery.**

Design: **Randomized, placebo-controlled, prospective study.**

Setting: **University cardiology center.**

Patients: **Two hundred fifty-four consecutive patients with chronic renal insufficiency (estimated creatinine clearance ≤60 mL/min) undergoing elective cardiac surgery.**

Interventions: **Patients were randomized to receive *N*-acetylcysteine (n = 129) or placebo (n = 125). Patients of the *N*-acetylcysteine group received four boluses of intravenous *N*-acetylcysteine (1200 mg every 12 hrs, starting immediately before cardiac surgery).**

Measurements and Main Results: **The incidence of postoperative acute renal failure (>25% increase in serum creatinine from baseline) and the in-hospital clinical course were evaluated. Acute renal failure occurred in 46% of patients and was associated with increased in-hospital mortality (7% vs. 0.7%; $p = .024$). It occurred in 52% of control patients and 40% of *N*-acetylcysteine-treated patients ($p = .06$). In-hospital mortality and need for renal replacement therapy were not affected by *N*-acetylcysteine, but a lower percentage of *N*-acetylcysteine-treated patients required mechanical ventilation prolonged for >48 hrs (3% vs. 18%; $p < .001$) and had an intensive care unit stay >4 days (13% vs. 33%; $p < .001$).**

Conclusions: **Intravenous administration of *N*-acetylcysteine does not clearly prevent postoperative acute renal failure in patients with renal insufficiency undergoing cardiac surgery. (Crit Care Med 2008; 36:81–86)**

KEY WORDS: *N*-acetylcysteine; acute renal failure; chronic renal insufficiency; cardiac surgery; cardiopulmonary bypass

Acute renal failure (ARF) is a common complication of cardiac surgery and is associated with significant morbidity and mortality rates and prolonged intensive care unit (ICU) and hospital stay. This is true for ARF necessitating renal replacement therapies (1, 2) as well as for ARF not requiring dialysis and even for patients with minimal increases in serum creatinine after surgery (3–5). Although several risk factors for postoperative ARF have been entertained, the most consistent are preexisting renal insufficiency, advanced age, history of congestive heart failure, diabetes mellitus, prolonged cardiopulmonary bypass (CPB), and recent exposure to nephrotoxic agents, such as contrast dye (1, 2, 6, 7). In patients with renal insufficiency, both short- and long-term mortality rates have been shown to increase in parallel with the increasing severity of the preoperative renal impairment (8–10). Acute renal dysfunction also has an important impact on nonrenal morbidity. Indeed, patients who develop ARF after cardiac surgery have higher incidences of gastrointestinal bleeding, respiratory infections, and sepsis (4, 11).

As high-risk patients can be easily identified before cardiac surgery, the institution of prophylactic measures is the best opportunity to prevent ARF, and many pharmacologic strategies, including dopamine, fenoldopam, calcium channel antagonists, furosemide, atrial natriuretic peptide, and angiotensin-converting enzyme inhibitors, have been proposed (12–14). However, most of them have shown conflicting or even negative results. Recently, *N*-acetylcysteine (NAC), an agent that buffers a variety of oxygen-derived free radicals and improves renal vasodilation through an endothelium-dependent mechanism, has been shown to confer protection against contrast-induced renal dysfunction (15), and preliminary data suggest that NAC ameliorates renal ischemia-reperfusion injury (16, 17) and preserves renal function from several nephrotoxic insults (18, 19). One of the final common pathways of ischemia-reperfusion injury involves release of oxygen free radicals; agents that buffer free radicals may be of benefit in limiting the reperfusion insult (16, 17).

We therefore designed a prospective, randomized, controlled trial to evaluate the effect of NAC administration, compared with placebo, in patients with renal insufficiency undergoing cardiac surgery.

***See also p. 338.**

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MATERIALS AND METHODS

Study Population. This prospective, randomized, controlled trial was conducted at the Centro Cardiologico Monzino at the University of Milan between January 1, 2005, and July 30, 2006. All consecutive patients scheduled for cardiac surgery and having at least moderate (stage 3 nephropathy) renal insufficiency were enrolled (20). Patients were included if their creatinine clearance, as calculated by the Cockcroft-Gault formula, was ≤60 mL/min (21). Patients in chronic peritoneal or hemodialytic treatment, those with known allergy to NAC, and those having received NAC for contrast-induced nephropathy prevention in the previous 7 days or contrast agents in the previous 72 hrs (in elective cases) were excluded. Patients undergoing emergency cardiac surgery were also excluded. The study was approved by the Ethics Committee of our institute, and written informed consent was obtained from all patients.

Study Protocol. Eligible patients were randomly assigned in a 1:1 ratio to receive NAC (NAC group) or placebo (control group). Allocation was based on random, computer-generated numbers. Patients of the NAC group received an intravenous bolus of 1200 mg of NAC (Acetilcisteina HEXAL 300 mg/3 mL; Agrate Brianza, Italy) immediately before induction of anesthesia, followed by three additional boluses administered at 12-hr intervals in the ICU (total dose of NAC = 4800 mg). Controls received a similar volume (12 mL for each bolus) of isotonic saline solution. Patients and physicians were blinded to treatment assignment.

Perioperative Management. Patients received their routine cardiac medication except for antiplatelets and angiotensin-converting enzyme inhibitors agents until the day of surgery. Premedication consisted of morphine (0.1 mg/kg) and atropine (0.05 mg/kg) 1 hr before surgery. A prophylactic intravenous antibiotic (cefazoline, 1.5 g/8 hr during the first 24 hrs) was given, starting just after the positioning of a venous access. Anesthesia was induced with thiopental (4–6 mg/kg), sufentanil (1 μg/kg), and succinylcholine (1 mg/kg) and maintained with inhaled Sevorane and incremental doses of pancuronium to facilitate muscle relaxation. Patients were monitored with five-lead electrocardiogram, central venous catheter, radial artery catheter, Foley catheter, and nasopharyngeal and rectal temperature probes. A pulmonary artery flotation catheter was inserted through the right internal jugular vein for hemodynamic monitoring in case of left ventricular ejection fraction <30% or when a multiple surgical procedure was planned. Nonpulsatile CPB was conducted in moderate hypothermia (34°C) using a roller pump with a membrane oxygenator and a micron arterial filter. The circuit was primed with 1 L of Normosol R, 500 mL of glucose 5%, an ampoule of 18% sodium bicarbonate solution, and a 100-mL bolus of mannitol 18% given just before the opening of aortic cross-clamp. The flow rate was titrated to ensure a mean arterial pressure between 55 and 80 mm Hg but ≥2.4 L/min/m^2, and norepinephrine was injected if necessary. Additional Ringer's lactate solution was added to maintain the level in the venous reservoir, and hemodilution to a minimum hemoglobin level of 7 g/dL was allowed. Myocardial protection was achieved by means of intermittent antegrade and retrograde cold blood cardioplegia. After weaning from CPB, the entire content of the circuit was collected and slowly returned to the patient.

After surgery, patients were transferred to the ICU, sedated, and intubated; propofol was used for sedation until complete rewarming. Patients were weaned from mechanical ventilation as soon as they reached hemodynamic stability and consciousness with adequate pain control. The hemodynamic management consisted of maintaining the mean arterial pressure at ≥65 mm Hg with adequate vascular filling with crystalloids and colloids (gelatin-based plasma expanders were allowed), and dopamine or norepinephrine infusion were used, if necessary. If urinary output was <1 mL/kg/hr, incremental doses of 20 mg of furosemide, followed by continuous infusion of 0.02–0.04 mg/kg/hr in case of no effect, were given.

Study End Points. The primary end point of the study was the occurrence of ARF, defined as an increase in serum creatinine concentration >25% from baseline to the maximum value obtained within the 72-hr period following cardiac surgery. Creatinine was measured the day before surgery, and every day for the following days, until discharge from the hospital.

Secondary end points included the maximal change in calculated creatinine clearance, doubling of serum creatinine according to the RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease) definition for acute kidney injury (22), and the occurrence of major postoperative clinical events, including need for renal replacement therapy, acute myocardial infarction, prolonged (>48 hrs) mechanical ventilation, prolonged (>4 days) ICU stay, and death.

Definitions. Postoperative acute myocardial infarction was defined by the development of either pathologic Q waves lasting ≥40 msecs in at least two contiguous electrocardiographic leads or an increase in the creatine kinase MB isoenzyme level of more than five times the upper limit of normal at any time postoperatively. Renal replacement therapy (either hemofiltration or hemodialysis) was performed in case of ARF with prolonged (>24 hrs) oligo-anuria despite adequate continuous intravenous infusion of loop diuretics. It was performed earlier in the case of concomitant overt heart failure, severe hyperkalemia, or metabolic acidosis. Blood transfusion was performed when hemoglobin levels were <8 g/dL or were <9 g/dL in the presence of acute myocardial ischemia.

Statistical Analysis. The planned enrollment of 206 patients (103 in each group) provided a statistical power of 80%, with an α error of .05, to detect a 40% reduction in the rate of primary end point (from 50% in controls to 35% in the NAC-treated patients). This assumption was based on preliminary, unpublished results from our database showing a 50% incidence of >25% postoperative creatinine increase in patients with chronic renal insufficiency and from previous studies reporting a reduction in the incidence of contrast-induced nephropathy in patients treated with NAC (23). Continuous data are reported as mean ± SD. Categorical data are presented as absolute values and percentages. The clinical characteristics of the two groups were compared using analysis of variance or the Mann-Whitney test for continuous variables and chi-square test or Fisher's exact test for categorical variables. A p value <.05 was considered to indicate statistical significance. Relative risks and 95% confidence intervals were used to compare groups with regard to major clinical end points. Data were stored electronically and analyzed with the aid of the SAS software package (version 8.02; SAS Institute, Cary, NC).

RESULTS

During the study period 1,646 patients undergoing cardiac surgery were screened, and 254 (15.4%) patients with preoperative renal insufficiency were randomly assigned to receive either NAC (n = 129) or placebo (n = 127) and were then included in this study (Fig. 1). The demographic, clinical, and perioperative characteristics of the two study groups are given in Table 1. There were no significant differences in age, gender, baseline indexes of renal function, left ventricular ejection fraction measure, indication to cardiac surgery or EuroSCORE (24), and the number of patients undergoing cardiac surgery with CPB. Intraoperative data were also well balanced between the two groups.

ARF occurred in 118 (46%) of the 254 patients and required renal replacement therapy in 16 (6%). As expected, development of ARF was associated with longer ICU stay and increased mortality rate, particularly for patients treated with renal replacement therapy (Fig. 2). No significant difference in the incidence of ARF was observed in several possible high-risk subsets of patients, as defined by age, gender, diabetes, reduced (≤40%) left ventricular ejection fraction, and cardiac surgery with CPB (Fig. 3). Figure 4 shows the maximal changes in creatinine

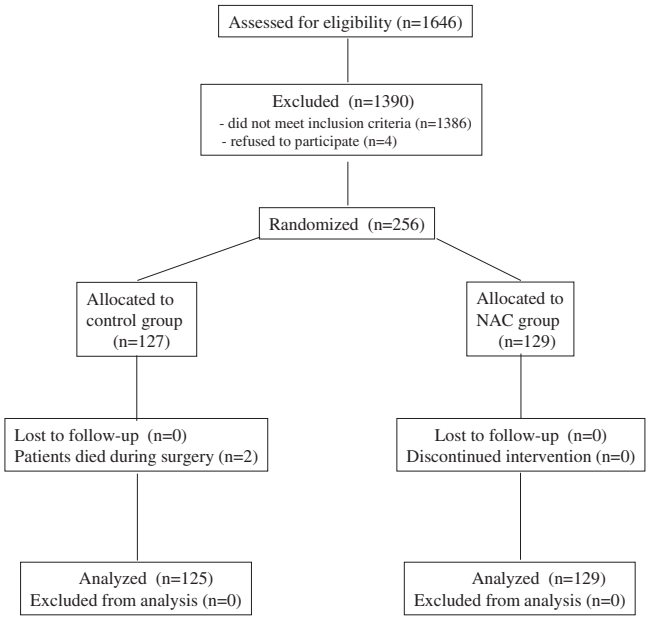

Figure 1. Flow of participants through each stage of the trial. *NAC*, *N*-acetylcysteine.

Table 1. Preoperative and operative characteristics of the study patients

	Controls (n = 125)	NAC Group (n = 129)	*p* Value
Age, yrs	72 ± 6	73 ± 6	.18
Men, n (%)	60 (48)	65 (50)	.70
Weight, kg	65 ± 12	66 ± 11	.48
Diabetes mellitus, n (%)	26 (21)	26 (20)	.97
Hypertension, n (%)	99 (79)	102 (79)	.89
Previous cardiac surgery, n (%)	11 (9)	7 (5)	.42
LVEF, %	54 ± 12	56 ± 12	.18
Serum creatinine, mg/dL	1.24 ± 0.4	1.27 ± 0.3	.49
Creatinine clearance, mL/min	46 ± 9	46 ± 7	1.00
EuroSCORE	7.3 ± 3.2	6.9 ± 2.4	.26
CPB, n (%)	112 (90)	116 (90)	.93
CABG, n (%)	54 (43)	51 (40)	.64
Aortic or mitral valve repair, n (%)	42 (34)	47 (36)	.73
Combined CABG and valve repair, n (%)	19 (15)	13 (10)	.29
Combined mitral/aortic valve repair, n (%)	10 (8)	18 (14)	.18
Urgent surgery, n (%)	8 (6)	8 (6)	.94
CPB time, mins	111 ± 42	120 ± 58	.15
CPB >3 hrs, n (%)	7 (6)	13 (10)	0.18

NAC, *N*-acetylcysteine; LVEF, left ventricular ejection fraction; CPB, cardiopulmonary bypass; CABG, coronary artery bypass graft surgery.

and calculated creatinine clearance values in the two groups during the ICU stay. When the maximal creatinine increase vs. baseline was considered, regardless of the time of occurrence, a mean value of 34 ± 44% was found in patients treated with NAC and 39 ± 50% in controls ($p = .39$).

Table 2 shows the major postoperative clinical complications and mortality rates in the two study groups. The rates of ARF were 52% (n = 65) in the control group and 40% (n = 52) in the NAC group ($p = .06$). The relative risk of ARF in the control group, compared with the NAC group, was 1.60 (95% confidence interval 0.98–2.63; $p = .06$). In NAC-treated patients, a lower percentage of patients required prolonged (>48 hrs) mechanical ventilation (3% vs. 18%; relative risk 6.67; 95% confidence interval 2.32–19.08; $p < .001$) and a prolonged (>4 days) ICU stay (13% vs. 33%; relative risk 3.22; 95% confidence interval 1.72–6.01; $p < .001$) (Table 2). ICU length of stay and ventilation time were significantly correlated ($r = .51$; $p < .0001$) among the entire population. When the effect of NAC on the primary study end point was analyzed in different subsets of patients, a significant benefit, in terms of ARF incidence, was observed in patients undergoing cardiac surgery with CPB (40% of ARF in NAC-treated patients vs. 54% in controls; $p = .03$). No positive effect of NAC was observed in patients who did not require CPB (46% of ARF in NAC-treated patients vs. 31% in controls; $p = .41$). No significant interaction was found between NAC effect and kind of operation (chi-square 0.6; $p = .89$).

The overall in-hospital mortality in our population was 3.5% (n = 9) and was not affected by NAC. Indeed, four (3%) patients died in the control group and five (4%) patients died in the NAC group ($p = .77$).

DISCUSSION

Our study confirms that ARF is a frequent complication of cardiac surgery occurring in almost 50% of patients with moderate and severe renal insufficiency, as defined by a calculated creatinine clearance <60 mL/min. In agreement with previous studies (1–6), a close association between postoperative ARF development and increased morbidity, mortality, and prolonged ICU stay was also found. Indeed, a 10-times higher mortality rate was observed in patients developing this complication, increasing >30 times for patients requiring renal replacement therapy. Therefore, prevention of ARF in patients with preexisting renal insufficiency is needed and is a stimulating opportunity for development of new pharmacological approaches to such a costly injury. Notably, patients with renal insufficiency represented 15% of patients referred to our institute for cardiac surgery.

Although the pathogenesis of postoperative ARF remains poorly understood, it probably includes a broad pattern of mechanisms such as hemodynamic factors, effects of nephrotoxic drugs, systemic inflammatory reaction and vasoconstrictor compound release induced by CPB, and the interactions of blood components and artificial membranes (12, 25). All these mechanisms may contribute to vasoconstriction and renal ischemia and result in formation of oxygen free radicals.

NAC has direct vasodilating effects in the kidneys, contributing to improved renal hemodynamics; it may attenuate endothelial dysfunction; and, more important, it is able to scavenge oxygen-free radicals, thus preventing direct oxidative tissue damage (26, 27). Recent attention has been focused on the use of NAC as a

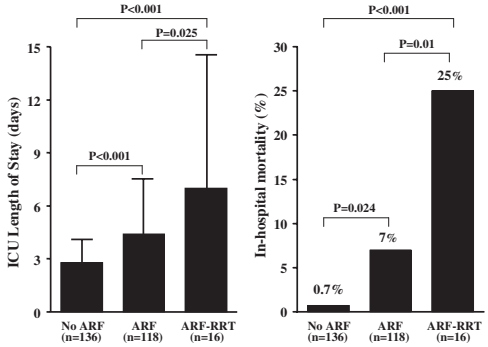

Figure 2. Length of stay in the intensive care unit (*ICU*; *left*) and in-hospital mortality (*right*) in patients without acute renal failure (*no ARF*), those with acute renal failure (*ARF*), and those with acute renal failure requiring renal replacement therapy (*ARF-RRT*).

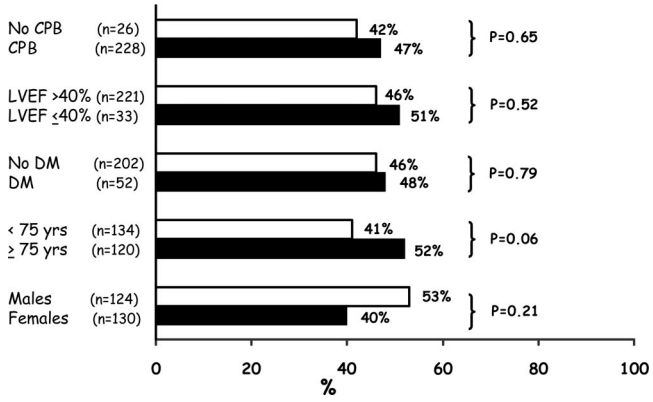

Figure 3. Incidence of postoperative acute renal failure in various subgroups of patients. *CPB*, cardiopulmonary bypass; *DM*, diabetes mellitus; *LVEF*, left ventricular ejection fraction.

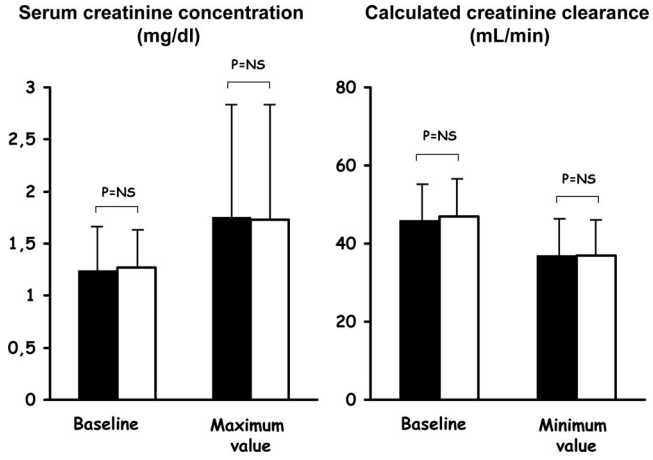

Figure 4. Baseline and maximum values of serum creatinine concentration (*left*) and baseline and minimum values of calculated creatinine clearance (*right*) in patients treated with *N*-acetylcysteine (*filled bars*) and in controls (*unfilled bars*). Values are mean ± SD. *NS*, not significant.

measure to attenuate renal toxicity due to contrast agent exposure (15, 23, 26–30).

The use of NAC to prevent ARF in patients undergoing cardiac surgery has been recently investigated with conflicting results (31–35). In the study by Burns et al. (31), no difference in the proportion of patients with postoperative ARF was found (30% in NAC-treated patients and 29% in control group), nor was it found in the proportion of patients requiring a renal replacement therapy (0.7% vs. 2.1%, respectively). Furthermore, in-hospital mortality was not affected by NAC (3.4% vs. 2.7%, respectively). The NAC dose used in this study was similar to that initially proposed by Tepel et al. (15) for the prevention of contrast-induced nephropathy in patients undergoing a low-dose contrast exposure during computed tomography (cumulative dose of 2400 mg). Further studies have clearly demonstrated that higher NAC doses may be required when larger contrast volumes are used (28–30). NAC dose-dependent preservation of renal function was also recently demonstrated after cardiopulmonary bypass in a rat model (36). A recent study by Haase et al. (35), using high doses of NAC (300 mg/kg) in a small population of high-risk cardiac surgery patients, also yielded negative results. However, in the studies by Burns et al. (31) and by Haase et al. (35), only a minority of patients (23% and 17%, respectively) had baseline renal insufficiency. The renoprotective action of NAC in patients with risk factors other than renal insufficiency has never been clearly established. Therefore, due either to the nonhomogeneous population considered (31, 35) or to the small number of patients included in previous studies (32, 35), the effects of NAC in patients with baseline renal insufficiency undergoing cardiac surgery remain undefined, particularly when significant clinical end points are considered.

Only patients with baseline renal insufficiency were included in our study, and a greater cumulative dose of NAC (4800 mg) than that previously used in large studies was administered. Although we observed a reduction in the incidence of the primary end point, this reduction did not reach statistical significance. The requirement for renal replacement therapy and the in-hospital mortality rate were not influenced by the drug. There are a number of possible explanations for the lack of a clear clinical benefit from NAC. We can speculate that given the dose-dependent effects of NAC, an even greater dose of NAC is required to prevent kidney injury during surgery, or that among the several mechanisms underlying postoperative renal damage, oxidative stress does not play a major role. The negative results obtained by Haase et al. (35) with higher doses than those used in our study suggest that the second hypothesis is probably the true one.

Despite the overall negative results of our study, some interesting findings worthy of further future investigation must be emphasized. When only patients undergoing cardiac surgery with CPB support were considered (90% of our study population), NAC-treated patients showed a significantly lower incidence of ARF than controls (40% vs. 54%; $p = .03$). It is possible that the difference in ARF incidence reflects the

Table 2. Perioperative clinical complications

	Controls (n = 125)	NAC Group (n = 129)	*p* Value
Acute myocardial infarction	5 (4)	2 (2)	.23[a]
Hypotension or shock requiring i.v. catecholamines	58 (46)	55 (43)	.54
Cardiogenic shock requiring IABP	6 (5)	2 (2)	.13
Reoperation for any reason	7 (6)	10 (8)	.49
Prolonged (>48 hrs) mechanical ventilation	22 (18)	4 (3)	<.001[a]
Bleeding requiring blood transfusion	69 (55)	72 (56)	.92
Acute renal failure (>25% increase in serum creatinine)	65 (52)	52 (40)	.06
Acute kidney injury (increase in serum creatinine ×2)	11 (9)	12 (9)	.88
Acute renal failure requiring RRT	6 (5)	10 (8)	.33
Time between ICU admission and start RRT, days	2.3 ± 0.5	2.2 ± 0.4	.66
Need for high-dose furosemide (>250 mg/day)	22 (18)	18 (14)	.56
Infections requiring nephrotoxic antibiotics[b]	17 (14)	21 (16)	.55
ICU stay >4 days	41 (33)	17 (13)	<.001
In-hospital death	4 (3)	5 (4)	.77[a]

NAC, *N*-acetylcysteine; i.v., intravenous; IABP, intra-aortic balloon pump; RRT, renal replacement therapy; ICU, intensive care unit.

[a]By Fisher exact test; [b]vancomycin, gentamicin, amikacin, imipenem. Values are n (%) except for time between ICU admission and start RRT, which is given as mean ± SD.

counteracting action of NAC on oxidative stress, reperfusion injury, and systemic inflammatory response associated with CPB. Indeed, severe oxidative stress has been reported to result from the extracorporeal circulation of blood (37), from blood cardioplegia (38), and from reoxygenation injury (39). Moreover, off-pump procedures have been shown to be associated with lower degrees of oxidative stress than on-pump cardiac surgery (40). In addition to its antioxidant properties, NAC carries out an anti-inflammatory action by suppressing cytokine expression/release and inhibiting adhesion molecule expression and nuclear factor-κB (41, 42). Pretreatment with NAC has been found to reduce CPB-induced oxidative stress and inflammatory response and to preserve myocardial function after cardioplegic arrest (43, 44). Attenuation of myocardial dysfunction due to ischemia-reperfusion during CPB might in turn preserve renal perfusion and result in a lower incidence of ARF. This effect might be amplified in patients with chronic renal insufficiency, a clinical condition associated with increased oxidative stress (45).

In our study, patients treated with NAC were less likely to require mechanical ventilation for a prolonged period and, as a consequence, to have a long-lasting ICU stay. This suggests a positive effect of NAC on pulmonary function that influences a patient's clinical course. During CPB there is no blood flow in the pulmonary artery, and the lungs are made partially ischemic. Reperfusion occurs when the patient is weaned from extracorporeal support. Ischemic reperfusion is accompanied by release of oxygen free radicals, as well as an increase of several parameters of inflammation, which have been implicated as the main cause of postischemic lung injury (46, 47). Several studies have also demonstrated that after CPB, endothelial function in the pulmonary circulation is impaired and pulmonary vascular permeability and lung water are increased. These changes have been associated with a parallel rise in malondialdehyde levels, an important decomposition product of lipid peroxidation (48, 49). Moreover, wide experimental and clinical evidence exists that antioxidant agents, in particular NAC, reduce lung reperfusion injury after CPB. Indeed, NAC has been demonstrated to maintain the endothelium-dependent vasodilatation in the pulmonary circulation (50); to prevent, or attenuate, the deterioration of lung mechanics and gas exchange in endotoxemic sheep (51); to improve oxygenation and reduce ventilator-days after acute lung injury in humans (52); to attenuate lung water and malondialdehyde increase in dogs (48); and to lower the increase in postoperative arterial-alveolar oxygen gradient, thus improving systemic oxygenation in patients undergoing elective coronary artery bypass surgery with CPB (53). All these potential extrarenal properties of NAC might explain the more favorable clinical outcome observed in treated patients, most of whom underwent on-pump cardiac surgery. However, any inference drawn about the efficacy of NAC on these clinically meaningful end points should be regarded as premature, albeit promising, and further data are needed before any conclusion can be made.

A possible limitation of our study is the definition of ARF. Although this definition is widely used (14, 30–32, 35) and clearly related to clinical outcome in our study, it remains, at least in part, arbitrary. Additional studies should investigate the relevance of renal effects of NAC using a consensus definition of ARF (22), and of its extrarenal effects (particularly on respiratory function), in patients undergoing on-pump cardiac surgery, as well as their possible implications on meaningful clinical outcomes. Indeed, patients undergoing cardiac surgery with CPB are those typically exposed to a systemic tissue injury due to extensive ischemia and reperfusion, and they could benefit the most from a prophylactic strategy based on the administration of antioxidant agents. Nevertheless, based on results reported in the literature and in our present study, no recommendation on the use of NAC for the prevention of ARF in all high-risk patients undergoing cardiac surgery can be made at this time.

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