PRECLINICAL STUDIES

A Novel Contrast Removal System From the Coronary Sinus Using an Adsorbing Column During Coronary Angiography in a Porcine Model

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OBJECTIVES
This study examined the efficacy of a novel system to remove contrast from the coronary sinus (CS) using an adsorbing column during coronary angiography.

BACKGROUND
Contrast-induced nephropathy (CIN) has become a serious problem for patients with pre-existing renal insufficiency undergoing percutaneous coronary intervention (PCI).

METHODS
Eight swine were studied to evaluate the efficacy of the contrast removal system. A newly developed 8-F blood suction catheter was inserted into the CS via the right femoral vein. The venous blood from the CS was transferred into the 500-ml contrast-adsorbing column using an extracorporeal system. A total of 155 ml of contrast medium was infused selectively into the coronary artery. Five swine were treated extracorporeally for 90 min using adsorbing columns, and three were treated without columns as a control group.

RESULTS
The mean calculated iodine removal rate was 49.4%. The area under the curve of the iodine concentration in the group treated with the column was significantly smaller, by 60%, than that of the group treated without the column (p = 0.0003). No significant adverse effects were observed in the subjects’ vital signs throughout the experiments.

CONCLUSIONS
The contrast removal system from CS is effective and safe during coronary angiography in swine. This technique may be useful for preventing CIN in patients with renal insufficiency undergoing PCI. (J Am Coll Cardiol 2006;47:1866–70) © 2006 by the American College of Cardiology Foundation

Contrast-induced nephropathy (CIN) is the third leading cause of hospital-acquired renal insufficiency, accounting for 12% of all cases (1). Acute renal failure requiring dialysis after coronary intervention is associated with a poor clinical outcome, including 22.6% to 35.7% in-hospital mortality and 18.8% two-year survival (2,3). Percutaneous coronary intervention (PCI) has recently become a common therapy for coronary artery disease in the drug-eluting stent era. A large volume of contrast medium is sometimes administered in PCI for complicated lesions, including chronic total occlusion. Moreover, diabetes mellitus and diabetic nephropathy are becoming more common in Japan and throughout the world. It has been reported that diabetic patients with baseline creatinine values of <2.0 mg/dl are at higher risk than non-diabetic patients for acute renal failure after PCI, which is highly correlated with death during the index hospitalization and after dismissal (4). Even normal renal function patients with acute myocardial infarction undergoing primary PCI have a poor prognosis when their condition is complicated with CIN (5). Baseline renal insufficiency in patients with acute myocardial infarction undergoing primary PCI is associated with a markedly increased risk of mortality (6).

In order to prevent CIN, we have invented a novel contrast removal system from the coronary sinus (CS) using an adsorbing column during coronary angiography. The CS is the main drainage channel of venous blood from the myocardium. Most of the contrast medium injected into the coronary artery during coronary angiography is thought to drain into the CS. In the present study, we have evaluated the safety and efficacy of the novel contrast removal system in the porcine model.

METHODS
Animal preparation. This study was performed under the supervision of the Animal Research Committee in accordance with the guideline on animal experiments of IVTeC Company, NRT Lab, and the Japanese government Animal Protection and Management Law (No. 105). Eight swine (LWD strain, 3 to 4 months in age, weighing 41.5 to 57.3 kg) were studied. Five swine were treated extracorporeally with adsorbing columns, and three swine were treated without columns as a control group. After premedication with 10 mg ketamine hydrochloride intramuscularly and 2 mg xylazine intramuscularly, the animals were intubated and maintained with 5% isoflurane and maintained on mechanical ventilation throughout the study. Administration of 200 IU/kg heparin was carried out via the ear vein before the extracor-
contrast-induced nephropathy
CS = coronary sinus
PCI = percutaneous coronary intervention

Contrast removal from coronary sinus

Abbreviation and Acronyms
CIN = contrast-induced nephropathy
CS = coronary sinus
PCI = percutaneous coronary intervention

Cerebral perfusion and survival were then evaluated for 3 weeks.

Materials. The contrast-adsorbing columns were obtained from Kaneka Corporation (Osaka, Japan). Charcoal beads coated with a hydroxyethyl methacrylate polymer were used as the column resin, which was packed into the 500-ml columns. The column was pretreated with one liter of saline, one liter of saline containing 0.1% glucose, and then one liter of saline plus 4,000 IU/l heparin. The newly developed 8-F blood-suction catheter was also obtained from Kaneka (Fig. 1). Multiple holes were drilled in the distal end of this catheter for suction, and the catheter was placed in the CS. The contrast medium (Iopamiron 370) was obtained from Nihon Schering (Osaka, Japan), and was administered with 1,000 IU/100 ml heparin. The 2.7-F microwetometers and extracorporeal systems were obtained from Kaneka. The 7-F Fogarty catheters and 7-F Swan-Ganz catheters were obtained from Edwards Lifesciences (Irvine, California).

Study design. The new 8-F blood-suction catheter was equipped with an inner catheter for stiffness and guidewire control, and was placed under fluoroscopy into the CS via the right femoral vein in each animal. A Fogarty catheter was placed into the ostium of the CS via the left jugular vein and inflated to block any leakage from the CS into the right atrium. Another balloon was placed to block the blood flow from the CS into the azygous vein, which connects the CS to the inferior vena cava in swine but not in human beings (7). The balloon was placed at the end of the CS via the right jugular vein using a Swan-Gantz catheter. The venous blood from the CS was transferred into the contrast-adsorbing column using an extracorporeal system equipped with a roller pump and multiple sensors. The total extracorporeal volume including the content volume of the column, tubes, and chambers was 280 ml. A total of 155 ± 14 ml (mean ± SD) contrast medium was infused selectively into the coronary artery at 2.6 ± 0.2 ml/min for 60 min. The time taken for extracorporeal circulation following initiation of contrast medium administration was 90 min. The blood that had passed through the column was returned into the left femoral vein. Blood flow rates in this system were 50 to 80 ml/min, which were adjusted for suction pressures. Blood samples were withdrawn at 0, 20, 30, 40, 50, 60, and 90 min from the right femoral vein and artery and at 0, 10, 20, 30, 40, 50, 60, 65, 75, and 90 min from the pre- and post-column.

Calculation of iodine concentration. Iodine concentrations at the major points were measured with inductively coupled plasma optical emission spectrometer analysis (CMC Development Department, Nihon Schering) (8). Iodine concentrations at all points were measured with the ultraviolet method, in which the plasma obtained was diluted with saline, then the amount of iodine in the plasma was determined by measuring absorbance at 243 nm. As for the measured value by both methods, a high correlation coefficient (R2 = 0.993) was obtained. The concentration of iodine in the plasma was calculated from the calibration curve that had been made by using the plasma prepared from the same animal before administration of contrast medium. The amount of adsorbed iodine (ΣIads) was estimated by subtracting the amount of iodine flowing out of the column (ΣIout) from the amount of iodine flowing into the column (ΣIin) at each time point:

\[ ΣI_{ads} = ΣI_{in} - ΣI_{out} \]

Iodine removal rate was estimated by dividing the amount of adsorbed iodine by the amount of iodine used in the contrast medium.

The amount of iodine at each time point flowing out of the column (I_{out}) and flowing into the column (I_{in}) was calculated by the following formula, using the iodine concentration in plasma (C1) at a certain measuring time (t1), the iodine concentration (C2) at the next time (t2), flow rate (Qb), and hematocrit (Ht) of the animal:

\[ I_{in} = (C_1 + C_2) / 2 \cdot Qb \cdot (1 - Ht/100) \cdot (t_2 - t_1) \]

Area under the curve (AUC) of iodine was calculated by the linear trapezoidal rule.

Biochemical analysis of plasma component. A blood cell count was done using an automatic blood cell counter. Total protein was measured with the biuret method, and albumin was determined with the BCG kit (Wako Pure Chemical Industries Ltd., Osaka, Japan). Creatinine (Cr) was measured using an enzyme-linked immunosorment assay. Total cholesterol was measured with cholesterol oxidase/HDAOS (Wako Pure Chemical Industries Ltd.). Potassium, sodium, and chlorine were determined with the ionic choice electrode (ISE method; Hitachi Ltd., Tokyo, Japan). Calcium was assayed with an OCPC method (Wako Pure Chemical Industries Ltd.).
Statistical analysis. Data are presented as mean values ± SEM except for contrast infusion volume and rate, which are expressed as mean values ± SD. High coefficient of determination was obtained by doing the regression analysis by the least square method. The iodine concentrations in the flow at the inlet and the outlet of the column were analyzed by paired Student t test. The iodine concentrations in peripheral blood resulting from the use of the column and AUC in femoral venous blood treated with or without the column were analyzed by a non-paired Student t test. Significance was assigned to a value of p < 0.05. These analyses were performed with Stat View J-4.51.2 (SAS Institute, Cary, North Carolina).

RESULTS

Iodine concentrations of pre- and post-column. The iodine concentrations at the outlet of the column during the infusion of the contrast medium into the coronary artery (10 to 60 min circulation) were significantly lower than those at the inlet of the column, which were equal to those in the blood-suction catheter (p < 0.001) (Fig. 2). The mean iodine removal rate was 49.4% in the group treated with the column, accounting for 72% of the contrast medium that passed through the column (Fig. 3). This column was theoretically saturated with 120 ml contrast medium at maximum.

Iodine concentrations of peripheral vein and artery. The iodine concentrations in the femoral vein and artery throughout the extracorporeal circulation (20 to 90 min) in the group treated with the column were significantly lower than those in the group treated without the column (p < 0.0005; p < 0.003) (Fig. 4). The AUC of the iodine concentration in the group with the column was significantly smaller by 60% than that of the group without the column (p < 0.0003) (Fig. 5).

Effects of the system on biochemical data and vital signs. No significant differences in the red blood cell, white blood cell, or platelet counts, hematocrit levels, or the blood levels of total protein, albumin, total cholesterol, Cr, K, Na, Cl, or Ca were seen between the extracorporeal experiments with and without the column (Table 1). No significant adverse effects on the subjects' vital signs, including blood pressure, body temperature, and electrocardiogram data, were observed throughout the experiments (data not shown).

DISCUSSION

Human application of the system on contrast removal. The system used in the present study efficiently removed contrast medium injected into the coronary artery from the CS. Using the mean iodine removal rate of 49.4%, only 75.9 ml contrast medium would burden the kidney when the
contrast removal system and 150 ml contrast medium, injected only into the coronary artery during angiography or PCI, are used. The iodine removal rate would be reduced to some extent by not using the proximal balloon block with the Fogarty catheter for safety reasons in human applications and also by the bolus infusion of the contrast medium into the coronary artery, as in actual coronary angiography and PCI procedures. The new 8-F blood-suction catheter for the CS can be easily placed from the femoral vein into the CS under fluoroscopic guidance without the administration of contrast medium. Multiple side-holes in the distal catheter would help to withdraw CS flow efficiently and safely in human application from the left coronary artery as well as the right coronary artery, which mainly drains into or adjacent to the ostium of the CS. Because the communication between the azygous vein and the distal coronary sinus in swine does not normally exist in human beings, a distal balloon block would not be needed in human applications. **Efficacy of contrast removal from the coronary sinus.** Compared with continuous hemofiltration (9), the only proven adjunctive therapy for the efficient prevention of CIN, our system has several advantages. The system would theoretically be more effective and essential for the removal of contrast medium because it could remove most of the injected contrast medium directly from the CS, with only a small amount of leakage into the systemic circulation. The results in this experiment indicate that almost all of the contrast medium injected into the coronary artery is drained into the CS in swine when proximal and distal blocking balloons are used. Therefore, our system using coronary sinus suction prevents the first passage of contrast medium through the renal arteries better than any other system. **Efficacy of selective contrast removal.** Our system uses a selective adsorbing column to remove the contrast medium. Using hemofiltration systems, some plasma components are inevitably lost. In our system, no significant losses of plasma components were observed with great efficiency of contrast removal because the column used in the system has an affinity to and selectively adsorbs the contrast medium. In terms of efficacy and safety, selective plasmapheresis, consisting of a selective adsorbing column, directly or after plasma separation is best. In clinical practice, many adsorbing therapies are used because each adsorbing column has a unique affinity and selectivity, compared with hemofiltration and hemodialysis. In particular, low-density lipoprotein (LDL)-apheresis has been used to treat patients with hypercholesterolemia, coronary artery disease, cholesterol embolism syndrome, and peripheral artery disease (10–12). For the treatment of coronary artery disease with PCI, numerous clinical experiences of LDL-apheresis, even before and after PCI, have been compiled (13). Compared with LDL-apheresis, which requires a plasma separator and an adsorbing column with an extracorporeal volume of more than 400 ml, our system consists of a

![Figure 4](image-url)  
**Figure 4.** Changes of iodine concentrations in peripheral blood resulting from the use of the column. Values are presented as mean ± SEM (n = 5 or 3). *p < 0.0005; †p < 0.003.

![Figure 5](image-url)  
**Figure 5.** Area under the curve in femoral venous blood treated with or without the column. Values are presented as mean ± SEM (n = 5 or 3); p = 0.0003. AUC0-90 = area under the curve of iodine concentrations in the femoral vein from 0 to 90 min of the extracorporeal circulation time.
direct hemoperfusion column without a plasma separator suggests that this system may be safely used in human beings even during PCI (10,11).

Advantage of time- and cost-saving treatment. Our system offers time-saving benefits because it only needs to be used during PCI or angiography and does not require any pre- or post-procedures. Marenzi et al. (9) reported that continuous hemofiltration needed to be performed for 4 to 8 h before PCI and 18 to 24 h after PCI. Our system, which can be used only during PCI or angiography and can be used only in a catheterization laboratory, thus has both time and cost benefits. If more time and effort were required to place the blood-suction catheter in the CS, the system would not be applicable in human beings. In fact, the catheter can be easily placed in the CS without administering contrast medium.

Conclusions. The present study confirms that the novel contrast removal system from the CS using the adsorbing column is effective and safe in swine during coronary angiography. The indication of this system may have potential in human patients with pre-existing renal insufficiency, diabetic nephropathy, or many risk factors who are undergoing PCI for complicated lesions.

Acknowledgments

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Table 1. Comparison of Biochemical Data for Peripheral Blood Treated With or Without the Column

<table>
<thead>
<tr>
<th></th>
<th>With Column (n = 4)</th>
<th>Without Column (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>RBC, 10^12/ml</td>
<td>519 ± 37</td>
<td>535 ± 27</td>
</tr>
<tr>
<td>WBC, 10^3/ml</td>
<td>191 ± 16</td>
<td>167 ± 23</td>
</tr>
<tr>
<td>PLT, 10^4/ml</td>
<td>28.1 ± 6.7</td>
<td>23.1 ± 7.0</td>
</tr>
<tr>
<td>Hct, %</td>
<td>31.9 ± 2.0</td>
<td>32.9 ± 1.4</td>
</tr>
<tr>
<td>TP, g/dl</td>
<td>6.0 ± 0.5</td>
<td>5.8 ± 0.4</td>
</tr>
<tr>
<td>A/G</td>
<td>1.0 ± 0.2</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>ALB, g/dl</td>
<td>2.9 ± 0.3</td>
<td>2.8 ± 0.2</td>
</tr>
<tr>
<td>TC, mg/dl</td>
<td>62 ± 2</td>
<td>60 ± 1</td>
</tr>
<tr>
<td>Cr, mg/dl</td>
<td>1.11 ± 0.14</td>
<td>1.06 ± 0.11</td>
</tr>
<tr>
<td>Na, mEq/l</td>
<td>145 ± 2</td>
<td>143 ± 1</td>
</tr>
<tr>
<td>Cl, mEq/l</td>
<td>104 ± 1</td>
<td>101 ± 1</td>
</tr>
<tr>
<td>K, mEq/l</td>
<td>4.1 ± 0.1</td>
<td>4.7 ± 0.1</td>
</tr>
<tr>
<td>Ca, mg/dl</td>
<td>10.2 ± 0.5</td>
<td>10.4 ± 0.6</td>
</tr>
</tbody>
</table>

Values are presented as the mean ± SEM.

A/G = albumin/globulin; ALB = albumin; Cr = creatinine; Hct = hematocrit; PLT = platelets; RBC = red blood cells; TC = total cholesterol; TP = total protein; WBC = white blood cells.

REFERENCES