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N-Acetylcysteine–Enhanced Contrast Provides Cardiorenal Protection

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Objectives We sought to evaluate the cardiac and renal effects of an N-acetylcysteine (NAC)-enhanced intracoronary radiographic contrast agent.

Background Recent studies suggest that high-dose NAC provides better protection from contrast-induced nephropathy, and the antioxidant properties of NAC may also provide cardiac protection. The use of angiographic contrast agents as a drug delivery vehicle for cardiorenal protection effects has not been investigated.

Methods In a pig model of prolonged cardiac ischemia-reperfusion, NAC-enhanced contrast medium was tested and compared with iopamidol contrast only. Myocardium and renal function were assessed after 24 h.

Results There was no significant difference in the area-at-risk for myocardial infarction (MI) between contrast only and NAC-enhanced contrast medium. In contrast, MI size was about 40% smaller in NAC-enhanced contrast medium–treated animals. These findings were associated with a significant difference in MI morphology. MIs in the NAC-enhanced contrast medium group had a mottled appearance, whereas in the contrast only group they were homogeneous and had a discrete border zone. These differences could explain a higher incidence of periprocedural ventricular arrhythmias in the NAC-enhanced contrast medium group. Histopathological analysis of the myocardium revealed a reduction in programmed cell death by NAC-enhanced contrast medium that may explain the increase in ischemia tolerance. Last, NAC-enhanced contrast medium administration blunted the rise in serum creatinine levels by about 60% and protected from renotubular apotosis.

Conclusions NAC-enhanced contrast medium reduces MI size and protects renal function in a pig model of ischemia and reperfusion. (J Am Coll Cardiol Intv 2009;2:215–21) © 2009 by the American College of Cardiology Foundation

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Contrast-induced nephropathy (CIN) remains a significant complication after cardiovascular catheterization procedures. While the overall risk of CIN complicating cardiovascular procedures is now less than 5%, this risk can exceed 30% in the setting of pre-existent renal failure, diabetes mellitus, reduced left ventricular ejection fraction, and large contrast loads (1–3). Since a reduction in CIN would improve procedural outcomes, recent efforts have focused on finding adjunctive agents that reduce the nephrotoxic effects of the available contrast agents (4).

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N-acetylcysteine (NAC) is an antioxidant agent with potential myocardial and renal protective effects (5–7). Although the use of NAC for prevention of CIN is still controversial, many clinical trials indicate a beneficial effect (8). In a recent trial that combined oral and intravenous NAC administration, an enhanced benefit of high-dose NAC was demonstrated among patients undergoing percutaneous coronary interventions (9). The sample size in this trial was large enough to demonstrate a dose-dependent mortality reduction.

Abbreviations and Acronyms

CIN = contrast-induced nephropathy
DAPI = 4',6-diamidino-2-phenylindole
DCCV = direct countercurrent cardioversion
LAD = left anterior descending artery
NAC = N-acetylcysteine
TTC = (2,3,5)-triphenyltetrazolium chloride
TUNEL = terminal uridine deoxynucleotidyl transferase dUTP nick end labeling

We hypothesized that adding NAC to an intracoronary contrast agent would match the NAC dose to the contrast volume and provide adjusted renal protection with a potential for additional myocardial protection. A proof-of-concept study was designed that would maximize the cardiac protective effects of NAC. In a pig model of prolonged myocardial ischemia and reperfusion, a fixed volume of contrast NAC mixture was administered before and after the coronary occlusion. The study end points were infarct size, area of myocardium at risk, infarct morphology, cardiac/renal apoptosis, and renal function.

Methods

Safety of intracoronary NAC. Although intracoronary NAC infusions are reported to be safe in humans, the effects of intracoronary bolus injections are not known (10). Accordingly, the effects of intracoronary NAC mixed with contrast medium on blood pressure and cardiac rhythm were tested in 2 pigs. All aspects of animal care were in accordance with the National Institutes of Health guidelines and the standards of the Animal Care and Use Committee of the University of Vermont.

After pre-medication with ketamine (20 mg/kg), the pigs were anesthetized with isoflurane, intubated and ventilated. A femoral artery sheath was placed, and a JR 4 or HS guide catheter was placed at the left main coronary artery. Twelve-lead electrocardiogram (ECG) and catheter pressures were continuously recorded.

A NAC dose of 11.3 mg/ml of iopamidol contrast (Isovue 370, Bracco Pharmaceuticals, Princeton, New Jersey) was chosen because it would deliver between 1 to 2 g of NAC for an average interventional case. As a clinical reference point, this dose is similar to the highest dose administered by Marenzi et al. (9) and about 10-fold below the recommended intravenous dose for the treatment of acetaminophen overdose (11). The dose was obtained by adding 12 ml of NAC solution (Acetadote, Cumberland Pharmaceuticals, Nashville, Tennessee) to a 200-ml lopamidol glass container.

At least 5 injections of the contrast plus NAC per animal were performed. After the experiment, the pigs were monitored for an additional hour. Blood pressure and QT interval were analyzed at the end of 3 succeeding respiratory cycles (6, 12, and 18 s after injection) and are reported as a mean percent change from baseline.

Efficacy in ischemia-reperfusion. EXPERIMENTAL PROTOCOL. The pigs (28 ± 5 kg) were assigned to either iopamidol contrast alone (n = 5) or contrast containing NAC at a concentration of 11.3 mg/ml (n = 7). Adding the NAC solution to the contrast agent does not significantly reduce the contrast quality of the angiograms based on our measurements using our previously described technique of quantitative fluoroscopy (12). The pigs were prepared as described in the safety study. All pigs received a heparin bolus (2,000 U). A guidewire (PT2, Boston Scientific, Natick, Massachusetts) and balloon (Monorail Maverick, 2.5 × 15 mm, Boston Scientific) was advanced into the left anterior descending artery (LAD) followed by balloon inflation just distal to the second diagonal branch. Total occlusion time was 60 min. A fixed volume of 200 ml of contrast medium was administered to each animal. Approximately one-half of the contrast volume was used to place the equipment resulting in NAC administration before the ischemic event to maximize its potential beneficial effect. The remaining contrast was injected during the reperfusion period. After approximately 30 min, all equipment was withdrawn. A femoral artery closure device (Angio-Seal, St. Jude Medical, St. Paul, Minnesota) was deployed. After the extubation, the animals were transferred to the housing facility. No animal died during housing.

After 24 h, the animals were resedated and intubated. A sternotomy was performed. Ligatures were placed at the proximal balloon occlusion site, the aortic arch branches, and the descending aorta. A cannula was advanced into the aortic root from a right carotid arterial access and connected to 1.5% Evans Blue dye, Sigma-Aldrich, St. Louis, Mis-

souri. The vessels were then occluded in the following order: LAD, aortic arch branches, and descending aorta. The dye was then injected at a pressure of 120 mm Hg until the myocardium was stained. The unstained myocardium distal to the LAD ligature was defined as the area-at-risk. Two NAC-treated hearts could not be used for the morphometric analysis due to dye wash-out and a failed cardioversion.

HEMODYNAMIC AND ELECTROCARDIOGRAPHIC RECORDING. After the deflation of the balloon, blood pressure, heart rate, and ECG were recorded for another 30 min. Ventricular tachycardia (≥4 beats) or ventricular fibrillation during coronary occlusion or reperfusion were documented. Direct countercurrent cardioversion (DCCV) was provided for hemodynamic instability. No antiarrhythmic medications were used.

AREA-AT-RISK AND INFARCT MEASUREMENTS. The hearts were harvested, and the ventricles were sliced into 1-cm cuts in a bread loaf fashion, with the first slice at the apex. The basal surfaces of the slices were imaged. Samples of myocardium from areas of necrosis, area-at-risk, and normal left ventricular myocardium were obtained from the apical side of the second and third slice and stored for additional analyses. Thereafter, all slices were incubated in a solution containing 1.5% (2,3,5)-triphenyltetrazolium chloride (TTC) for 25 min. The basal surfaces were then reimaged, and area analysis (planimetry) was performed (Scion Image 4.0.2, Scion Corp., Frederick, Massachusetts). The size of the area-at-risk and infarct size for each slice was determined by multiplying the mass of the slice by the fraction of area-at-risk or by the fraction of area of infarction. Total infarct size and the area-at-risk size were expressed as a percentage of biventricular mass.

INFARCT MORPHOLOGY. In order to quantify the apparent differences in infarct morphology, a circumference/area index of the infarcted myocardium using TTC-stained sections was calculated. A low numerical value indicates a homogenous and discrete border zone, whereas a higher numerical value indicates a more complex, mottled border.

APOPTOSIS. Terminal uridine deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) stains (in-situ apoptosis detection, Roche, Indianapolis, Indiana) of nonischemic, area-at-risk, and infarcted tissue samples were performed. A total of 4 samples from 2 control animals and 6 samples from 3 NAC-treated animals were analyzed. Tissue sections were deparaffinized and permeabilized with proteinase K. Sections were mounted with Vectashield mounting medium containing 4',6-diamidino-2-phenylindole (DAPI) (Vector Laboratories, Burlingame, California) as a nuclear counterstain. The percentage of apoptotic nuclei per section was calculated by counting the total number of TUNEL-staining nuclei divided by the total number of DAPI-positive nuclei as previously described (13). Microscopic evaluation of TTC-negative myocardial infarction tissue revealed hemorrhage and areas of contraction band necrosis associated with a minimal loss in cross striations. This was not observed in the noninfarcted or area-at-risk tissue. Renal TUNEL results were quantified as the number of TUNEL plus DAPI-positive epithelial cell nuclei per proximal tubule cross section from 3 control and 4 NAC-treated samples.

Serum analysis. Serum that was collected before contrast exposure and 24 h after infarction was analyzed for creatinine concentrations.

Statistical analysis. End points were infarct and area-at-risk size, infarct morphology, percentage of TUNEL-positive cells, and change in serum creatinine at baseline and after 24 h of reperfusion. End points between the NAC-enhanced contrast group and iopamidol contrast only group were compared by 1-way analysis of variance. In the dose escalation study, the effect of each injection on blood pressure and QT interval was expressed as a percentage change from the immediately preceding baseline and analyzed by a Wilcoxon matched-pairs signed ranks test. A p value of <0.05 was accepted as statistically significant. All results are reported and depicted as mean (± SD).

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Intracoronary NAC dose escalation: blood pressure and QT interval. Injections of contrast containing NAC did not cause any arrhythmias or changes in heart rate. Immediately after the injection of 5 ml of contrast containing 11.3 mg/ml NAC, we observed a brief reduction of systolic blood pressures averaging 5% at the 6-s time point after the injection ($p < 0.05$). This was accompanied by a transient 17% reduction in diastolic blood pressure ($p < 0.05$). At 18 s, systolic pressure had returned to pre-injection pressures, whereas diastolic pressure continued to be decreased by 7% ($p < 0.05$). Complete normalization of blood pressure was achieved after 45 to 60 s. Control injections with iopamidol contrast did not show such effects.

Effect of intracoronary NAC on myocardial infarction. Comparison of the non–Evans Blue-stained areas reflecting the area-at-risk in NAC-treated animals ($n = 5$) and control animals ($n = 5$) did not reveal a significant difference. Expressed as a percentage of ventricular myocardium, area-at-risk was 15.1 ± 4.8% in control hearts and 18.4 ± 1.8% in NAC-treated hearts ($p = 0.2$). Infarct size as percent of ventricular myocardium determined by TTC staining was 13.9 ± 4.5% in control animals and 8.2 ± 2.3% in NAC-treated animals ($p < 0.05$). Infarct size expressed as a percentage of the area-at-risk was 92.4 ± 6.3% in controls hearts and 44.7 ± 12.4% in NAC-treated hearts ($p < 0.01$), suggesting a NAC-mediated protection from infarct progression (Fig. 1).

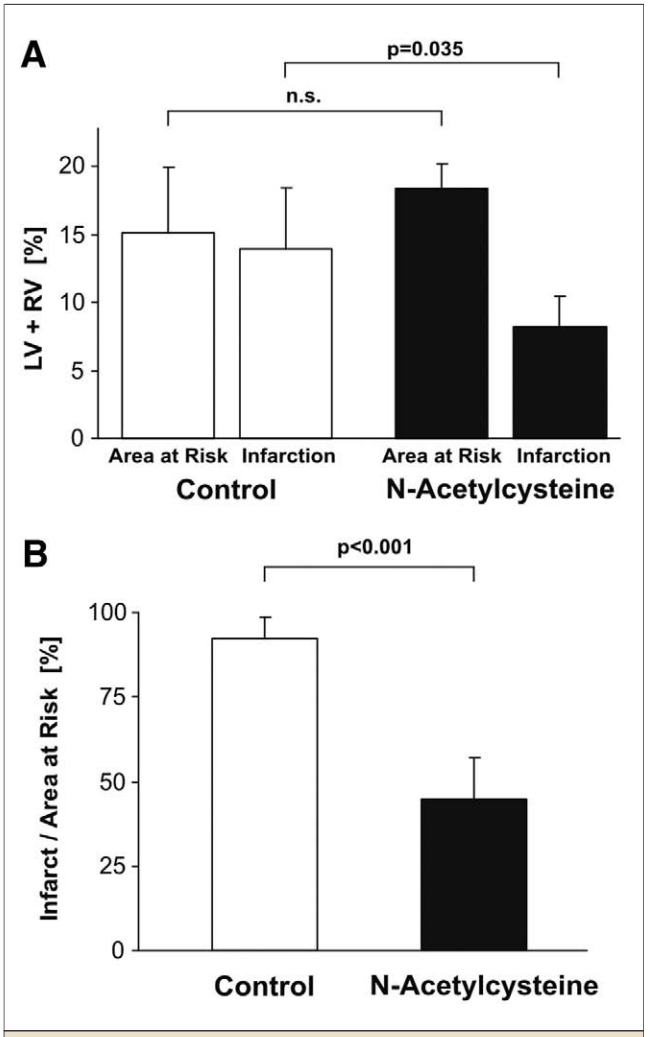

Figure 1. Myocardial Infarct Size and Area-at-Risk

A depicts the area-at-risk and the area of infarction in 5 control (iopamidol contrast-only) and 5 N-acetylcysteine (iopamidol contrast plus 11.3 mg/ml N-acetylcysteine) treated pig hearts expressed as percentage of ventricular myocardium. The bar graph in **B** depicts the percentage of the area-at-risk that was infarcted in both control animals and N-acetylcysteine–treated animals. LV = left ventricle; RV = right ventricle.

The morphologic appearance of the infarcted area differed markedly between the 2 groups. Infarcts in control animals were homogeneous with discrete borders while infarcts in NAC-treated animals contained areas of viable myocardium interspersed with infarcted areas resulting in a mottled appearance. Reflecting this difference, the ratio of infarct circumference to infarct area was greater in NAC-treated animals (Figs. 2A and 2B).

To investigate if the protective effect of NAC is mediated by protection from apoptosis, we performed TUNEL assays. In myocardium obtained from non-LAD territories (nonischemic), we found a low number of TUNEL-positive myocyte nuclei without a significant difference between NAC-treated and control animals. Within the infarct tissue of control animals, 35.8 ± 5.7% of nuclei stained positive for apoptosis compared with 33.0 ± 3.7% in NAC-treated animals ($p = 0.4$). In contrast, in tissue obtained from the noninfarcted area-at-risk obtained from control animals, 32.1 ± 4.0% of nuclei stained TUNEL positive, whereas this value was 1.6 ± 1.6% in NAC-treated animals ($p < 0.001$), suggesting NAC-mediated protection from apoptosis (Fig. 3). To further study if sample location within the area-at-risk might have contributed to our findings, we reviewed our microscopic slides for gradual changes in apoptosis rates within our samples (e.g., reduction in apoptosis rates towards the outer risk zones). No such gradients were apparent.

Periprocedural arrhythmias. Neither animal in the dose escalation study and none of the control ischemia-reperfusion animals developed ventricular fibrillation or required DCCV. One control animal had a brief episode of self-terminating ventricular tachycardia during reperfusion. In contrast, all NAC-treated animals developed ventricular tachycardia, fibrillation, or both during ischemia-reperfusion. All of these events occurred either in the second half of the balloon occlusion or during the first 15 min of reperfusion. There was no temporal association between

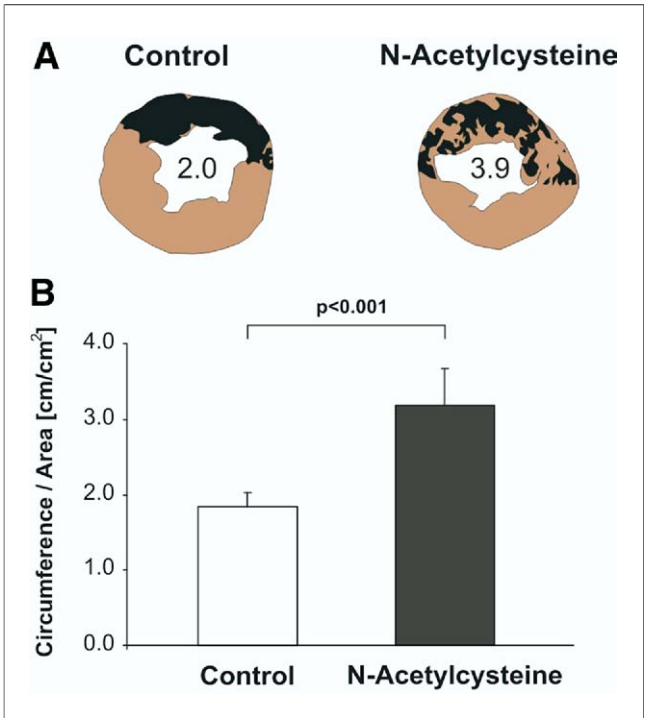

Figure 2. Myocardial Infarct Heterogeneity

A demonstrates an example of the infarcted area **(black)** in a left ventricular slice obtained from a control (iopamidol contrast-only) and N-acetylcysteine (iopamidol contrast with 11.3 mg/ml N-acetylcysteine) treated animal. The infarction in the N-acetylcysteine–treated animal is mottled with interspersed areas of viable myocardium **(brown)**. The numerical values reflect the ratio of the infarct circumference to infarct area an index for infarct heterogeneity. The bar graph in **B** depicts the results of the group analysis.

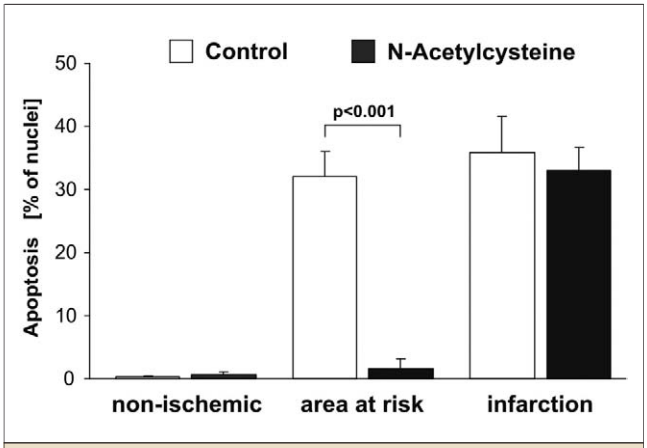

Figure 3. Myocardial Apoptosis

Bar graph depicting the percentages of terminal uridine deoxynucleotidyl transferase dUTP nick-end labeling positive nuclei reflecting apoptosis in nonischemic, area-at-risk, and in infarcted myocardium from control and N-acetylcysteine–treated animals.

NAC injection and the onset of the arrhythmia. Episodes of isolated ventricular tachycardia in the NAC group were of a longer duration compared with the one observed episode in a control animal. Most often ventricular tachycardia degenerated rapidly into ventricular fibrillation in the NAC-treated animals. DCCV only failed once due to a 4-min time delay. One animal in the NAC group that could not be used for the morphometric myocardial infarction analysis due to insufficient Evans Blue staining had an episode of ventricular tachycardia followed by fibrillation after initiating anesthesia on day 2 of the study. Periprocedural arrhythmias are summarized in Table 1.

Effect of intracoronary NAC on serum creatinine levels and renal apoptosis. Blood samples for creatinine were obtained before the administration of the contrast agent and 24 h after infarction. Baseline creatinine level before contrast medium administration was 1.32 ± 0.26 mg/dl in the control group and 1.29 ± 0.15 mg/dl in the NAC-treated group. One day after contrast exposure, creatinine levels rose to 1.82 ± 0.24 mg/dl in the control group ($p < 0.05$) and 1.49 ± 0.06 mg/dl in the NAC-treated animals ($p < 0.05$). The comparison of the 24-h creatinine levels in the NAC versus control groups showed a significant reduction in creatinine levels indicating a protective effect of NAC ($p < 0.05$). These data are summarized in Figure 4.

Additionally TUNEL assays of renal tissue revealed that apoptosis rates of epithelial cells in the proximal tubules were reduced by approximately 75% in NAC-treated animals (0.42 vs. 0.11 TUNEL plus DAPI-positive nuclei/proximal tubule).

Table 1. Significant Arrhythmias During Occlusion and Reperfusion

Control	
1	none
2	none
3	none
4	VT, self-terminating (2 min reperfusion)
5	none
N-acetylcysteine	
1	VT, VF, successful cardioversion (7 min reperfusion)
2	VT, self-terminating, (45 min occlusion)
3	VT, self-terminating (5 min reperfusion)
4	VF, successful cardioversion (10 min reperfusion)
5	VT, VF, unsuccessful cardioversion (38 min occlusion)
6	VT, VF, successful cardioversion (5 min reperfusion)
7	VT, VF, successful cardioversion (33 min occlusion)

Ventricular tachycardia (VT), ventricular fibrillation (VF), and direct countercurrent cardioversion in pigs undergoing an ischemia-reperfusion protocol. The control animals received iopamidol contrast only, whereas animals in the N-acetylcysteine group received N-acetylcysteine added to the iopamidol contrast agent.

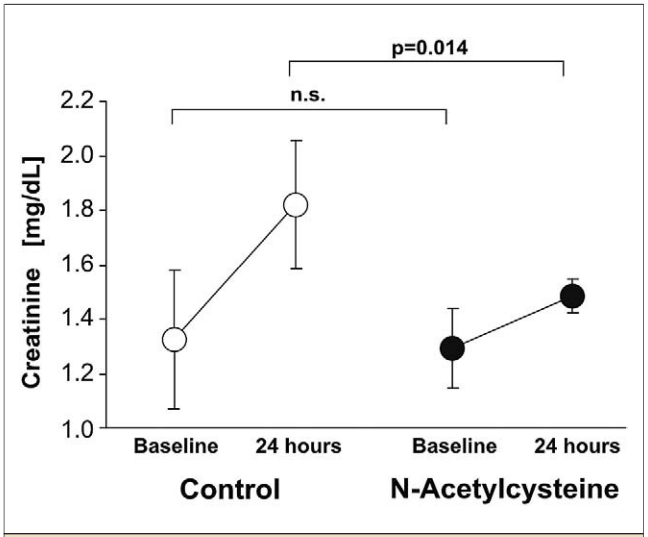

Figure 4. Contrast-Induced Nephropathy

Graph demonstrating creatinine concentrations before (baseline) and 24 h after administration of intracoronary iopamidol contrast agent (200 ml). Where indicated N-acetylcysteine (11.3 mg/ml) was added to the contrast agent.

Discussion

The present study demonstrates that intracoronary administration of a radiographic contrast agent mixed with NAC at a dose similar to those used in a recent clinical trial provides cardiorenal protection in a model of ischemia-reperfusion. Infarct size as a percentage of area-at-risk was reduced by about one-half, and the rise in serum creatinine after contrast administration was blunted in NAC-treated animals.

Direct effects of intracoronary NAC. A small transient QT prolonging effect of NAC at a dose of 11.3 mg/ml contrast was observed after intracoronary bolus injections. The transient, mild decrease in both systolic and diastolic blood pressure may indicate a myocardial depressant or a vasodi-

lator effect. The latter appears more likely in light of a previous human trial of intracoronary NAC administration (480 mg over 10 min) that found a NAC-mediated improvement in endothelial function leading to enhanced vasodilation without significant hypotension (10). NAC may enhance the bioavailability of nitric oxide by forming biologically active byproducts or by scavenging the oxygen free radicals that are largely responsible for the short half-life of nitric oxide (14). The blood pressure effect in healthy pigs was small and transient in nature and may have been induced by the bolus injections since no such effects were seen in the human study (10).

Cardiac and renal protection. The antioxidative properties of NAC have been implicated as the mechanism of its cardioprotective effect (5). In a canine model of myocardial ischemia-reperfusion, both infarct size and reperfusion arrhythmias were reduced when intravenous NAC was given predominantly during reperfusion (15). In 2 clinical studies, intravenous NAC was combined with fibrinolytic therapy in patients with acute ST-segment elevation myocardial infarction (5,6). A decrease in infarct size and improved R-wave recovery were reported in association with improved global and regional ejection fraction. Our study design differs from the previous animal and human studies in 2 ways: first, we utilized an intracoronary route of administration and second, NAC was given both before and after coronary occlusion to maximize the cardioprotective effect. As a result, a component of the approximately 40% reduction in infarct size in the NAC group may be mediated by an increase in the ischemia tolerance that slows infarction progression (16). This could explain the pronounced difference in infarct morphology in the contrast NAC-treated animals. Analysis of the infarcted myocardium revealed viable areas within the infarct zone in the NAC-treated animals, resulting in a heterogeneous and mottled appearance; however, infarcts in control animals were homogenous, with distinct border zones.

The 37% increase in creatinine levels in healthy young pigs with an average body weight of 28 kg was not unexpected considering that a total of 200 mm of contrast was administered without periprocedural hydration. This observation underscores the impact of contrast volume on renal function. Our results indicate that NAC administered with contrast reduced the rise in creatinine levels by about 60%, which is in line with recent human trials in which high doses of NAC were used (9,17). Our results show for the first time that NAC contrast coadministration without NAC loading is sufficient to mediate a renal protective effect. Similar to previous human trials, NAC could be administered intravenously. However, coadministration guarantees that the protective agent (NAC) is delivered simultaneously leading to a dose increase that is proportional to the injurious agent (contrast volume).

In extension of the functional improvement in renal function, we found an about 75% reduction in the proximal tubular apoptosis rate in NAC-treated animals. This level of protective effect is similar to the results from a human study demonstrating a NAC-mediated antioxidative protection from contrast-induced renotubular injury (18).

Arrhythmias. Our results indicate that NAC at a concentration of 11.3 mg/ml can be safely delivered as a bolus to the coronary circulation during diagnostic angiography in exactly the same fashion as contrast agents without inducing hemodynamic instability, arrhythmias, or prolonged QT interval changes. In contrast, we found an increase in ventricular tachycardia and fibrillation during ischemia-reperfusion in animals that received NAC. These arrhythmias were not temporally associated with the bolus injections and responded well to electrical cardioversion if delivered in a timely manner. No animal died during the 24-h period of housing that followed the procedure.

Our finding in regards to ventricular arrhythmias was unexpected. It contrasts with a study in which NAC administration at the time of reperfusion in a canine model was associated with a marked reduction in ventricular arrhythmias (15). No increase in arrhythmias were reported in 3 human trials in which intravenously administered NAC was given either with lytic therapy or primary percutaneous intervention in patient with ST-segment elevation infarctions (5,6,9). Our finding may be related to the changes in the infarct morphology with areas of viable myocardium interspersed into infarcted areas. Such mottled infarction patterns are well documented to provide foci and re-entry pathways for ventricular arrhythmias (19,20). Since this proof-of-concept study was designed to maximize the cardiac efficacy, our results in regard to the arrhythmias may have been introduced by pre-loading the animals with NAC thus altering the evolution of the myocardial infarction.

Study limitations. We did not measure the antioxidative effects of NAC although this has been done directly in a prior human trial (5). It is possible that other mechanisms may contribute to our findings of cardiorenal protection. The occurrence of a potentially life-threatening ventricular arrhythmia presents a very serious issue that if reproduced in a clinical setting would prevent the use of this novel agent in acute myocardial infarctions. Initial clinical evaluation may thus be first targeted towards elective PCI cases at high risk for acute renal failure and lower risk for ventricular arrhythmias. Despite a significant difference in the studied end points between the groups the sample size in this proof-of-principle study is small. A larger animal study that more accurately simulates clinical practice in respect to the timing of the NAC contrast mixture is necessary. Altering the protocol in a way that the NAC contrast administration occurs during the myocardial infarction is not expected to affect renal efficacy but could significantly reduce the cardiac

benefit, which in turn may reduce the incidence of ventricular arrhythmias.

Conclusions

We have demonstrated the feasibility and efficacy of delivering NAC in conjunction with an intracoronary contrast agent to provide combined cardiac and renal protection in the setting of ischemia-reperfusion. This observation may have potential application in clinic practice. The use of contrast agents enriched with NAC would guarantee that patients who receive large amounts of contrast medium and are, therefore, at a higher risk of CIN would be protected by larger doses of NAC. Furthermore, our results are consistent with prior studies suggesting that NAC provides significant myocardial protection during ischemia-reperfusion. As noted earlier, the potential risk of ventricular arrhythmias as well as the magnitude of cardiac and renal protection will need to be carefully assessed in future animal studies that more closely simulate clinical practice.

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Key Words: contrast medium ■ ischemia ■ reperfusion ■ antioxidants.