



Original Article

A prospective study of contrast preservation using ultra-low contrast delivery technique versus standard automated contrast injector system in coronary procedures

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ABSTRACT

Background: We aimed to assess the decrease in contrast media volume (CMV) with ultra-low contrast delivery technique (ULCD) developed at our institution versus the usual automated contrast injector system (ACIS) contrast delivery in coronary procedures.

Methods: We analyzed the amount of contrast given in the consecutive 204 patients of the operators who use ULCD technique versus consecutive 200 patients of the other operators who use ACIS without ULCD technique for coronary angiograms and/or percutaneous coronary interventions (PCIs) from May 2017 to July 2018 at our center. We calculated the mean CMV between these groups.

Results: We observed a significant reduction in mean CMV with ULCD technique versus standard ACIS, respectively: angiogram 24.8 ± 15.8 mL ($n = 194$) vs 42.3 ± 25.1 mL ($n = 200$) ($p < 0.0001$); PCI 23.5 ± 19.7 mL ($n = 52$) vs 48.2 ± 30.8 mL ($n = 16$) ($p < 0.0070$); angiogram with *ad hoc* PCI 53.4 ± 32.1 mL ($n = 23$) vs 89.7 ± 35.6 mL ($n = 16$) ($p < 0.0024$); and overall angiogram and PCI 27.4 ± 20.5 mL ($n = 204$) vs 44.9 ± 28.0 mL ($n = 181$) ($p < 0.0001$).

Conclusion: Our study showed a highly significant reduction in CMV using ULCD technique compared to standard ACIS contrast delivery in coronary invasive procedures. Even in the standard ACIS arm, CMV was significantly lower than values reported in literature, possibly due to operators' bias toward contrast preservation.

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1. Introduction

Contrast-induced acute kidney injury (CI-AKI) is associated with short- and long-term consequences comprising worse in-hospital mortality, 1-year mortality, steady decline in renal function, need for renal replacement therapy, and increased health care costs.^{1–4} Most cases result from the intravascular contrast media (CM) exposure during cardiac catheterization and percutaneous coronary intervention (PCI).⁵ The currently recommended strategies to prevent CI-AKI in those who are at risk are holding nephrotoxic medications, adequate periprocedural intravenous hydration, use of iso-osmolar or low-osmolar contrast media,

lowering the volume of contrast media administered, and short-term high-dose statin therapy.⁶ Among these, the intravenous hydration and minimizing contrast volume are considered most effective in decreasing the risk of CI-AKI.⁷

The contrast media volume (CMV) is a modifiable factor, and various strategies have been described with a goal to reduce the adverse renal outcomes by minimizing the CM exposure, including specific devices. These include automated contrast injector systems, CM modulating devices, and removal of contrast from the coronary sinus or by hemodialysis.⁸ With the growing aging population and potential for these patients to have baseline renal dysfunction when they present for the coronary procedures, the efforts to reduce CMV become even more important. We previously published an ultra-low contrast delivery (ULCD) technique with the use of automated contrast injector system (ACIS) and showed a significant reduction in CMV in patients undergoing coronary procedures with less CI-AKI in high-risk patients.⁹ Recently, we

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reported a nanomedical *ex vivo* study showing that the toxic effect of the CM on endothelial and renal cells decreased exponentially with a linear decrease of contrast media concentrations.¹⁰ Here, we sought to prospectively evaluate the CMV administered using ULCD technique with and without ACIS in “all-comers” who underwent invasive coronary procedures.

2. Materials and methods

2.1. Study population and design

We conducted a prospective, observational study at the Sanford University Medical Center, Sioux Falls, SD, USA. We enrolled all consecutive patients who were undergoing cardiac catheterization and/or PCI between May 2017 and July 2018. There were no exclusions for this study. Informed consent was obtained from all patients enrolled. The study protocol was approved by our institutional review board. All coronary procedures were performed using Iodixanol (Visipaque), an iodine-containing nonionic isosmolar contrast agent. ACIST CVi® (ACIST Medical Systems, Eden Prairie, Minnesota) ACIS was used in all cases. Patients were allocated to either ULCD technique arm ($n = 204$) or ACIS ($n = 200$) arm. The ULCD technique has been previously described in detail and is briefly outlined below.⁹ A total of 204 patients underwent diagnostic catheterization and/or PCI in the ULCD technique arm. A total of 200 patients underwent diagnostic catheterization, and 28 patients underwent PCI using standard ACIS programming (the ACIS arm). A total of 26 patients underwent PCI using ULCD technique in the ACIS arm. We then further divided the patients into subgroups consisting of those who underwent diagnostic catheterization only, PCI only, and those who underwent diagnostic catheterization followed by an *ad hoc* PCI. All cardiovascular specialists who conducted the procedure reported the amount of CMV delivered. The CMV administered was compared between these two arms who underwent coronary procedures. Total procedure time and fluoroscopy dose were also compared between the two groups. The quality of images was assessed and deemed adequate by an experienced interventional cardiologist as per usual practice. Baseline demographic, angiographic, and procedure-related information was obtained from the review of the electronic medical records. Patients who underwent elective procedures received 1–2 mL/kg/hour intravenous (IV) fluids for 2–4 h before and after procedure and those who underwent emergent/urgent procedures received 1–2 mL/kg/hour IV fluids for 4 h after procedure per our institutional protocol.

2.2. Ultra-low contrast delivery technique

The ULCD technique requires the automated contrast injectors such as ACIST device. The volume (mL), flow (mL/s), rise time (sec), and pressure (psi) are adjusted for left/right coronary artery based on the initial small volume of injection of 0.5 mL (spill-over). Based on the catheter filling, the size of the coronary artery and flow is determined. Then the ACIS programming is done, with, in general, 1–4 mL, 2–4 mL/s, 0.2–0.5 s rise time, and 300–450 psi depending on “spill-over” findings during catheter filling. The detailed description of the technique has been previously published⁹ (Figs. 1 and 2).

2.3. Statistical analysis

Continuous variables are displayed as mean \pm standard deviation, and categorical variables are displayed as numbers and percentages. Continuous variables were analyzed using student *t*-test, and categorical variables were analyzed by a chi-square test. *T*-tests

were used to compare mean contrast volumes between ULCD and ACIS groups (Table 2). Descriptive statistics were also compared between ULCD and ACIS groups (Table 1). The *p*-value is a result of the comparison between these two groups, and the significant difference was defined as $p < 0.05$.

3. Results

Of the consecutive 204 patients in the ULCD arm, 194 underwent diagnostic catheterization, 59 underwent PCI, and 24 underwent diagnostic coronary angiogram with *ad hoc* PCI. Two hundred patients underwent diagnostic catheterization, and 28 patients underwent diagnostic catheterization with *ad hoc* PCI in the ACIS arm. No separate PCI-only procedure was conducted in the ACIS group. The baseline characteristics did not differ significantly between these two groups (Table 1). Most patients underwent coronary procedures through the radial approach. Overall, patients with Stage 3 and 4 chronic kidney disease represent 70% of the study population.

The amount of CMV was significantly lower in the ULCD arm across all the subgroups (Fig. 3). For patients who underwent diagnostic catheterization only, the mean CMV was significantly lower in the ULCD arm compared to ACIS arm: 24.8 ± 15.8 mL ($n = 194$) vs 42.3 ± 25.1 mL ($n = 200$) ($p < 0.0001$). For patients who underwent PCI only, the mean CMV was significantly lower in the ULCD arm compared to ACIS arm: 23.5 ± 19.7 mL ($n = 52$) vs 48.2 ± 30.8 mL ($n = 16$) ($p < 0.0070$). For patients who underwent diagnostic catheterization with *ad hoc* PCI, the mean CMV was significantly lower in the ULCD arm compared to ACIS arm: 53.4 ± 32.1 mL ($n = 23$) vs 89.7 ± 35.6 mL ($n = 16$). When the total amount of CMV administered combining diagnostic catheterization and PCI in the ULCD arm compared to ACIS, the mean CMV was significantly lower: 27.4 ± 20.5 mL ($n = 204$) vs 44.9 ± 28.0 mL ($n = 181$) ($p < 0.0001$). Besides, the total procedure time is significantly lower in the ULCD group compared to the ACIS group (18.0 ± 11.3 min vs 29.3 ± 27.2 min, $p < 0.001$). We also observed a significant reduction in the total amount of radiation dose in ULCD arm compared to ACIS arm (535.0 ± 500.4 mGy vs 720.7 ± 674.8 mGy, $p < 0.002$).

4. Discussion

Depending on the baseline renal function, risk factors, and clinical setting, the incidence of CI-AKI varies from 2% to as high as 50% in patients undergoing invasive coronary procedures and CI-AKI is considered a third leading cause of the hospital-acquired acute kidney injury.^{11,12} Aside from providing adequate periprocedural intravenous hydration and minimizing CMV, no other pharmacological preventive or treatment measures have proven to be efficacious in preventing CI-AKI. The CMV is a procedural variable that is modifiable by the operator in coronary procedures, and the degree of benefit in reducing CK-AKI is proportional to the amount of reduction in CMV.¹³ The recent National Cardiovascular Data Registry CathPCI reported a mean CMV of 197.7 mL for patients undergoing PCI.¹⁴

Although reducing the CMV has been shown to reduce the incidence of the CI-AKI during the coronary procedures, the safe limit of contrast dose is not well known. In 1989, Cigarroa et al. proposed maximal acceptable contrast dose derived by a formula 5 mL/kg body weight divided by baseline serum creatinine (mg/dl) to decrease CI-AKI.¹⁵ Although this formula has been tested in a large study of 16,952 PCIs in predicting the nephropathy requiring dialysis, it is not commonly used.¹⁶ Laskey et al. reported that the ratio of the volume of contrast media to the creatinine clearance

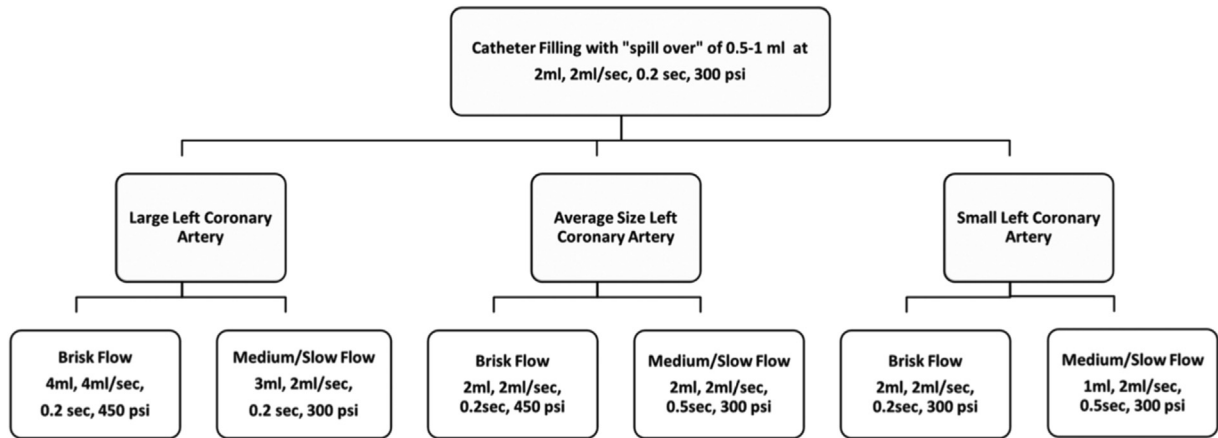


Fig. 1. Left coronary artery ACIST algorithm using ULCD technique (Reproduced with permission from the *Journal of Invasive Cardiology*). ULCD, ultra-low contrast delivery.

>3.7 was a predictor of CI-AKI in patients undergoing PCI and may be used to estimate the highest amount of contrast media that can be administered to decrease the risk of CI-AKI.¹⁷ Another study suggested a ratio of amount of contrast given to calculated creatinine clearance of more than 3 is associated with an increased risk of CI-AKI and dialysis in invasive coronary procedures.¹⁸ In addition, a computational model was developed to assess the degree of contrast media volume reduction and the occurrence of the AKI among patients receiving PCI. This modeling study showed a 12.8% and 8.8% reduction in AKI with 30% and 20% reduction in contrast media volume, respectively, and the benefit corresponded to the degree of contrast reduction.¹³

The definition of low contrast volume differs from study to study but the basic principle for the contrast media volume administered for a coronary procedure is as low as reasonably achievable (ALARA) for at-risk patients,^{19–21} and this approach has found its way into the guidelines.^{22,23} Devices have been developed and studied to limit the CMV, including ACIST CVi® (ACIST Medical Systems, Eden Prairie, Minnesota), Avanta system (MEDRAD Inc., Warrendale, Pennsylvania) and AVERT system (Osprey Medical, Minnetonka, Minnesota).^{8,24} A meta-analysis comparing the administered CMV using the ACIS versus the manual injection in patients undergoing coronary procedures showed a significant reduction in contrast administered using ACIS. In this study, there was a 45 mL reduction in CMV per case and a 15% reduction in the

incidence of CI-AKI in the ACIS cohort.²⁵ However, the individual studies comparing ACIS use versus manual manifold system for the contrast delivery in coronary procedures showed conflicting results in reducing the CMV delivered and CI-AKI.^{26–30}

The DyeVert System, a next-generation AVERT System, has been tested for CMV reduction with and without assessing CI-AKI outcome. Sapontis et al. reported that overall attempted mean CMV injected was 172.9 ± 116.8 mL and actual mean CMV injected was 88.7 ± 56.9 mL with a saved volume of 84.1 ± 66.1 mL due to the device in all diagnostic angiograms and PCIs (n = 44).³¹ Another small study of patients (n = 10) who underwent coronary and peripheral procedures reported an injected mean CMV of 79.9 ± 48.8 mL and absolute CMV of 55.8 ± 31.9 mL, with one case of asymptomatic CI-AKI.³² A prospective, single-center, open-label randomized controlled trial of 96 patients who underwent diagnostic coronary angiograms only using DyeVert system showed 36.9 ± 10.9 mL contrast utilization versus 62.5 ± 12.7 mL with no DyeVert system, reporting 41% contrast media volume reduction.³³ Lately, a prospective, multicenter AVERT (AVERT Clinical Trial for Contrast Media Volume Reduction and Incidence of CIN) randomized trial (n = 578) compared the AVERT system plus periprocedural hydration versus procedural hydration in reducing the contrast media volume and preventing CI-AKI events in at-risk individuals undergoing coronary angiogram with or without PCI.³⁴ Using the first-generation AVERT system, this trial reported a

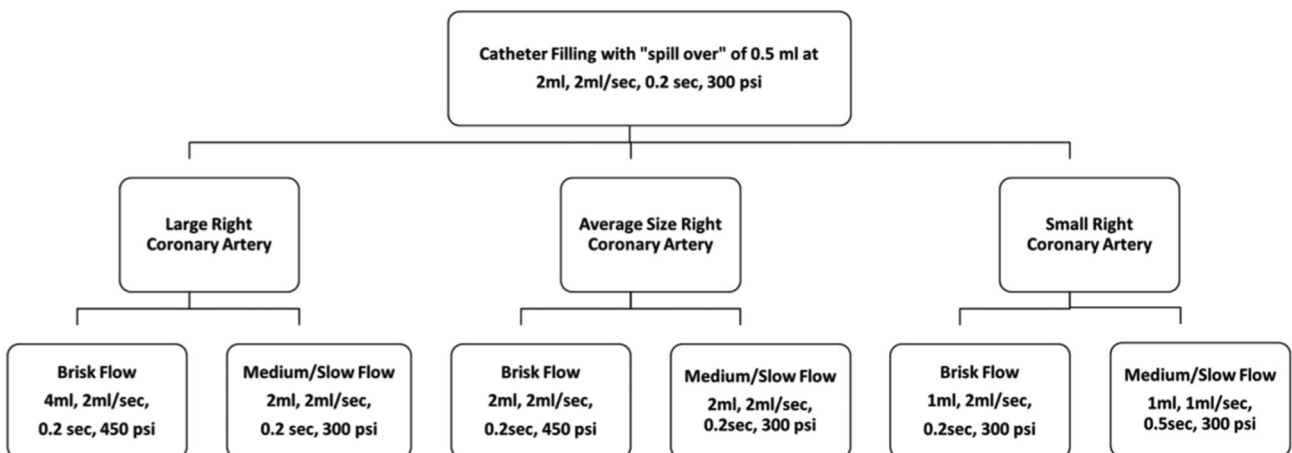


Fig. 2. Right coronary artery ACIST algorithm using ULCD technique (Reproduced with permission from the *Journal of Invasive Cardiology*). ULCD, ultra-low contrast delivery.

Table 1
Clinical and procedural characteristics.

Clinical variable	ULCD N = 204	ACIS N = 200	p value
Age in years (mean ± SD)	67.75 ± 11.21	68.56 ± 11.91	0.482
Male	121 (59.3%)	113 (56.5%)	0.567
Female	83 (40.7%)	87 (43.5%)	
Weight in kkg (mean ± SD)	94.41 ± 24.08	93.84 ± 24.28	0.814
Height in cm (mean ± SD)	171.51 ± 11.57	171.37 ± 11.36	0.905
Body surface area in m ²	2.05 ± 0.30	2.04 ± 0.28	0.828
Creatinine clearance			
eGFR <30%	9 (4.4%)	7 (3.5%)	0.638
eGFR 30–59%	40 (19.6%)	40 (20.0%)	0.921
eGFR 60–89%	97 (47.5%)	99 (49.5%)	0.695
eGFR >90%	57 (27.9%)	53 (26.5%)	0.745
History of CABG	28 (13.7%)	19 (9.5%)	0.185
No. of diagnostic coronary angiogram	194	200	N/A
No. of percutaneous intervention	59	28	N/A
No. of diagnostic coronary angiogram and <i>ad hoc</i> percutaneous intervention	24	28	N/A
Indication for the procedure			
Elective	181 (88.7%)	185 (92.5%)	0.194
Urgent	23 (11.3%)	14 (7.0%)	0.136
Emergent	2 (1.0%)	0 (0.0%)	0.159
No. of biplane used	116 (58.0%)	118 (59.3%)	0.793
No. of single plane used	84 (42.0%)	80 (40.2%)	0.715
Radial access	173 (84.8%)	183 (91.5%)	0.038
Ulnar access	2 (1.0%)	0 (0.0%)	0.160
Femoral access	32 (15.7%)	31 (15.5%)	0.959
Total fluoro dose in mGy	535.04 ± 500.37	720.67 ± 674.82	0.002
Total procedure time in min	18.02 ± 11.27	29.35 ± 27.20	<0.001

ULCD, ultra-low contrast delivery; ACIS, automated contrast injector system; eGFR, estimated glomerular filtration rate; CABG, coronary artery bypass graft surgery.

Table 2
Mean amount of contrast media volume delivered per patient using ACIST device with and without ULCD technique.

Type of procedure	ULCD No. of patients	Contrast volume (mL)	ACIS No. of patients	Contrast volume (mL)	Mean percent contrast reduction (%)	p value
Diagnostic angiogram	194	24.8 ± 15.8	200	42.3 ± 25.1	41.5	<0.0001
PCI	52	23.5 ± 19.7	16	48.2 ± 30.8	51.2	0.0070
Diagnostic angiogram + <i>ad hoc</i> PCI	23	53.4 ± 32.1	16	89.7 ± 35.6	40.4	0.0024
Combined diagnostic angiogram and PCI	204	27.4 ± 20.5	181	44.9 ± 28.0	45.7	<0.0001

ULCD, ultra-low contrast delivery; ACIS, automated contrast injector system; PCI, percutaneous coronary intervention.

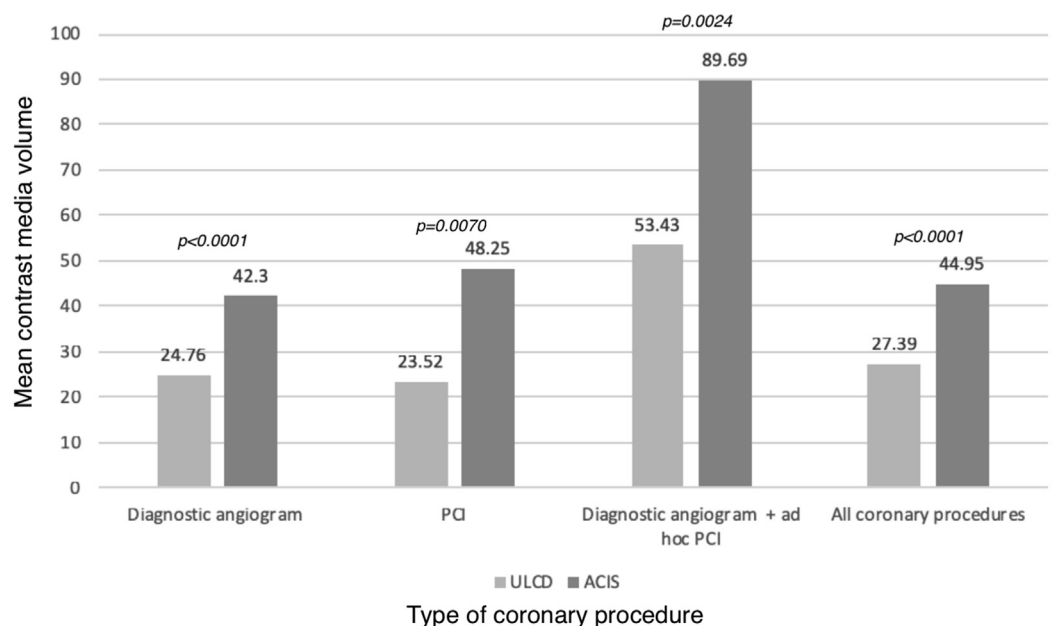


Fig. 3. Bar-graph representation of contrast media volume administration using ULCD technique vs. ACIS across all coronary procedures. ULCD, ultra-low contrast delivery; ACIS, automated contrast injector system.

Table 3
Comparison of contemporary studies in contrast volume reduction.

Study	Device and/or technique used	Number of patients	Type of study	Type of procedure	Amount of contrast media volume delivered in mL
Sapontis J et al.	DyeVert	44	Prospective, observational	Diagnostic catheterization and/or PCI	88.7 ± 56.9
Corcione N et al.	DyeVert NG	10	Retrospective, observational	Diagnostic catheterization and/or PCI and peripheral angiogram and stenting	79.9 ± 48.8
Desch et al.	DyeVert	96	Prospective, randomized	Diagnostic catheterization	36.9 ± 10.9
Mehran et al.	AVERT	578	Prospective, randomized	Diagnostic catheterization and/or PCI	All procedures: 85.6 ± 50.5 PCI: 114 ± 55 67 ± 51
Gurm et al.	DyeVert Plus System	114	Prospective, multicenter, single-arm, observational	Diagnostic catheterization and/or PCI	67 ± 5
Our study	ULCD technique + ACIS	204	Prospective, single-center, observational	Diagnostic catheterization and/or PCI or <i>ad hoc</i> PCI	Diagnostic angiogram: 24.8 ± 15.8 PCI: 23.5 ± 19.7 Diagnostic angiogram + <i>ad hoc</i> PCI: 53.4 ± 32.1 Combined diagnostic angiogram and PCI: 27.4 ± 20.5

ULCD, ultra-low contrast delivery; ACIS, automated contrast injector system; PCI, percutaneous coronary intervention.

statistically significant reduction from 101.3 ± 71.1 mL to 85.6 ± 50.5 mL CMV in all coronary procedures and from 147 ± 81 mL to 114 ± 55 mL CMV in PCIs. However, no significant reduction in CI-AKI was observed in the two study arms, and attributable reasons to this finding were multifactorial etiology of the CI-AKI, relatively lower CMV reduction in patients who underwent diagnostic coronary angiograms, and inadequate power to detect CI-AKI events in the PCI-only group.³⁴ A recent multicenter, prospective, observational study by Gurm et al. reported that a mean CMV delivered in patients undergoing coronary angiogram and/or PCI was 67 ± 5 mL using DyeVert Plus System in patients with CKD and noted an AKI incidence rate of 9.6%.³⁵

Our previous study with ULCD technique demonstrated a remarkable lowering of CMV administered with a mean CMV of 17.9 mL ($n = 123$) in Stage 3 and 4 CKD patients who underwent diagnostic coronary angiogram and/or PCI. Only 7.3% ($n = 9/123$) patients developed CIN at 30-day follow-up period.⁹ In the present study, we aimed to assess the role of our ULCD technique with ACIS in reducing the contrast media volume compared to ACIS alone in “all comers” series of consecutive patients undergoing invasive coronary procedures.

Regardless of the type of the coronary procedure, diagnostic catheterization, PCI, or diagnostic catheterization with *ad hoc* PCI, the mean CMV administered was significantly lower in the ULCD group compared to ACIS group. Across all groups, there was a 40–50% reduction in CMV administered with ULCD technique compared to ACIS only. The procedure time was also significantly lower in the ULCD group compared to ACIS. This could be due to higher procedural efficiency of interventionalists vs. invasive cardiologists in performing angiograms, but also time-saving advantage of the ULCD technique is a possibility. In addition, the ULCD technique is associated with lower radiation compared to standard ACIS for possibly similar reason(s). We did not assess the incidence of CI-AKI in our study. Overall, our ULCD technique with the use of ACIS significantly lowers the CMV administration and compared to the contemporary studies; the ULCD technique delivers lowest CMV in the literature^{31–35} (Table 3). Another very pertinent in our opinion observation is the relatively low CMV in our control arm compared to other studies. We think that this is due to the experience gained by the cath lab technicians from the ULCD arm operators and application of some of the reduced volumes programming in the ACIS arm by the operators. Simple awareness

of contrast preservation efforts by operators and staff alone could have contributed to this finding.

In parallel to the clinical study presented here, we performed a separate study using nanomedical sensors to monitor *in vitro* the interaction of contrast media molecules and their toxicity on human endothelial and renal cells.¹⁰ The preliminary results already indicate the toxic effect can be significantly reduced at low concentration of contrast media 2.5 mg/mL (equivalent to 39 mL of infused contrast). At a concentration of 6 mg/mL (equivalent to 94 mL of infused contrast), a dramatic increase in cytotoxic peroxynitrite (ONOO^-), the main component of oxidative stress, and a decrease in cytoprotective nitric oxide (NO) were observed. This can lead to endothelial dysfunction and CI-AKI. These data provide molecular basis justifying reduction of CMV administered to a patient, as means of reducing CI-AKI.

Given the substantial amount of the contrast media reduction, we think that the ULCD technique is very useful clinically. We believe that at present, ALARA CMV for the coronary procedures is most efficiently obtained with our ULCD technique without sacrificing image quality.

4.1. Study limitations

First, this is an observational study conducted at a single center. Second, we did not study the incidence of the CI-AKI in our study as we did not check the renal function after procedure routinely. Third, our operators are relatively experienced; thus, application of this technique by invasive cardiologists elsewhere might involve some learning curve. However, our second-year fellows in the catheterization laboratory have been already quite handy with this technique; thus, we do not anticipate a steep learning curve in practicing cardiologists. In fact, the standard algorithm 9 and use of ACIS makes it easier to teach than teaching manual injections, where it is difficult to exactly explain parameters like pressure applied and rate of rise.

5. Conclusion

We report that the ULCD technique with the use of ACIS during the coronary procedures can be applied in all patients with a very significant reduction in the contrast media volume delivered without compromising the angiographic image quality. This

technique is a relatively simple and inexpensive, yet it may translate into the meaningful reduction in CI-AKI events in a broad patient population.

Conflicts of interest

All authors have none to declare.

Financial disclosure statement

The authors have no financial disclosures to report.

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