Contrast Removal from Coronary Sinus for Prevention of Contrast-Induced Nephropathy, A Review

Kyvan Irannejad [1], Mehrbod Vakhshoori [1], Rostam Khoubyari [1], and Mohammad Reza Movahed[1]

[1]Affiliation not available

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Introduction:

Epidemiology:

Each year, there are millions of procedures done in the United States that utilize iodinated contrast agents. The main risk of iodinated contrast is kidney injury which could lead to morbidity and mortality [(1–6)]. Contrast-induced nephropathy (CIN), also known as contrast-induced acute kidney injury (CI-AKI), is one of the most common causes of impairment of renal function in the United States (7–10) and is the third common cause of hospital-acquired renal insufficiency (11). Different studies have used various definitions for contrast-induced nephropathy including an increase in serum creatinine [?]0.5 mg/dl or [?]25% from baseline creatinine within 24 to 72 hours after contrast medium administration (3,6,12–16). The mortality rate is increased among patients who developed CIN during and after hospitalization, especially among those who required dialysis (6,17,18). Therefore, any preventive measures that can reduce CIN risk can be lifesaving with a reduction in mortality and morbidity in patients undergoing iodinated contrast exposure.

Brief Summary of CIN preventive measures:

* **Hydration and fluid optimization**

Several methods have been proposed to prevent CIN in clinical settings. However, none of them has been proved to be consistently effective except for hydration and reduction in the amount of contrast exposure. Hydration is the most common prophylactic technique to reduce CIN occurrence in a way that all high-risk patients undergoing contrast exposure should receive appropriate hydration if possible before the procedure in high-risk patients and after the procedure in all patients if feasible without contraindication to hydration (14,19–23). It has been shown that intravenous fluid administration with isotonic saline is more effective compared to the half saline infusion (14,22). However, the optimal fluid volume and infusion rate is controversial. Current guidelines recommend intravenous administration of 1-1.5 ml/kg/h of normal saline six hours before and after contrast injection (24). With respect to proper fluid administration, left ventricular end-diastolic pressure (LVEDP) can be assessed and adjusted accordingly. This theory was assessed in the POSEIDON trial. Their findings suggested patients who received adjusted fluid based on LVEDP had a significantly lower risk of CIN after cardiac catheterization (relative risk: 0.41, 95% confidence interval (CI): 0.22 – 0.79, P= 0.005). However, three cases of shortness of breath, probably in the context of pulmonary edema, were reported in both intervention and control groups (25). Also, Maioliet et al. used bioimpedance vector analysis (BIVA) for the assessment of body fluid status. After randomization of low BIVA patients to normal or double volume normal saline administration, they found no significant difference in CIN occurrence defined by standard criteria (increase serum creatinine by [?] 0.3 mg/dl within 48 hours) between those groups (10.8% vs. 4.7%, P= 0.08, respectively) (26).

* **Avoidance of nephrotoxic agents**

Another factor that can raise CIN risk might be related to nephrotoxic drugs. Although there are not enough trials to strongly prove the benefit of nephrotoxic drugs discontinuation before contrast exposure, it is generally recommended to hold potentially nephrotoxic drugs including nonsteroidal anti-inflammatory drugs, aminoglycosides, vancomycin, sulfonamides, penicillins, amphotericin, loop diuretics, and metformin in high-risk patients. The latter drug has been associated with metabolic acidosis which might predispose kidneys to the development of CIN but this concept has not been proven (27,28).

* **N-Acetylcysteine administration**

N-Acetylcysteine (N-AC) was initially reported by Tepel et al. to be protective against contrast-induced nephropathy in a small trial (29). However, numerous trials and meta-analyses have completely failed to show any benefit and therefore its use is not recommended (29–31).

* **Type of contrast media**

Contrast media typed based on osmolality is thought to be important for CIN pathogenesis and has been categorized into three different types based on the osmolality (high osmolar, low osmolar, and iso-osmolar) (32). Initially, several studies have shown that iso-osmolar contrast media have the lowest risk of CIN incidence in comparison to low-osmolar contrast agents (33–36), but numerous other trials failed to show any significant differences in the occurrence of contrast-induced nephropathy (37–40).

* **Dialysis and hemofiltration**

In terms of dialysis and hemofiltration which directly removes the contrast from the systemic circulation, there is no clinical evidence suggesting prophylactic use of dialysis can prevent CIN (41). No benefit has been reported for post-procedural dialysis either (42). Marenzi et al. reported the use of hemofiltration might be beneficial in the prevention of CIN (43). However, it remains unclear whether it was related to increased clearance through dialysis or due to alkalinizing agents used during filtration.

* **Treatment of hypoperfusion**

Due to the negative effect of renal hypoperfusion, regardless of its etiology, with contrast administration resulting in increased CIN risk, utilization of short time assisted devices increasing cardiac output might reduce this risk. Flaherty and colleagues performed a randomized clinical trial and found usage of a Microaxial percutaneous assist device (Impella) was associated with a lower likelihood of acute kidney injury among high risk percutaneous coronary intervention (PCI) patients with reduced left ventricular ejection fraction [?] 35% (odds ratio (OR): 0.13, 95% CI: 0.09 – 0.31, P$<$ 0.001) (44). These findings might be associated with resultant reduced CIN risk. However, larger studies are warranted.

* **Balanced hydration system**

Another proposed mechanism in CIN prevention has been attributed to a balanced hydration procedure. This process has been suggested based on the theory that as urine output becomes higher, the contrast concentration in kidneys would become lower ultimately resulting in decreasing CIN risk. Briguori et al. implemented Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II) trial to assess the feasibility of the RenalGuard system (PLC Medical Systems, Inc, Franklin, MA) in the prevention of CIN. Briefly, the mentioned system consists of closed-loop fluid management that consistently monitors and evaluates hydration status and urine output. 294 candidates for coronary or peripheral angiography/angioplasty with an estimated glomerular filtration rate (eGFR) of [?] 30 ml/min/1.73 m^2 and/or risk score of at least 11 were selected and randomly allocated to control (sodium bicarbonate and N-AC administration) or RenalGuard (hydration with saline and N-AC under RenalGuard system control with furosemide administration) group. The intervention group received an initial bolus for 30 minutes and furosemide (0.25 mg/kg) would be prescribed to increase urine output to [?] 300 ml/h. They found CIN was significantly decreased in the RenalGuard arm compared to controls (11% (16 out of 146 subjects) vs. 20.5% (30 out of 146 subjects),

OR: 0.47, 95% CI: 0.24 – 0.92). Different administration routes of N-AC (oral agent for controls and intravenous route for intervention group) resulting in probable variable bioavailability of the drug as well as their reported data applicable to a subset of chronic kidney disease (CKD) patients might be considered for extension of the outcomes (45).

Likewise, the Induced Diuresis With Matched Hydration Compared to Standard Hydration for Contrast-Induced Nephropathy Prevention (MYTHOS) trial using the RenalGuard system was performed for CKD patients who underwent coronary procedures. 170 subjects with eGFR< 60 ml/min/1.73 m^2 were randomly assigned to standard intravenous saline hydration as a control group (n= 83) or furosemide with matched hydration as an intervention group (n= 87). The intervention arm received 250 ml of normal saline as well as 0.5 mg/kg of furosemide to reach a urine output of more than 300 ml/h. Patients in the intervention group experienced CIN less frequently rather than controls (4.6% vs. 18%, P= 0.005). Single-center and not-blinded study design, as well as pre-determined hydration protocol in the intervention group, were some limitations related to the mentioned project (46).

* **Renal cooling**

Also, a cooling renal method based on the theory of decreasing oxidative injury in lower temperatures in the context of contrast injection has been announced. However, it did not show any promising outcome in terms of CIN prevention. For instance, Stone and colleagues performed a randomized trial and allocated 128 cardiac catheterization candidates with CKD (estimated creatinine clearance: 20-50 ml/min) to control (n= 70) and intervention (n= 58) groups. In addition to hydration, the latter group underwent systemic hypothermia at 33-34 °C starting before contrast injection toward three hours post-procedure followed by rewarming to 36 °C with a rate of 1 °C per hour afterward. CIN was observed in 18.6% and 22.4% of normothermia and hypothermia groups, respectively. However, there was no significant association neither in unadjusted nor in adjusted models (OR: 1.27, 95% CI: 0.53 – 3.00, P= 0.59 and OR: 0.83, 95% CI: 0.18 – 3.78, P= 0.81, respectively) (47).

* **Ischemic preconditioning**

The hypothesis of ischemic preconditioning, as multiple short cycles of ischemia and reperfusion in one organ, could be effective on another organ, on reduction of CIN has been tested in a randomized clinical trial on 100 subjects which revealed four 5-minute inflation-deflation cycles of blood pressure cuff to 50 mmHg above each patient systolic blood pressure before coronary angiography (CA) had been associated with a decreased likelihood of CIN compared to controls (OR: 0.21, 95% CI: 0.07 – 0.57, P= 0.002) (48). Although this procedure can be applied in all clinical settings, further studies with a larger sample size are required.

* **Other agents**

One small study showed infusion of sodium bicarbonate might be more effective in the prevention of CIN rather than isotonic saline (49). However, subsequent larger trials failed to prove this association (25,26). Therefore, sodium bicarbonate is not recommended to be used for this purpose by the Consensus Working Panel (22).

Other pharmacologic agents include ascorbic acid, diuretics, mannitol, calcium channel blockers, fenoldopam, dopamine, atrial natriuretic peptide, L-arginine, theophylline, and statins have been reported in the literature in terms of CIN prevention with controversial results (50–62).

The role of contrast volume

* **Contrast volume as a risk for CIN**

Contrast volume has been shown to be an independent risk factor for CIN (63–65). It has been previously proved the amount of contrast correlates with the incidence of CIN (66). After a data analysis of 53780 vascular interventions, Lee et al. indicated CIN was correlated with CKD stage in a way that the incidence of AKI in the context of contrast administration raised with each CKD stage (CKD stage 1: 0.39%, CKD

stage 2: 0.45%, CKD stage 3: 1.5%, CKD stage 4: 4.3% and CKD stage 5: 7.5%). They suggested the risk of post-contrast AKI could be reduced by using safe thresholds of contrast volume (67).

Rihal et al.'s study reported the volume of contrast media administered during the PCI was correlated with acute renal failure (6). Kooiman and colleagues analyzed data from 82,120 PCI procedures and found patients who received high contrast, as defined by division of contrast volume over calculated creatinine clearance resulting in more than 3, had increased CIN odds in both univariate and multivariate regression models (OR: 1.61, 95% CI: 1.46 – 1.79, P< 0.001 and OR: 1.77, 95% CI: 1.58 – 1.98, P< 0.001, respectively) (68). Likewise, another observational study on 561 patients suffering from myocardial infarction who underwent PCI revealed CIN was significantly higher among those with a contrast ratio (measured by administered contrast volume divided by calculated maximum contrast agent dose) of more than 1 in comparison to the ratio of less than one (34.6% vs. 3%, P< 0.001) (65).

Kane et al. reported the rate of CIN in patients with CKD undergoing CA could be reduced by ultra-low contrast volumes (69). However, even small amounts of contrast can deteriorate renal function, especially among high-risk patients (70). A small study on 30 patients with eGFR< 45 ml/min/1.73m^2 underwent CA/PCI with ultra-low volume contrast media showed utilization of this kind of agent was safe with no reported increased serum creatinine 48 hours post-procedure (71). However, a single study design and small sample size are potential limitations needed to be considered. 123 subjects with at least stage 3 of CKD experienced CA/PCI was selected by Kelly and colleagues. They used a novel ultra-low contrast delivery technique with an automated contrast injector for their procedures and reported a CIN rate of 3.3%. Quite a small sample size, as well as retrospective study design and performance in a single-center, should be considered for the generalization of their findings (72). Although the CIN rate was lower among CKD patients who underwent PCI with ultra-low contrast (n= 8) compared with the conventional group (n= 103) in another retrospective study, the difference was not statistically significant (0 vs. 15.5%, P= 0.28). Asymmetric sample distribution between groups and their small cohort size might limit their outcomes (73).

Mariani et al. proposed the theory of zero contrast volume and performed MOZART (Minimizing cOntrast utiliZation With IVUS Guidance in coRonary angioplasTy) trial to assess whether intravascular ultrasound (IVUS) could decrease contrast exposure compared to the routine method. 83 PCI candidate patients were selected and randomly assigned to routine angiography (n= 42) or IVUS method (n= 41) with matched clinical and laboratory data. The median contrast volume was significantly lower in IVUS rather than in the routine angiography group (20 ml, interquartile range (IQR): 12.5 – 30 ml vs. 64.5 ml, IQR: 42.8 – 97 ml, P< 0.001). Also, the ratio of contrast volume to creatinine clearance was remarkably lower in the IVUS group (0.4, IQR: 0.2 – 0.6 vs. 1.0, IQR: 0.6 – 1.9, P< 0.001) (74). Although they found a promising outcome, the higher cost of IVUS might be a limiting factor for usage in clinical settings. On the other hand, it has been suggested that contrast volume reduction before contrast exposure may lower the risk of CIN (75).

* **Methods for reducing contrast volume administration**

In terms of reducing contrast volume administration, few studies are available. Mehran et al. performed a randomized clinical trial to assess the efficiency of contrast reduction in patients with underlying renal diseases who underwent CA. 578 patients in stage III (eGFR between 30 and 60 ml/min) and IV (eGFR between 20 and 30 ml/min) of CKD with at least two further criteria of New York heart association (NYHA) functional class of III or IV of heart failure, diabetes mellitus (treated with either insulin or oral agents), anemia, hypertension, albuminuria or age of at least 75 years were randomly assigned to hydration (n= 286) or hydration plus AVERT system group (n= 292). The latter system is a contrast modulation system designed to adjust the pressure of contrast injection toward the patient. The relative reduction in contrast volume was 15.5% (hydration group: 101.3 +- 71.1 ml vs. hydration plus AVERT group: 85.6 +- 50.5 ml, P= 0.02). The distribution of AKI induced by contrast did not differ significantly (26.6% vs. 27%, P= 0.70, respectively) (76). Likewise, Gurm and colleagues performed an observational study on 114 patients with eGFR of 20 – 60 ml/min/1.73m^2 to assess the feasibility of contrast volume reduction during CA or PCI using DyeVert^{TM} Plus Contrast Reduction System (DyeVert Plus System, Osprey Medical). Data analysis of 105 successfully recruited patients revealed the contrast volume saving of 40.1 +- 8.8% per each performed

procedure. AKI induced by contrast agent was observed in three (2.6%) of patients (77). The small sample size and observational design of the study should be considered for the generalization of reported data.

* **Automated contrast injection devices**

Although data analysis of 60,884 candidates who underwent PCI revealed contrast agent usage was lower in centers that used automated contrast injectors compared to those centers not used this method (199 +- 84 ml vs. 204 +- 82 ml, P< 0.0001), no difference had been found in terms of CIN occurrence (3.11% vs. 3.42%, P= 0.15) (78). On the other hand, Minsinger and colleagues performed a meta-analysis and found automated contrast injectors decreased contrast volume up to 45 ml per subject (95% CI: 0.78 – 0.93, P< 0.001), and it was associated with a 15% reduction in CIN compared to manual injection methods (OR: 0.85, 95% CI: 0.78 – 0.93, P< 0.001) (79).

* **Direct contrast removal from general circulation**

Contrast removal during CA has been reported to be correlated with decreased CIN occurrence. This contrast removal can be done by direct aspiration from general circulation through different methods including hemodialysis or continuous veno-veno hemofiltration with conflicting results (80). Moreover, the contrast agent would be still in the circulation and might damage the renal tissue.

A summary of potential methods to decrease CIN risk is shown in **Figure 1.**

Review of contrast removal from coronary sinus:

* **Introduction:**

Any methods that can extract contrast from a coronary sinus (CS) prior to reaching the general circulation may reduce CIN. Anatomically, major veins of the heart drain blood to the CS with minimal connection with systemic veins through Thebesian veins. Thus, it might be theoretically possible to be able to remove the injected contrast before it reaches the systemic circulation and negatively affect the kidneys.

* **Coronary sinus and venous anatomy:**

The anatomy of cardiac veins is depicted in **Figure 2** . The coronary venous system is anatomically divided into two groups, named greater and lesser cardiac venous system. The former contains three different groups including CS and tributary veins (CS, great and small cardiac veins, anterior and posterior interventricular veins, left marginal vein, left posterior vein, an oblique vein of Marshall, ventricular septal veins), veins draining to the atria and veins draining to the left ventricle (right marginal vein, anterior cardiac veins, infundibular veins). The lesser cardiac venous system consists of Thebesian veins including venous sinusoids and small vascular channels (81–84).

The CS is located in the inferior portion of the left atrioventricular groove and drains to the posteromedial right atrium. CS is the largest structure in the cardiac venous system with a normal diameter and length of up to 12 mm and 30-63 mm, respectively. CS has two valves which include the valve of Vieussens and the Thebesian valve. The former valve is present at the junction between CS and the great cardiac vein. The latter is found at the junction of the right atrium and SC (81–83,85).

* **Animal studies regarding coronary sinus contrast removal**

Animal studies have shown the clinical utility of this procedure. Movahed and colleagues performed first study of its kind and assessed the safety and feasibility of contrast removal from CS in pigs for the first time. They selected five swine. Through the left carotid artery with an 8-F multipurpose catheter, the left main coronary artery was accessed, and 5 ml of non-ionic iodinated contrast was injected. Heartport catheter (Ethicon Inc., Cornelia, Georgia) was used for the engagement of CS through the external jugular vein (**Figure 3**). For three times, each time for 10 seconds, the tip of the catheter was inflated immediately after coronary injection and the CS blood was collected. The Catharos SENTINEL system used for contrast capture contains aspiration and 0.035 inches wire lumen as well as optical fibers for contrast detection. The catheter would be connected to the aspiration system and primed with normal saline. The catheter tip is

positioned in a desirable place in the CS and holding and slowly pulling back the handle would result in deployment of the basket. They quantified the contrast amount in aspirated blood with high-performance liquid chromatography as well as a dual-energy technique. The latter technique was used to assess iodine mass. Recovered iodine was calculated from the collected iodine mass ratio which was assessed from dual-energy logarithmic subtraction per injected iodine. The procedure was tolerated well in all recruited samples. They finally reported that 50.6 +- 12% of injected iodine contrast was successfully aspirated from CS. It must be taken into account that although a pig's heart closely resembles a human heart, a large left azygos vein drains into the CS and this point might be a potential explanation for lower than expected contrast removal (86).

Michishita et al. selected eight swine and sedated them with ketamine and xylazine with subsequent intubation using isoflurane. Five swine were treated with an extracorporeal system with adsorbing columns and three others were treated as controls. The right femoral vein was accessed and an 8-F blood suction catheter with multiple holes at the distal end was inserted into the CS. They also used a Fogarty catheter on the ostium of CS through the left jugular vein to protect any blood leakage from the CS to the right atrium. Due to the presence of the azygos vein receiving blood from CS, another balloon was also utilized to block this blood flow through the right jugular vein. The total contrast volume was 155 +- 14 ml and the swine were treated for 90 minutes with an extracorporeal system. All subjects tolerated the experiment with no adverse events. They found the mean contrast removal rate was 49.4% and iodine concentration was significantly lower compared with controls (P= 0.0003) (87).

Chang et al. introduced a novel method for contrast removal using a reflectance typed optical sensor. Five canines were anesthetized, and an 8-Fr Judkins catheter was used to access the coronary artery. An aspiration catheter with a fiberoptic sensor was inserted into the CS (**Figure 4**). They injected contrast to the coronary artery and analyzed reflected signals with the fiber optic sensor in the CS. Also, they assessed the contrast removal rate through a spectrophotometric absorbance assay. The mean contrast removal rate was reported to be 59.3 +-11% (range: 42-76%) (88).

Meyer and colleagues anesthetized two dogs and accessed CS from the right jugular vein through a 6-F balloon-tipped catheter (Pressure Products, Model BVCS 6180, San Pedro, CA). After contrast administration to the left main coronary artery, the balloon was inflated and the contrast agent was captured from CS (**Figure 5**). The procedure was performed two times for each recruited animal and the mean contrast extraction was reported to be 70 +- 6% (range: 60 – 88%) (89).

* **Studies of coronary sinus contrast removal in human**

The effectiveness of contrast removal in the prevention of CI-AKI has been shown in different human studies. Danenberg et al. recruited seven male individuals (range of age: 56-83 years) who suffered from previous renal failure with a mean serum creatinine of 262 +- 46 mg% to assess the safety and feasibility of contrast removal from CS during CA procedure. They engaged CS in six patients through a femoral vein with the usage of a 5-Fr Simmons II catheter (Cordis, Miami, FL) and via jugular vein with the usage of a 6-Fr catheter (Cordis) in one patient.

A two-lumen balloon-tipped catheter equipped with multiple holes in its distal end (Reverse Berman Angiography Catheter, 7 Fr, Arrow Int, Reading, PA, USA) was exchanged over the wire in order to be positioned in proximal CS. Although they could not deploy the catheter in four patients, CS was successfully accessed in three subjects. The catheter tip located at CS was inflated prior to each contrast injection. Approximately 12-16 ml of blood was aspirated manually at 5-7 seconds post-injection. The contrast removal rate was reported to be 44 +- 8%. None of the patients experienced creatinine rise and the procedure was safely performed (90) (**Figure 6**).

Likewise, in another study, a designed 11-F aspiration catheter (CINCOR Contrast Removal System, Osprey Medical, St. Paul, Minnesota) was inserted successfully in 31 out of 41 patients and the contrast aspiration rate from the CS was 32 +- 3% (range: 6-64%) (**Figure 7**). 26 of them had eGFR of less than 60 ml/min and were assessed for further outcomes. No remarkable alteration in eGFR had been found from the baseline to

72 hours after completion of the procedure (41.8 +- 2.2 ml/min to 41.1 +- 2.3 ml/min, P= 0.55). They also analyzed data with 148 matched comparators under standard care (no CS aspiration) with the administration of the same contrast volume and figured out eGFR declined significantly from 42.7 +- 0.8 ml/min to 40.1 +- 0.9 ml/min (P< 0.001) at 48-h post-procedure and the comparator group showed a greater decrease in eGFR (-2.5 +- 0.5 ml/min vs. -0.7 +- 1.2 ml/min, P< 0.05). They also compared data of those with eGFR of less than 40 ml/min (n=11) and the comparator group (n=56) and reported eGFR was not significantly changed in the first group that underwent CS contrast aspiration (from 30.7 +- 1.6 ml/min to 31.4 +- 1.8 ml/min, P= 0.42). However, a significant decline was observed in the latter group that underwent standard care (from 33.1 +- 0.7 ml/min to 31.7 +- 0.8 ml/min, P= 0.003). Between-group eGFR difference was also significant (+ 0.5 +- 0.7 ml/min vs. -1.5 +- 0.5 ml/min, P< 0.05) (35,91,92)

Diab and colleagues recruited 43 CA candidates who suffered from diabetes mellitus with a serum creatinine of 1.5 – 3 mg/dl and divided them into CS aspirate groups (n= 18) and controls (n= 25) with matched laboratory and clinical parameters. A transseptal sheath (Mullins, Medtronic, and St Jude Medical; 8 or 8.5 F) was used to access CS through the left subclavian (n= 8) or right femoral vein (n= 10). The contrast was aspirated directly through the sheath or a balloon-tipped catheter (7 F, single lumen; Arrow Int, Reading, PA). The mean reported contrast aspiration percentage was 39.35 +- 10.47% (**Figures 8 and 9**). All subjects in the CS group tolerated the experiment well. Although one patient (5.55%) in the CS arm experienced CI-AKI, this percentage was higher among controls (n= 9 (36%)) (P= 0.028) (93). Also, the contrast extraction rate was reported to be 27% in a 60-year-old man who underwent CA using CINCOR contrast extraction catheter from CS (94) (**Figure 10**).

* **Devices and methods for coronary sinus contrast extraction:**

Heart Port Catheter:

Different catheters have been used in animal and human studies to remove contrast agents from CS. Movahed et al. used a Heartport catheter (Ethicon Inc., Cornelia, Georgia) (**Figure 11**) for engaging CS through external jugular veins of pigs plus 11-Fr sheath. This catheter has a balloon at its end and it was inflated after contrast injection to collect blood from the CS. Fluoroscopy images were taken to confirm the complete CS occlusion by injecting contrast to the distal of the inflated balloon. Obstruction of CS by catheter tip did not show any negative effects on CA findings and it was well tolerated in all five recruited swine samples and no significant hemodynamic changes were reported after blood extraction. They measured iodine concentration by quantitative dual energy method (86).

Suction Catheter

Michishita and colleagues used an 8-Fr suction catheter with distal holes (**Figure 12**) and accessed CS with the usage of an inner catheter as a guidewire control as well as for its stiffness. Another balloon using Swan-Gantz catheter and a Fogarty catheter was implemented to prevent blood leakage from CS to the right atrium and azygous vein, respectively. They transferred the extracted blood to an absorbing column with the usage of an extracorporeal system. Afterward, the blood was returned back to the swine through the left femoral vein. The total procedure time was 90 minutes and serial blood samples were taken at different pre-and post-column time frames (0, 10, 20, 30, 40, 50, 60, 65, 75, and 90 minutes). Iodine contrast concentration was measured through an inductively coupled plasma optical emission spectrophotometer (CMC Development Department, Nihon Schering) with the use of ultraviolet methods. None of the study samples experienced alterations in vital signs including body temperature and blood pressure as well as an electrocardiogram. They also suggested this system can be inserted through femoral access into the CS by fluoroscopic guidance with no usage of contrast administration. Also, the specific design of distal holes on the catheter enables it to efficiently remove contrast from left or right coronary arteries draining into or near the CS ostium. They also claimed this system is quite time-saving because it does not need any pre- or post-procedure interventions (87).

SENTINEL Catheter

Another catheter was an optical catheter which was a Sentinel catheter (SENTINEL Catheter, Catharos Medical Systems, Campbell, California) with a fiber-optic probe. This designed catheter contains aspiration lumen and basket tip as well as fiber optic sensors. This Catharos Sentinel system detected signal changes upon contrast injection to the CS. The mechanism was associated with signal variation in a way that after CS administration of the contrast agent, the alteration in hematocrit (Hct) was detected by fiber optic sensors located in the catheter tip. A guidewire (Terumo Corp., Japan) was used for engaging CS and the Sentinel catheter was introduced to the CS through GlideWire. Fluoroscopic images were used to confirm the proper location of the expanded basket in CS (**Figure 13**). The contrast removal rate was calculated using a spectrophotometric assay. In order to assess the safety of this method, the hearts of two canines were fixed with formaldehyde. The gross pathology report on CS integrity and other major branches including great and middle cardiac veins as well as anterior interventricular vein revealed all lumens were patent and no evidence of hemorrhage or thrombosis had been observed. Although some places of superficial endothelial cell disruption were found on histological view, the underlying stroma was normal. Additionally, they found insignificant mural inflammation in their samples. Their study was the first in the literature to evaluate the usage of endovascular detection methods for contrast removal. By defining signal to noise ratio as s trigger point, they also indicated this system is an active method for contrast removal and no interventionist's attention is required during the procedure. However, some points should be considered. Despite the reflectance signal for contrast aspiration being somewhat noisy, signal detection could be differentiated from baseline signals. The aspiration threshold was set to sown-crossing four volts in their study, but it was possible that some portion of the contrast agent escaped from the collection before crossing this threshold. Therefore, the implementation of exact algorithms to detect this falling edge in an automatic manner rather than by noise seems pivotal (88).

Balloon Tip Catheters

In another study, an 80-cm balloon-tipped 6-Fr catheter (Pressure Products, Model BVCS 6180, San Pedro, CA) (**Figure 14**) was inserted into the right jugular veins of two dogs and advanced to CS. Their left main coronary arteries were also engaged through a 5-Fr AL2 catheter. A small amount of contrast was injected to confirm the CS occlusion after inflation of the balloon followed by its deflation to clear the contrast agent from the CS. Concurrently with contrast injection, the balloon located in CS was inflated and manual blood suction into a heparinized syringe was performed for 30 seconds. Captured contrast was calculated according to grayscale analysis using a polynomial regression curve. Meyer and colleagues suggested due to the presence of small lumen in currently available CS balloon catheters, the flow rate is low leading to enhanced withdrawal times. Thus, increasing the flow capacity of available catheters might be associated with heightened contrast removal efficiency. They also claimed this technique can be applied in any circumstances when a noxious agent should be administered in a selected organ if the draining venous system can be accessed (89).

On the other hand, different catheters are used in humans. Danenberg et al. used a balloon-tipped catheter with two lumens and multiple distal holes (Reverse Berman Angiography Catheter, 7 Fr, Arrow Int, Reading, PA, USA) (**Figure 15**) for accessing the CS. They occluded CS before contrast injection and blood was manually extracted 5-7 seconds post coronary contrast administration and the balloon was deflated for 20-30 seconds after contrast disappearance shown by fluoroscopic images. Extracted contrast concentration was measured by assessing reduction in Hct levels in collected samples compared with simultaneous Hct levels from aorta using the following formula: (1 – Hct in CS extracted blood / Hct in the aorta) * collected blood volume. Although CS was successfully accessed in all seven enrolled patients, the catheter slipped out of the CS led to procedure failure in four participants. However, the entire process was one without difficulties in the remaining three subjects. Another issue was related to fluoroscopy time. The extra time needed for CS cannulation increased the mean fluoroscopy tome in comparison to routine interventions. However, they reported this method can be done in most catheter laboratories with no special equipment. The additional benefit was associated with intermittent CS obstruction. It has been reported that periodic occlusion of CS decreases coronary artery blood flow regardless of the aortic pressure or CS obstruction (95,96) . This reduced flow could be used to decrease contrast volume per injection. Therefore, a reduced amount of used

contrast agent and significant contrast extraction can additively decrease CIN risk. They also suggested using superior vena cava to enter the right atrium for CS cannulation as a common technique. However, using femoral access might be quite difficult with standard catheters and they used Simmons II catheter for CS engagement (90).

CINCOR Contrast Removal System

Another catheter is a 11-Fr aspiration catheter (CINCOR Contrast Removal System, Osprey Medical, St. Paul, Minnesota) (**Figure 7A).** Duffy and colleagues were able to successfully cannulate the CS with an aspiration catheter using a 14-Fr right internal jugular vein sheath in 31 out of 41 recruited patients. Contrast aspiration was done by pushing the foot pedal in this contrast removal system after coronary contrast injection. Using inductively coupled plasma optical emission spectroscopy, the amount of contrast extraction was measured. Those who underwent CS aspiration, they did not observe any serious adverse events associated with the device (91).

This system was also successfully placed in CS ostium through a 12-Fr femoral venous sheath in one case. After four seconds of delay post each cine angiography acquisition, contrast extraction was done using the 11-Fr CINCOR system for 10 seconds (**Figure 10A**). The procedure was performed uneventfully and the patient did not experience an apparent hemoglobin drop (91,94).

Arrow Int PA Catheter

Another device was a 7-Fr balloon-tipped catheter (7 F, single lumen; Arrow Int, Reading, PA) used by Diab et al (**Figure 16**). After accessing the CS through either right femoral or left subclavian veins and before contrast injection, the balloon was inflated by air to obstruct the CS and contrast aspiration was performed using a syringe. In order to determine the volume of extracted contrast, reduction of patients' blood Hct from Hct levels in CS blood was calculated and the result was divided by the patients' Hct. Finally, the result of this equation was multiplied by the volume of aspirated blood from the CS. All the procedures are done without any failures. However, direct CS cannulation was just performed successfully in six patients and CS quadripolar or decapolar catheters were used to help cannulation in the remaining 12 individuals. Contrast aspiration was performed through a balloon-tipped catheter in 10 patients or direct extraction from the sheath in the other eight participants. Although patients who underwent CS contrast removal through the balloon catheter had remarkably higher time to clearance of the contrast compared to the direct aspiration group, the fraction of extracted contrast was not significantly different between groups. The possible mechanisms for shorter contrast clearance time in those undergoing CS contrast extraction via the sheath might be associated with the faster rate of aspiration and wider sheath caliber. Also, the sheath tip has a lower probability of collapsing or facing the vessel wall during the procedure and it also creates a more negative suction pressure. They suggested the possible safety of CS cannulation using trans-septal sheath due to its favorable curves and proper manipulation and rotation with or even without dilator support. They also claimed the simplicity of this method as well as its cost-effectiveness without the requirement of advanced technologies. Despite their suggestion for optimal choice between balloon catheter or direct sheath is defined by CS caliber in relation to the sheath, complementary studies are required. Their potential concern on CS obstruction on limitation of coronary arterial blood flow might be explained by reactive hyperemia leading to increased microcirculation after balloon deflation. Additionally, this enhanced coronary transit time in the context of CS occlusion might be associated with decreased necessary contrast volume (93).

* **Expected challenges in CS engagement for contrast removal:**

Although the safety and feasibility of CS contrast removal have been indicated in several animal and human studies and this procedure is quite accessible in most clinical settings, there are still some possible challenges that should be considered. Despite its rareness, CS anatomical abnormalities are one of the culprits in this regard. CS length of less than 20 mm is considered to be short CS and might be associated with difficult CS cannulation (97–99). Also, the CS can be varied from enlarged to hypoplastic or even absent in a few individuals. CS enlargement could be either primary or secondary to other pathologies including unroofed CS, interrupted inferior vena cava, coronary artery fistula, and total or partial anomalous pulmonary venous

return. The former abnormality is a unidirectional left to right or a bidirectional shunt between the left atrium and superior segment of CS (99,100). Also, CS manipulation during catheterization or contrast aspiration might be associated with CS trauma or thrombosis, or ectopia of atria or ventricles (90). It seems CS morphology and proper catheter placement might play pivotal roles in successful cannulation and should be individually assessed. Moreover, blood loss per coronary injection might be considerable. Danenberg et al. reported aspiration of 12-16 ml of blood per injection (90). This was 16.6 +- 3.23 ml per injection in Diab et al.'s study. Also, post-procedural hemoglobin was slightly lower in the CS group in the aforementioned study, but it was statistically insignificant (10.85 +- 1.3 g% vs. 11.62 +- 1.3 g%, P= 0.06) (93).

Patient discomfort, unstable sheath position, and difficulty in advancing the sheath to the CS ostium have been reported to be some difficulties during CS cannulation (100). Another study reported an approximate 10% of minor myocardial damage during CS catheter placement, but all complications were not clinically evident (97). Another considerable factor might be attributed to CS cannulation time which has been reported in different ranges. The time was 19.27 +- 3.54 minutes in one study compared to 11.1 +- 9.3 minutes in another one (80,93). The equipment, the procedure (angiography versus intervention) as well as skillfulness of the interventionist might be some possible explanations for these reported differences.

* **Future directions:**

Contrast extraction from CS seems to be a novel method ultimately leading to a decrease in CIN incidence among CA/PCI patients. However, some questions are currently needed to be investigated by further comprehensive studies. For instance, despite PCI or CA being common in origin, the required time for completion of each method is quite different. Acceptable catheter sheath size should also be more investigated. Appropriate training for proper CS manipulation should also be considered. The blood loss amount is another potential concern that needs to be evaluated and probably corrected by returning the aspirated blood without contrast media to the patient. Normal blood loss during conventional CA should be less than 300 cc (86). Moreover, studies are probably necessary to define the exact CS contrast aspiration time to prevent CIN.

Summary:

CIN in the context of CA and PCI is a major concern. Despite several proposed methods to prevent CIN, CIN occurs in high rates with high morbidity and mortality. New means that can reduce CIN is desirable. Contrast removal from CS has been shown to be such a mean with future potential in order to decrease CIN risk during coronary procedures with a great safety profile. Large randomized trials are required to assess the efficacy and safety of this approach.

Competing interests : Mohammad Reza Movahed has the Patent holder for the contrast removal device.

Abbreviations:

- BIVA: Bioimpedance Vector Analysis - CA: Coronary Angiography - CI: Confidence Interval - CI-AKI: Contrast-Induced Acute Kidney Injury - CIN: Contrast-Induced Nephropathy - CKD: Chronic Kidney Disease - eGFR: estimated Glomerular Filtration Rate - Hct: hematocrit - IQR: Interquartile Range - IVUS: Intravascular Ultrasound - LVEDP: Left Ventricular End-Diastolic Pressure - MOZART: Minimizing Contrast UtiliZation With IVUS Guidance in Coronary AngioplasTy - MYTHOS: Induced Diuresis With Matched Hydration Compared to Standard Hydration for Contrast-Induced Nephropathy Prevention - N-AC: N-Acetyl Cysteine - NYHA: New York Heart Association - OR: Odds Ratio - PCI: Percutaneous Coronary Intervention - REMEDIAL II: Renal Insufficiency After Contrast Media Administration Trial II

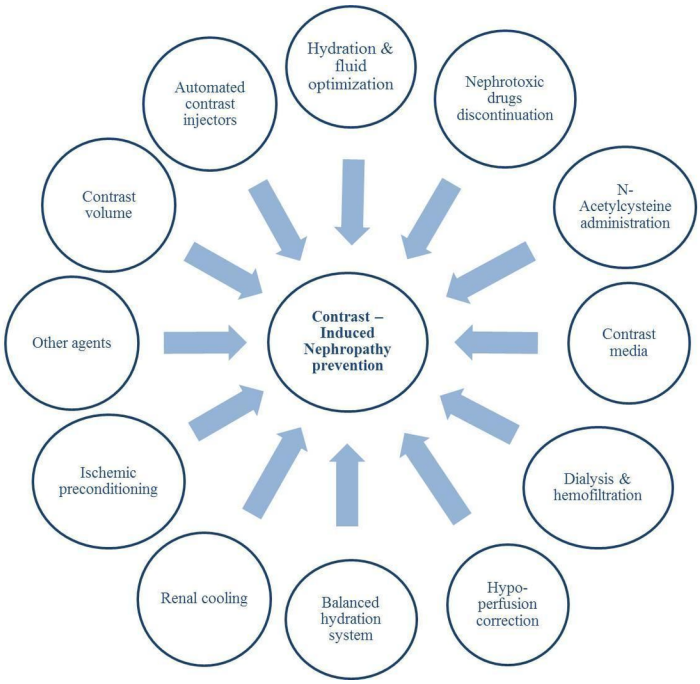

Figure 1. Potential methods to decrease the risk of contrast-induced nephropathy

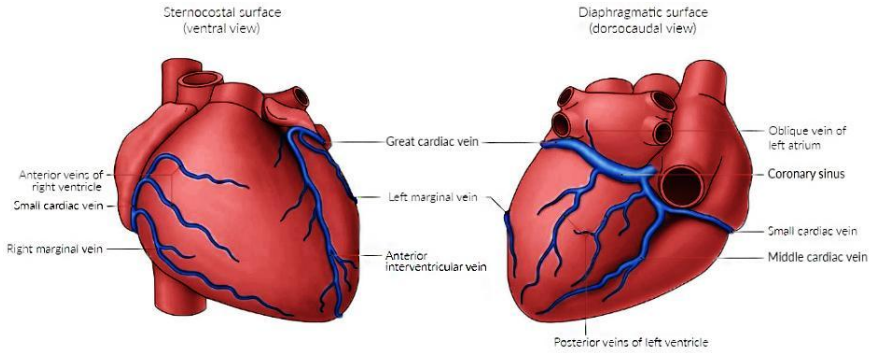

Figure 2. Anatomy of cardiac veins

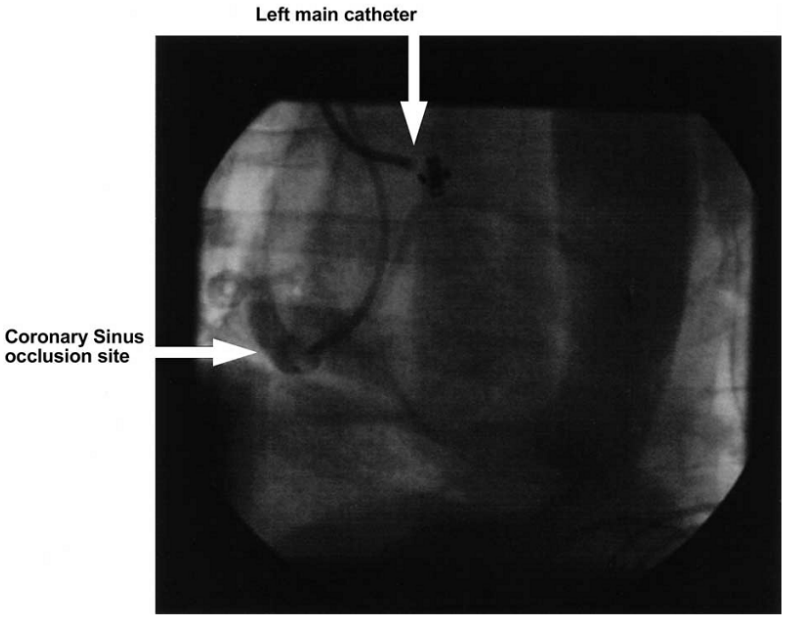

Figure 3. Contrast agent presented in coronary sinus after simultaneous contrast injection in the left main coronary artery and coronary sinus obstruction, reported by Movahed et al. (86). (with permission from the journal of the American college of cardiology)

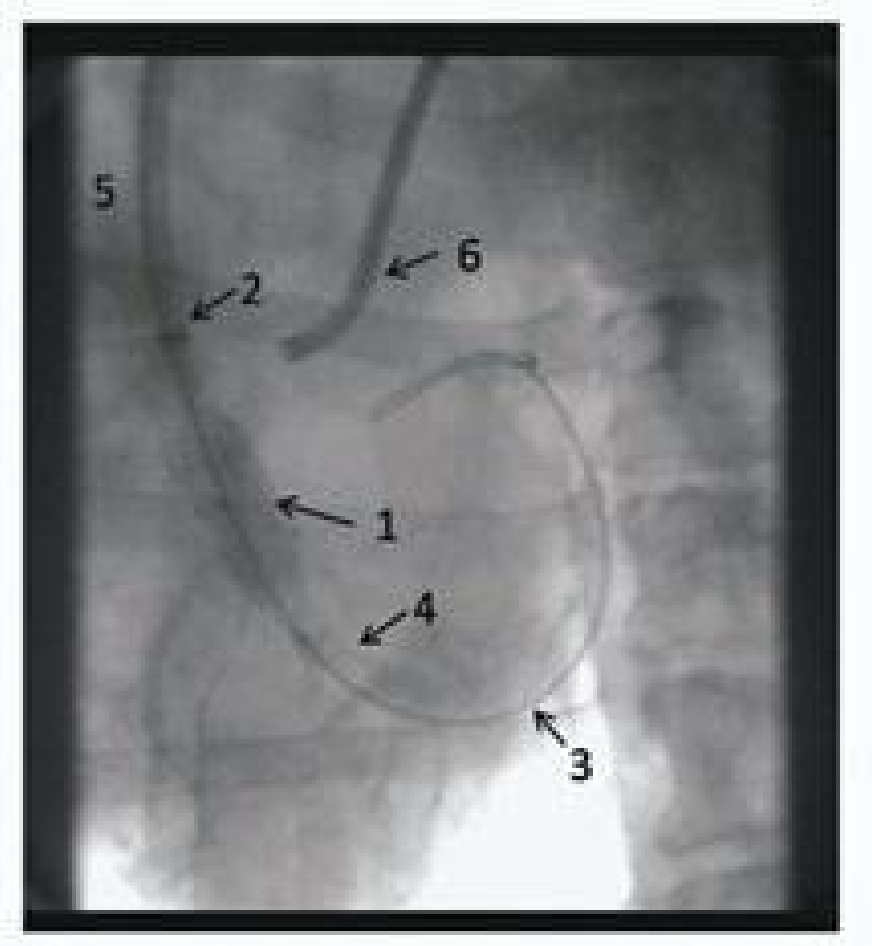

Figure 4. Fluoroscopic image of successful deployed Sentinel catheter in canine coronary sinus, reported by Chang et al. (88) (with permission from journal of invasive cardiology). 1: centering basket, 2: aspiration catheter, 3: guidewire, 4: great cardiac vein, 5: right atrium, 6: arterial catheter

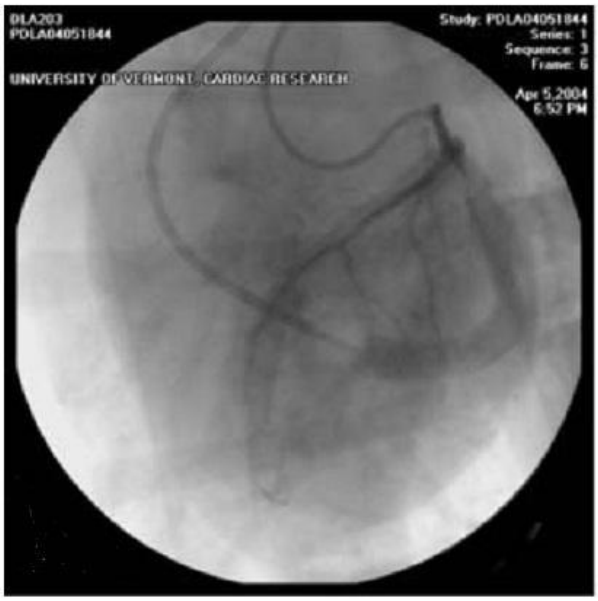

Figure 5. Fluoroscopic image of contrast filling the dog coronary sinus and occluded coronary sinus by the balloon, reported by Meyer et al. (with permission from journal of interventional cardiology)

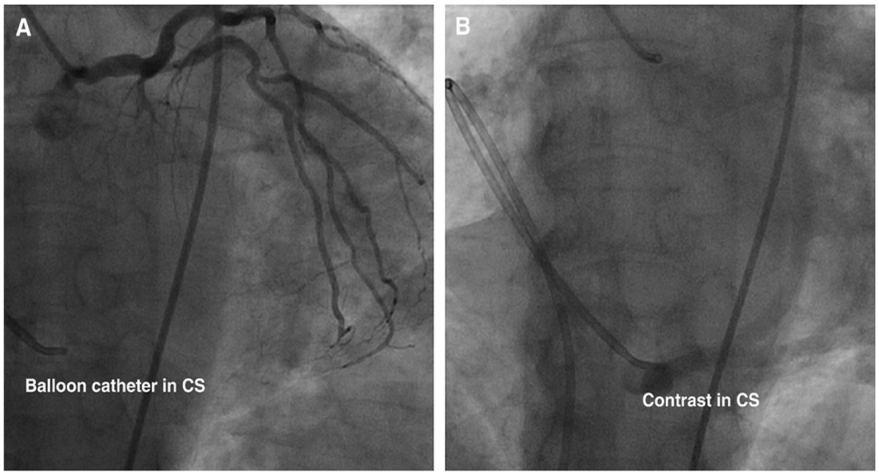

Figure 6. Coronary angiography images during left coronary contrast injection (A) and contrast collection from CS (B), reported by Danenberg et al. (90). (with permission from the

journal of cardiovascular revascularization medicine)

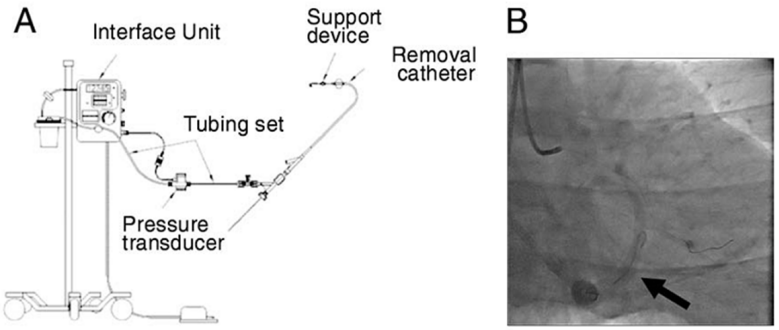

Figure 7. Contrast removal system used for contrast removal in the schematic (A) and fluoroscopic (B) images, reported by Duffy et al. (91).

(with permission from the journal of the American college of cardiology)

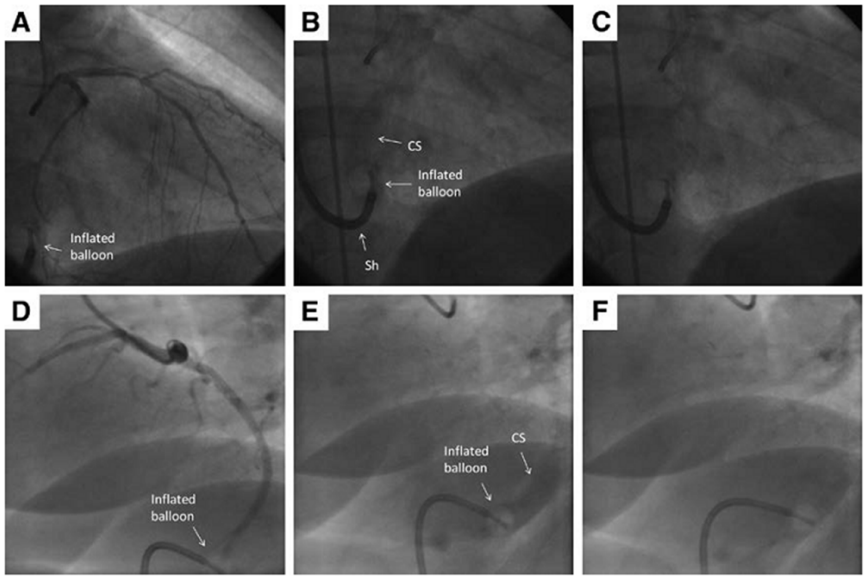

Figure 8. Serial fluoroscopic images of contrast injection (subclavian approach: A, femoral approach: D), contrast retention (subclavian approach: B, femoral approach: E), and contrast aspiration (subclavian approach: C, femoral approach: F) from coronary sinus with a balloon-tipped catheter, reported by Diab et al. (93).(with permission from the journal of circulation: cardiovascular intervention)

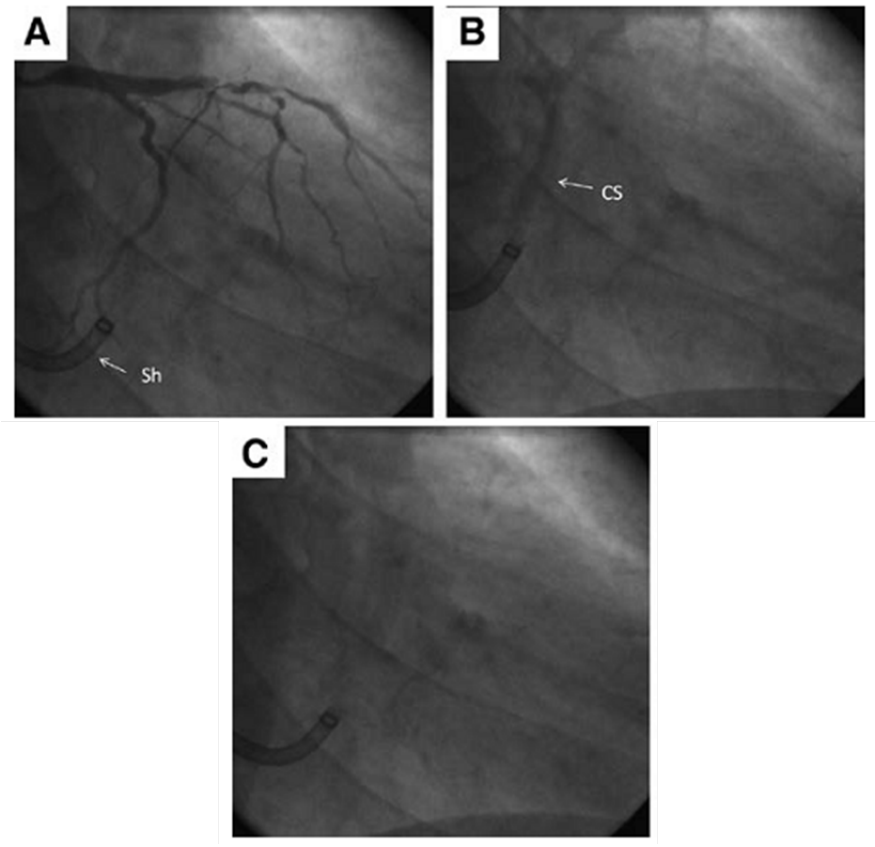

Figure 9. Serial fluoroscopic images of coronary contrast injection (A), contrast emergence in the coronary sinus (B), and contrast clearance (C) from coronary sinus with direct sheath aspiration through the subclavian approach, reported by Diab et al. (93).(with permission from the journal of circulation: cardiovascular intervention)

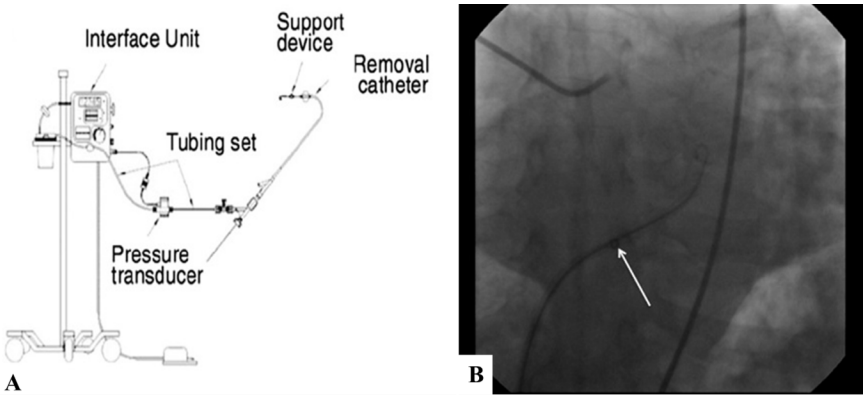

Figure 10. Schematic CINCOR contrast removal system (A) and the CINCOR catheter in the coronary sinus (B), reported by Watson et al. (94).

(with permission from the international journal of cardiology)

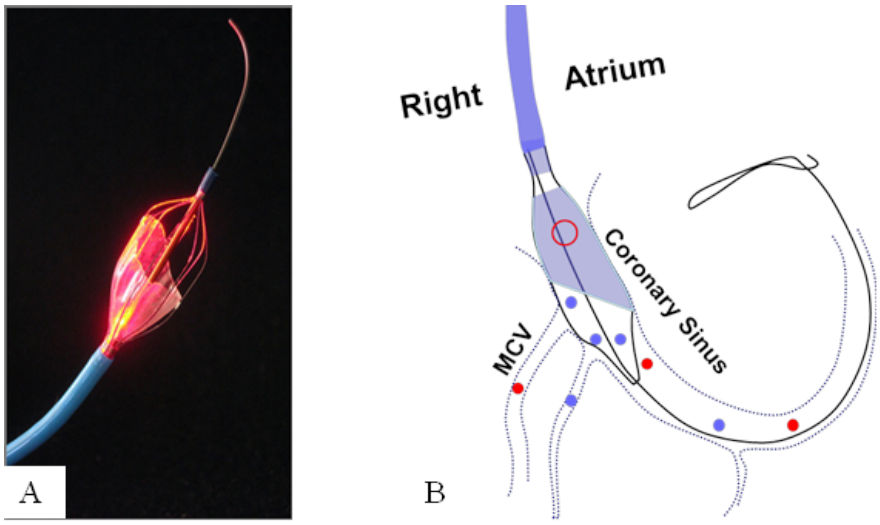

Figure 11. Catharose image (A) and schematic illustration of contrast capture from a coronary sinus (B). MCV: middle cardiac vein

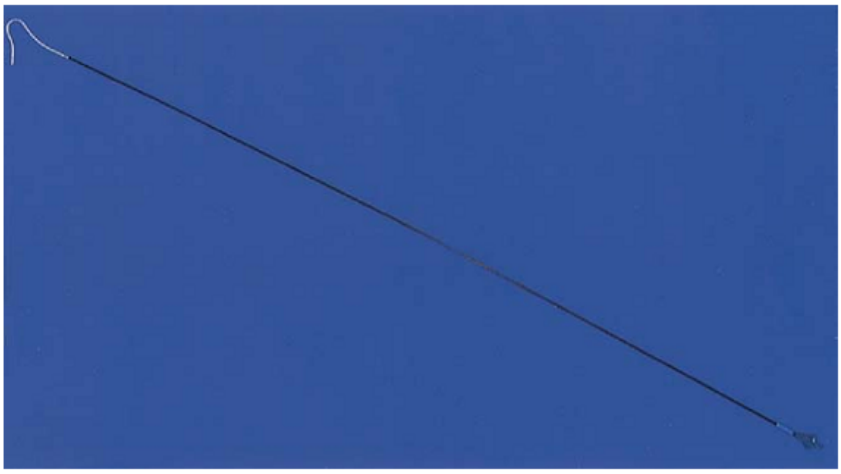

Figure 12. 8-Fr suction catheter with distal holes, reported by Michishita et al. (87). (with permission from the journal of the American college of cardiology)

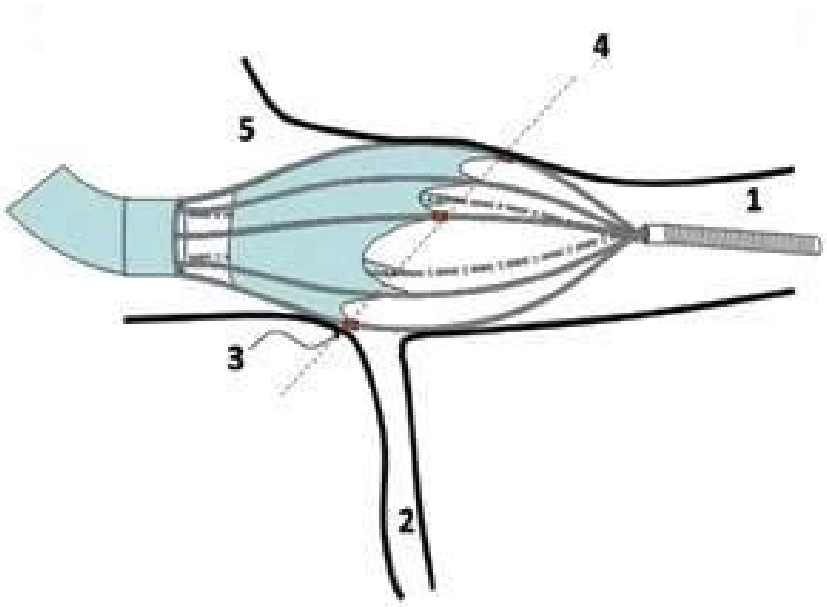

Figure 13. Schematic view of ideal basket position, reported by Chang et al. (88) (with permission from journal of invasive cardiology). 1: great cardiac vein, 2: middle cardiac vein, 3: marker band for middle cardiac vein, 4: line of three marker band, 5: right atrium

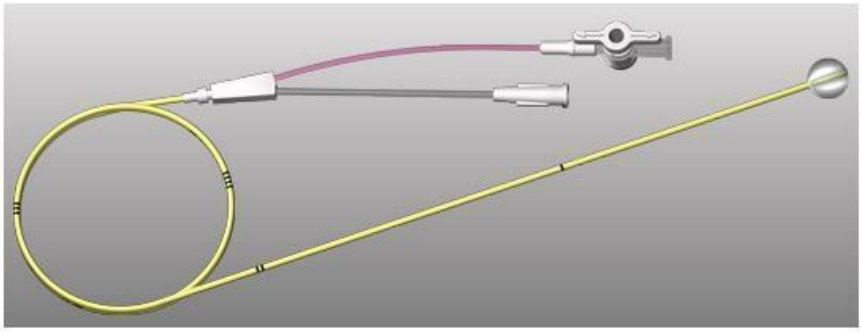

Figure 14. Balloon-tipped 6-Fr catheter (Pressure Products, Model BVCS 6180, San Pedro, CA), reported by Meyer et al. (89). (with permission from

www.pressure-products.com)

Figure 15. Balloon-tipped catheter with two lumens and multiple distal holes (Reverse Berman Angiography Catheter, 7 Fr, Arrow Int, Reading, PA, USA), reported by Danenberg et al. (90). (with permission from*www.teleflex.com*)

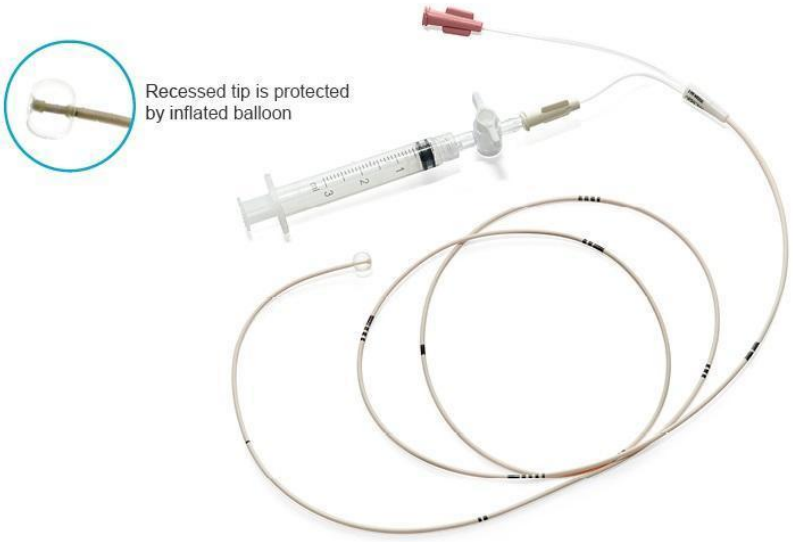

Figure 16. 7-Fr balloon-tipped catheter (7 F, single lumen; Arrow Int, Reading, PA), reported by Diab et al. (93). (with permission from*www.teleflex.com*)

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