



Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc



Original article

Pre-procedural peripheral endothelial function is associated with increased serum creatinine following percutaneous coronary procedure in stable patients with a preserved estimated glomerular filtration rate[☆]

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ARTICLE INFO

Article history:

Received 17 December 2016

Received in revised form 11 March 2017

Accepted 14 March 2017

Available online xxx

Keywords:

Endothelial dysfunction

Worsening renal function

Contrast media

ABSTRACT

Background: Worsening renal function, indicated by increased serum creatinine (SCr), is a common complication of percutaneous coronary procedures. Risk factors for increased SCr overlap with coronary risk factors involved in endothelial dysfunction. We hypothesized that endothelial dysfunction, measured using the reactive hyperemia peripheral arterial tonometry index (RHI), can predict periprocedure-increased SCr.

Methods: RHI was assessed before elective coronary procedures in 316 consecutive stable patients with a preserved estimated glomerular filtration rate (eGFR, >60 mL/min/1.73 m²). SCr was measured before and 2 days after procedures.

Results: There was no significant correlation between natural logarithmic transformations of RHI (Ln-RHI) and basal Ln-eGFR. Periprocedure increase in SCr was observed in 148 (47%) patients. The increased SCr group had significantly lower Ln-RHI [0.48 (0.36, 0.62) vs. 0.59 (0.49, 0.76), $p < 0.001$]. Multivariate linear regression analysis identified body mass index (BMI) ($\beta = 0.148$, $p = 0.005$) and Ln-RHI ($\beta = -0.365$, $p < 0.001$) as significant determinants of percent changes in SCr. Multivariate logistic regression analysis identified Ln-RHI (per 0.1) [odds ratio (OR) 0.672, 95% confidence interval (95% CI) 0.586–0.722; $p < 0.001$], Ln-B-type natriuretic peptide (OR: 1.484, 95% CI: 1.130–1.974; $p = 0.004$), current smoking (OR: 2.563, 95% CI: 1.379–4.763, $p = 0.003$), BMI (OR: 1.113, 95% CI: 1.031–1.203; $p = 0.007$), coronary intervention (OR: 1.736, 95% CI: 1.036–2.909; $p = 0.036$), and Ln-hemoglobin A1c (OR: 6.728, 95% CI: 1.093–41.392, $p = 0.040$) as independent determinants of increased SCr. Receiver-operating characteristics curve analysis showed that Ln-RHI correlated significantly with increased SCr (area under the curve, 0.684, 95% CI: 0.626–0.742, $p < 0.001$). The optimum cut-off point of Ln-RHI for the periprocedure increased SCr was 0.545.

Conclusions: Pre-procedure measurement of endothelial function by RHI is an effective strategy to assess the patient's risk conditions for worsening renal function after percutaneous coronary procedures.

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[☆] Trial registration: UMIN-CTR (<http://www.umin.ac.jp/ctr/>); Identifier: UMIN000008283.

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Introduction

Radiology procedures using iodinated contrast media and intravascular catheters are being used for both diagnostic and therapeutic purposes in clinical practice, resulting in an increased incidence of worsening renal function [1–4]. The exact mechanism behind worsening renal function is unknown, although direct toxicity from iodinated contrast media and microshowers of atheroemboli in the kidneys have been suggested [5,6]. Severe worsening renal function that requires acute dialysis is rare, yet mild worsening renal function is often associated with small and reversible changes in serum creatinine (SCr) [7]. The Acute Kidney Injury Network defined contrast-induced acute kidney injury (CI-AKI) as worsening renal function with a rise in SCr of more than 50% or 0.3 mg/dL from baseline [8]. Evidence suggests that short- and long-term mortality rates correlate well with the severity of CI-AKI [9–12]. Furthermore, small increases in SCr to less than the above values are associated with an increased risk for adverse outcomes [3,13]. Therefore, any increase in SCr after a percutaneous coronary procedure should be considered an important clinical manifestation in a practical setting.

Previous studies have identified risk factors for the development of CI-AKI [14–16], with many overlapping with coronary atherosclerotic risk factors. Vascular endothelial dysfunction is observed from the early phase of arteriosclerosis to advanced atheroma [17]. Endothelial function can be assessed clinically using the phenomenon of reactive hyperemia. Kuvin et al. described a new technology to evaluate endothelial dysfunction called reactive hyperemia peripheral arterial tonometry (RH-PAT) using EndoPAT-2000 (Itamar Medical, Caesarea, Israel) [18]. RH-PAT is a noninvasive, automatic, and quantitative clinical test for digital measurement of the hyperemic response. The Framingham Heart Study reported that RH-PAT indexes (RHI) inversely correlate with various cardiovascular risk factors [19], indicating the practical usefulness of the RH-PAT test. Furthermore, we have reported that RHI were impaired in various cardiovascular conditions [20–23]. Endothelial dysfunction is a significant risk factor for future cardiovascular complications and renal dysfunction [24,25]; however, its role in the pathogenesis of periprocedure increased SCr is not clear.

We hypothesized that peripheral endothelial function is impaired in patients with periprocedure increased SCr and that peripheral endothelial dysfunction assessed by RHI can be used to predict the development of increased SCr in stable patients who have undergone a percutaneous coronary procedure and have a preserved estimated glomerular filtration rate (eGFR).

Materials and methods

Study population

Consecutive stable patients with suspected coronary artery disease who were referred and scheduled for percutaneous coronary procedures at Kumamoto University Hospital between August 2006 and March 2011 were registered for the study ($n = 2682$). Patients with an eGFR ≤ 60 mL/min/1.73 m² were excluded ($n = 1521$) because an eGFR ≤ 60 mL/min/1.73 m² is the strongest contributor to CI-AKI, and some special pre-treatments before the procedure, including administration of sodium bicarbonate and N-acetyl cysteine, are performed to avoid the occurrence of CI-AKI, followed by careful follow-up and appropriate additional hydration in the clinic settings after the procedure. Exclusion criteria were patients who had other contrast exposure within 1 week from the index procedure ($n = 124$), acute coronary syndrome requiring an emergency procedure [26,27] before RH-PAT examination ($n = 445$), heart failure [left ventricular ejection

fraction $< 50\%$ and/or plasma B-type natriuretic peptide (BNP) level > 200 pg/mL] [28] ($n = 485$), collagen disease ($n = 24$), neuromuscular disease ($n = 12$), malignant disease ($n = 36$), and unavailability of urine samples ($n = 23$). In total, 316 stable patients were enrolled (scheduled percutaneous coronary intervention: $n = 117$, coronary spasm provocation test using acetylcholine and left ventriculography: $n = 114$, coronary angiography and left ventriculography: $n = 85$).

Ethical considerations

The study was conducted in accordance with the principles contained within the Declaration of Helsinki and followed the guidelines of the ethics committee of our institution and was approved by Kumamoto University Institutional Review Board. Written informed consent was obtained from each patient before participation. The study is registered with the University Hospital Medical Information Network Clinical Trials Registry (Identifier: UMIN000008283).

Study protocol

SCr was measured before and 2 days after coronary procedures. The increased SCr group comprised patients who showed any increase in SCr after coronary procedure, while patients of the non-increased SCr group showed no increase in SCr. Peripheral endothelial function was assessed by RH-PAT before the procedure. In order to achieve a urine flow rate of at least 1.5 mL/kg/min, intravenous hydration using normal saline (0.9%) was achieved at least 500 mL before contrast exposure, with > 1 mL/kg/h for 3–6 h before procedure and continued 12 h after procedure [29]. All patients were encouraged to drink water after the procedure if they were thirsty [30–32]. Iopamidol (370 mg-I/mL), a nonionic, low-osmolality contrast medium, was used in all patients. All decisions regarding procedural hemodynamics, including contrast volume, were at the discretion of the attending cardiologist.

Evaluation of covariates

Fasting blood and urine samples for measurement of baseline characteristics were obtained in the morning on the day after admission. Risk factors for cardiovascular disease were defined as current smoking (smoking within 1 year), hypertension ($> 140/90$ mmHg or taking antihypertensive medications), dyslipidemia [high-density lipoprotein cholesterol (HDL Chol) < 40 mg/dL for men and < 50 mg/dL for women, low-density lipoprotein cholesterol (LDL Chol) ≥ 140 mg/dL, or triglycerides ≥ 150 mg/dL, or taking medication for dyslipidemia], and diabetes mellitus [symptoms of diabetes plus casual plasma glucose concentration ≥ 200 mg/dL, fasting glucose concentration ≥ 126 mg/dL, 2-h glucose concentration ≥ 200 mg/dL during 75-g oral glucose tolerance test, serum hemoglobin A1c (HbA1c) level $\geq 6.5\%$, or taking medication for diabetes mellitus]. Gram-iodine/eGFR (g-I/eGFR) ratio was calculated as $0.37 * (\text{volume of contrast media}) / \text{eGFR}$.

Assessment of renal function

Pre-procedure kidney function was assessed using the Modification of Diet in Renal Disease Study equation for eGFR [33,34]. The change in SCr concentration was calculated using the baseline value measured on the day before and 2 days after the procedure. Urinary albumin concentration was measured before the procedure and albuminuria was defined as a urinary albumin-to-creatinine ratio (ACR) ≥ 30 mg/g creatinine [35].

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