Ultra-Low Contrast Volume for Patients with Advanced Chronic Kidney Disease Undergoing Coronary Procedures

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Keywords

Chronic kidney disease · Contrast-induced nephropathy ·
Coronary artery disease

Abstract

Background/Aims: Contrast induced nephropathy (CIN) is associated with adverse clinical outcomes in patients undergoing coronary interventions, particularly in patients with advanced chronic kidney. The study was aimed to assess the real-life feasibility and safety of ultra-low volume coronary procedures in patients with advanced chronic kidney disease. **Methods:** A prospective study that included patients with an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m² was conducted. Coronary procedures were performed using an ultra-low contrast volume technique. **Results:** The 30 patients had a mean eGFR of 31.8(±8) mL/min/1.73 m². Indications for coronary angiography were non-ST elevation myocardial infarction (63.3%), unstable (20%), and stable angina pectoris (16.7%). Median contrast volume for diagnostic coronary angiography was 13 mL (in-

terquartile ranges [IQR] 12–14.9), and an additional 13 mL (IQR 8.8–14.3) for percutaneous coronary intervention (PCI). In 3 patients (10%), a ≥25% increase was demonstrated in serum cystatin C levels 48 h following the procedure. None of the patients demonstrated a ≥25% increase in serum creatinine levels at 48 h. Following 6 months, no patient required renal replacement therapy or unplanned coronary intervention. **Conclusions:** In patients with advanced chronic kidney disease, the ultra-low contrast technique is feasible and effective and can be used safely without a significant deterioration in renal function. This technique may increase the utilization of PCI in high-risk coronary patients with chronic kidney disease.

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Introduction

Contrast induced nephropathy (CIN) is associated with adverse clinical outcomes in patients undergoing coronary interventions [1–3]. Various interventions have

been studied in order to reduce the risk of CIN [4, 5]. However, no specific measures have been determined for patients with advanced chronic kidney disease. The only 2 established approaches to prevent CIN in this high-risk group are periprocedural hydration [6] and minimizing contrast volume [7]. Despite these measures, percutaneous coronary intervention (PCI) in patients with advanced renal failure is associated with up to 30% risk of CIN [3]. This leads to the underutilization of PCI in high-risk coronary patients with chronic kidney disease [8, 9].

PCI with ultra-low contrast volume has been described in a small study that included selected patients with chronic kidney disease [10]. Furthermore, PCI using various techniques and imaging modalities with no contrast use has recently been reported [11]. These studies were performed at a single high-volume center and included only patients with stable coronary artery disease. Moreover, several techniques and imaging modalities, which may not be widely accessible in many laboratories, were extensively employed.

The current study was aimed to assess the real-life feasibility and safety of ultra-low volume coronary procedures in patients with advanced chronic kidney disease.

Material and Methods

Study Population

We performed a prospective study that included consecutive patients with chronic kidney disease stages 3B-5 (estimated glomerular filtration rate [eGFR] <45 mL/min/1.73 m² by the 4-component Modification of Diet in Renal Disease [MDRM] equation [12]) for whom coronary angiography was planned to be performed. Indications for coronary angiography included non-ST-elevation acute coronary syndrome (ACS) with a GRACE score >110, and patients with stable angina pectoris and a positive non-invasive myocardial ischemia involving >10% of left ventricle [13]. Patients were recruited at least 24 h prior to the procedure. Excluded were patients over 80 years of age, patients on dialysis or those planned for dialysis in the next 3 months, and patients with a history of coronary artery bypass graft. Of note, patients presenting with ST-elevation myocardial infarction or acute renal failure (defined as a creatinine elevation of >0.3 mg/dL compared to baseline values) or patients with acute heart failure (Killip class >1, or those in need of treatment with intravenous diuretics during the 3 days prior to the procedure) were also excluded from the study.

Renal Function Assessment

Screening of patients amenable for the study was conducted using the simplified MDRM formula:

$$\text{eGFR} = 186 \times (\text{sCr [in mg/dL]})^{-1.154} \times (\text{age [in years]})^{-0.203}$$

For women, the product of this equation was multiplied by a factor of 0.742.

Following enrollment to the study, renal function was assessed by measuring serum cystatin C and creatinine. Cystatin c was measured using Siemens N-Latex enhanced reagent with calibration traceable to the international standard reference material. Blood samples were obtained just prior to the procedure (day 0), after 24 h (day 1) and following 48 h (day 2).

Endpoints

The primary endpoint was defined as a $\geq 25\%$ raise in serum cystatin C or creatinine 48 h following the coronary procedure. Secondary endpoints included cardiovascular mortality, a need for renal replacement therapy, or unplanned coronary intervention at 6 months following the coronary procedure.

Coronary Procedures

All procedures were performed by a single experienced interventional cardiologist. All patients received prehydration with intravenous isotonic saline at a rate of 1 mL per kilogram of body weight per hour (or 0.5 mL per hour in patients with severely reduced left ventricular function) starting 12 h prior to the procedure. The same hydration protocol was maintained for 12 h following the procedure. High-dose statin (mainly Atorvastatin of 40–80 mg) was given to patients who were not on that treatment prior to hospital admission. Angiotensin-converting-enzyme inhibitors/angiotensin II receptor blockers were not discontinued prior to the coronary procedure. The decision regarding access site, diagnostic and guide catheters, stent type, intra-procedural imaging, and pharmacotherapy was left to the discretion of the interventional cardiologist. The contrast used in all cases was Ultravist 370 (Bayer): a nonionic low osmolar contrast medium with 2 h half-life that may increase to 6–11 h in patients with renal impairment.

The ultra-low contrast technique used in the current study has been previously described [10] and has been used in patients with renal failure in our institution for several years. Key elements of this technique included use of small catheters without side-holes, a limit of contrast volume to 2 mL per injection, removal of contrast from the guide catheter prior to exchange of devices, an absolute avoidance of contrast “puffing” during the procedure and positioning of PCI wires and balloons with minimal contrast. When available, previous angiographic images were reviewed prior to the procedure and were displayed alongside active fluoroscopy screen as a reference.

Ethical Considerations

Preprocedural discussion with the patients included potential benefits of coronary revascularization and risks of complications, especially CIN and the possible need for renal replacement therapy. The study was approved by the institutional ethics committee and all participants provided their written informed consent. The study was registered in the NIH ClinicalTrials.gov (NCT02468401).

Statistical Analysis

Categorical variables were expressed as percentage and continuous variables were expressed as mean $\pm$ SD. Continuous variables were tested for normal distribution using histogram and Q-Q plot or medians with interquartile ranges (IQR). Variables were compared using the Mann-Whitney test. We conducted a linear regression with time as the independent variable and creatinine and cystatin C as the dependent variables. The multivariate analy-

sis was conducted in the forward method for baseline characteristic according to Table 1 in addition to age and gender. The final creatinine model included mitral regurgitation, prior myocardial infarction, peripheral vascular disease, smoking, age, and gender. The final cystatin C model included peripheral vascular disease, age, and gender. Results were reported as b-coefficients (95% CI). Analyses were performed with SPSS IBM Corp., Released 2013. IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Patient Characteristics

Baseline characteristics of the study population are presented in Table 1. The 30 consecutive patients included in the study had a mean age of 71 (± 7) years and were comprised of 46.7% females. The majority had multiple cardiac risk factors and a previous history of cardiovascular disease. All patients had advanced chronic renal failure with median creatinine of 1.85 (IQR 1.6–2) mg/dL and eGFR of 31.8 (± 8) mL/min/1.73 m². The most common indication for coronary angiography was a non-ST elevation myocardial infarction (19 patients), followed by unstable (6 patients) and stable (5 patients) angina pectoris.

Procedural Characteristics

Procedural characteristics are presented in Tables 2 and 3. Procedures were performed via the radial approach in 80% of cases. Diagnostic coronary angiography was performed with ultra-low contrast volume of 13 mL (IQR 12–14.9). Nonsignificant coronary disease suitable for conservative treatment was demonstrated in 12 patients. Two patients demonstrated multi-vessel coronary disease requiring coronary artery bypass grafting and were referred for surgery. Of the remaining 16 patients who were found suitable for an ad hoc PCI, 11 underwent a single-vessel PCI, while in the remaining 5 patients, a double-vessel PCI was performed. In 2 patients who underwent PCI, staged PCI was planned at an interval of 4 weeks. Of the coronary lesions that were treated, 8 (38%) were class B2 or C on the American College of Cardiology/American Heart Association classification system [14]. Only third-generation drug eluting stents were used in the study and the majority of patients received 1 or 2 stents with pre- and post-dilatation. Drug eluting balloons were used for the treatment of in-stent restenosis. Heparin was the anticoagulation agent of choice in all cases. Similar to diagnostic angiography, PCI was also performed with ultra-low contrast volume of 13 mL (IQR 8.8–14.3).

Table 1. Baseline characteristics of the study participants

	<i>n</i> = 30
Age, years, mean $\pm$ SD	71.4 $\pm$ 6.9
BMI, kg/m ² , mean $\pm$ SD	29.5 $\pm$ 4.8
Gender, female, %	46.7
Diabetes mellitus, %	63.3
Hypertension, %	96.7
Dyslipidemia, %	93.3
Current smoking, %	13.3
Prior MI, %	26.7
Prior PCI, %	46.7
PVD, %	30
CVA/TIA, %	20
COPD, %	20
LV systolic function, %	
Normal	40
Mild LV dysfunction	30
Moderate LV dysfunction	23.3
Severe LV dysfunction	6.7
Chronic medications, %	
Aspirin	76.7
Plavix	20
Statin	80
ACEI/ARB	70
Beta blocker	53.3
Diuretics	23.3
Insulin	46.7
Laboratory parameters	
Hemoglobin, mg/dL, mean $\pm$ SD	12.1 $\pm$ 1.5
Cholesterol, mg/dL, mean $\pm$ SD	183.6 $\pm$ 40.1
LDL, mg/dL, mean $\pm$ SD	97 $\pm$ 25.7
HDL, mg/dL, median (IQR)	37 (33–43)
Triglycerides, mg/dL, median (IQR)	152 (134–175.5)
Indication for angiography, %	
Elective	16.7
Unstable angina	20
STEMI	63.3

ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blockers; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; HDL, high density lipoprotein; IQR, interquartile range; LDL, low density lipoprotein; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; STEMI, ST segment elevation myocardial infarction; TIA, transient ischemic attack.

Periprocedural Renal Function

Median creatinine values (IQR) at 0, 24, and 48 h were 1.85 (1.6–2), 1.75 (1.53–1.9), and 1.75 (1.6–2) mg/dL respectively. Median cystatin C (IQR) at 0, 24, and 48 h were 1.83 (1.5–2.1), 1.85 (1.7–2.2), and 1.9 (1.6–2.3) mg/L respectively. There was a significant reduction in mean serum creatinine and cystatin C levels at baseline and at 24 and 48 h (Fig. 1). In 3 patients (10%), a $\geq 25\%$ increase was

demonstrated in serum cystatin C levels 48 h following the coronary procedure. Of them, 2 underwent only coronary angiography without angioplasty due to nonobstructive coronary artery disease (overall contrast volume of 12 and 14 mL), and 1 patient underwent a double vessel angioplasty using drug eluting stents (overall contrast volume of 26 mL). Interestingly, none of the patients (including the 3 patients who developed CIN based on serum cystatin C levels) demonstrated a $\geq 25\%$ increase in serum creatinine levels 48 h following coronary procedure. There were 10 patients with baseline eGFR < 30 mL/min/1.73 m². A sub-analysis of these patients with advanced renal dysfunction did not demonstrate a significant change in creatinine ($p = 0.179$) or cystatin C ($p = 0.614$) in serial measurements. During the 6-month follow-up, 1 patient died due to end-stage heart failure and no patient required renal replacement therapy or unplanned coronary intervention. For the 3 patients who developed CIN based on serum cystatin C levels, serum creatinine levels remained stable 5–6 months following the procedure. We further conducted a linear regression to assess renal function as a function of time that did not demonstrate a statistically significant relation for both cystatin C and creatinine. For creatinine, a 24-h increment demonstrated a -0.05 mg/dL change (95% CI -0.19 to 0.09 , $p = 0.506$) in a univariate analysis and a -0.05 mg/dL change (95% CI -0.17 to 0.07 , $p = 0.432$) in a multivariate analysis. For cystatin C, a 24-h increment demonstrated a change of 0.04 mg/L (95% CI -0.1 to 0.19 , $p = 0.553$) in a univariate analysis and 0.04 mg/L (95% CI -0.07 to 0.16 , $p = 0.453$) in a multivariate analysis.

Discussion

The current study is the first to demonstrate the feasibility and safety of coronary angiography and PCI with ultra-low contrast volume in consecutive real-life patients with advanced chronic kidney disease. In 3 patients (10%), $\geq 25\%$ increase was demonstrated in serum cystatin C levels 48 h following the coronary procedure. Interestingly, none of the patients (including the 3 patients who developed CIN based on serum cystatin C levels) had $\geq 25\%$ increase in serum creatinine levels during the 48 h following the coronary procedure. During the follow-up after 6 months, it was found that none of the patients required renal replacement therapy or unplanned coronary intervention.

Traditionally, CIN has been assessed using serum creatinine measurements. Due to the tubular secretion of creatinine, creatinine-based equations mildly overestimate the measured glomerular filtration rate. Cystatin C

Table 2. Procedural characteristics of the diagnostic coronary angiography (30 patients)

Access site, %	
Radial	80
Femoral	20
Stenosis $\geq 70\%$	
LAD	37.7
Circumflex	33
RCA	19
LM	0
Contrast material, mL, median (IQR)	13 (12–14.9)

IQR, interquartile range; LAD, left anterior descending; LM, left main; RCA, right coronary artery.

Table 3. Procedural characteristics of the PCI (16 patients)

Target vessel, %	
LAD	31.3
Circumflex	50
RCA	18.7
LM	0
PCI vessel number, mean $\pm$ SD	1.3 $\pm$ 0.5
DEB, %	25
DES, %	75
Stent number, mean $\pm$ SD	1.31 $\pm$ 1.01
Staged angiography planned, %	12.5
Medications during procedure, %	
Heparin	100
Plavix	62.5
Ticagrelor	37.5
Contrast, mL, median (IQR)	13 (8.8–14.3)

DEB, drug eluting balloon; DES, drug eluting stent; IQR, interquartile range; LAD, left anterior descending; LM, left main; PCI, percutaneous coronary intervention; RCA, right coronary artery.

is an alternative serum measure of kidney function that approximates direct measures of glomerular filtration rate, since it is filtered freely by the renal glomerulus and is less influenced by age, gender, or muscle mass [15, 16]. On the other hand, different processes unrelated to kidney function such as acute inflammation may result in a significant increase in serum cystatin C that could erroneously be interpreted as acute kidney injury [17, 18]. Whether renal function assessment using cystatin C is superior to creatinine for the detection of CIN, especially in patients with advanced renal dysfunction, remains unclear. Therefore, in the current study, renal function was assessed using both serum cystatin C and creatinine.

Even though the volume of iodine contrast seems to be a major factor leading to CIN, there has been little

Fig. 1. Mean serum creatinine and cystatin C measurements of patients according to time from procedure. **a** Serum cystatin C (p for trend 0.048). **b** Serum creatinine (p for trend <0.001).

investigation on the effect of contrast dose-response in patients with advanced chronic kidney disease undergoing coronary procedures with very low doses. A study on 185 patients with stages 3–5 chronic kidney disease undergoing diagnostic coronary angiography compared the risk for developing CIN according to the amount of contrast material volume [7]. The median contrast volume was 27 mL (IQR 20–50) and patients at the lowest quartile of contrast material administration (14 ± 4 mL) were sevenfold less likely to develop CIN compared to those in the highest quartile. The ultra-low contrast material volume technique was tested in a small study that included 4 patients with advanced chronic kidney disease undergoing coronary procedures [10]. In 3 cases, coronary angiogram and PCI were performed with ultra-low contrast volume (7.5, 10, and 14 mL). The 4th patient underwent a diagnostic study and multi-vessel PCI without the use of any contrast media using previous angiographic images and extensive intravascular ultrasound (IVUS) employment. None of the 4 patients demonstrated any deterioration of renal function during a 7-day follow-up period. A recent study included 31 patients with stable angina and stages 4–5 chronic kidney disease that required PCI based on a recent coronary angiogram [11]. These highly selective patients underwent zero contrast PCI using extensive IVUS images and measurement of fractional and coronary flow reserve. This technique resulted in successful PCI, no major adverse cardiovascular events, and preservation of renal function. However, these studies included highly selective patients with stable coronary artery disease and included

extensive use of coronary imaging modalities, and therefore may be relevant to most cath labs worldwide. The lack of evidence regarding patients with ACS is another important limitation. The current study was designed to evaluate the feasibility and efficacy of the ultra-low contrast volume technique in 30 consecutive patients with stage 3b–5 chronic kidney disease referred for coronary angiography. The most common indication for coronary angiography was ACS (25 patients) followed by stable angina pectoris (5 patients), and 16 patients underwent subsequent coronary angioplasty. The study showed for the first time that the ultra-low volume technique may be applicable, effective, and safe in real-life practice.

CIN refers to a sudden deterioration in renal function within 48 h of intravascular administration of iodinated contrast medium. The mechanism of CIN is not completely clear and seems to be multifactorial [19]. It includes cellular damage via reactive oxygen species [20], direct cytotoxic effect on renal tubular cells [21], increased resistance to renal blood flow and renal vasoconstriction [22], and increased blood viscosity [23]. Furthermore, the contrast agent may act as an osmotic agent that can decrease water reabsorption and increase salt and water load to the distal tubules leading to reduced glomerular filtration rate [24]. On the other hand, in patients with chronic kidney disease undergoing coronary procedures, acute kidney injury may be caused by factors other than CIN. These factors may include cholesterol embolization [25], dehydration [26], medication such as ACE-inhibitors [27] and diuretics [28], heart failure, and hemodynamic instability [29].

Of the 30 patients included in the study, 12 (40%) had nonsignificant coronary artery disease that was treated conservatively. This rate is comparable to data from the PLATO study that compared treatment with Ticagrelor or Clopidogrel in patients with ACSs [30].

The current study has several limitations that warrant consideration. First, this is a single-center study that included a small number of patients; it is not possible to arrive at definitive conclusions with such a small number. However, the present study is the largest to test the ultra-low contrast volume technique and the only one that included real-life consecutive patients. Second, patients with acute ST segment elevation myocardial infarction, cardiogenic shock or heart failure, history of coronary artery bypass graft, and above the age 80 were excluded. Therefore, our results should be extrapolated to these patients with extreme caution. Finally, patients did not undergo urine collection for protein or albumin. Microalbuminuria, even though very mild, has clearly been shown to be a risk factor for both cardiovascular morbidity and mortality as well as for the progression of renal dysfunction [31].

In conclusion, in patients with advanced chronic kidney disease, the ultra-low contrast technique is feasible and effective and can be used safely without a significant deterioration in renal function. This technique may increase the utilization of PCI in high-risk coronary patients with chronic kidney disease. Since cystatin C was more sensitive than creatinine for the detection of CIN, future studies should prefer its use for the assessment of renal function following contrast exposure.

Ethics Statement

The study was approved by the institutional ethics committee and all participants provided their written informed consent. The study was registered in the NIH ClinicalTrials.gov (NCT02468401).

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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