Original Paper

The Importance of Contrast Volume/ Glomerular Filtration Rate Ratio in Contrast- Induced Nephropathy Patients after Transcatheter Aortic Valve Implantation

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Key Words

Severe aortic stenosis · Transcatheter aortic valve implantation · Contrast-induced nephropathy · Contrast volume · Glomerular filtration rate

Abstract

Background/Aim: Transcatheter aortic valve implantation (TAVI) is a method which is increasingly applied in severe aortic stenosis treatment. The development of contrast-induced nephropathy (CIN) after TAVI increases morbidity and mortality rates. Within the scope of this study, the importance of the contrast medium volume to glomerular filtration rate (CV/GFR) ratio in determining the development of CIN and the amount of CV that could be applied was evaluated. **Methods:** Seventy-two patients (aged 78.6 ± 11.6 years; 38 females) who underwent aortic valve replacement with the TAVI method between June 2013 and August 2014 were included in the study. CIN was defined as an absolute increase in serum creatinine of >0.5 mg/dl or a relative increase of $>25\%$ within 48–72 h after TAVI. CIN+ and CIN– patients were classified into two groups. The χ^2 test, t test, Mann-Whitney U test, ROC analysis, and univariate and multivariate regression analyses were applied for statistical analyses. **Results:** CIN was detected in 16 patients (22%) in our study. Baseline creatinine, baseline GFR, the Mehran risk score, CV, and the CV/GFR ratio were determined as the predictive factors of CIN development. A CV/GFR ratio of 3.9 was specified to predict CIN development with 71% sensitivity and 80% specificity. **Conclusion:** After TAVI, CIN may develop due to various reasons. In patients to whom TAVI was applied, the CV/GFR ratio may be a guideline helping to prevent the development of renal pathologies. The amount of contrast medium that can be given to a patient can be calculated in terms of baseline GFR.

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Introduction

If severe aortic stenosis (AS) is not treated, it develops into heart valve pathology with a high rate of morbidity and mortality [1]. Surgical methods or transcatheter procedures can be implemented for AS treatment. Aortic valve replacement with the transcatheter aortic valve implantation (TAVI) method can be performed in patients considered to be at high surgical risk or inoperable by the heart team [2]. As a result of clinical studies, it was determined that the TAVI method more effectively reduces morbidity and mortality rates compared to medical therapy [3]. In studies comparing TAVI and surgical aortic valve replacement, similar rates of efficiency were determined initially [4]. However, recent studies have suggested that TAVI is the more reliable method for high-risk or inoperable patients [5].

Contrast media are used for illustration purposes during TAVI. Renal function, which has been stable before TAVI, can be disrupted after the operation. According to the Valve Academic Research Consortium criteria, acute kidney injury (AKI) was defined as a change in serum creatinine up to 72 h compared with baseline, categorized as follows: stage 1, a 1.5- to 2-fold increase in creatinine or an absolute increase in the highest value of creatinine; stage 2, a 2.0- to 3.0-fold increase in creatinine, and stage 3, a ≥ 3.0 -fold increase in creatinine [6]. In the case of AKI after invasive interventional operations, morbidity and mortality increase [7–9]. Contrast-induced nephropathy (CIN) is one of the reasons for AKI development in the hospital [10]. CIN was defined as an absolute increase in serum creatinine of >0.5 mg/dl or a relative increase of $>25\%$ within 48–72 h after TAVI [11]. Thus, factors that can lead to the development of CIN after interventional cardiovascular operations must be well known. It has been specified that the contrast medium volume (CV) used in invasive operations is the most important factor causing AKI [12, 13]. The CV/glomerular filtration rate (GFR) ratio, a useful indicator of the development of nephropathy, depends on the amount of contrast medium administered after percutaneous coronary intervention (PCI) [14]. CIN appearing in elderly and high-risk TAVI patients can influence the overall condition of the patients. Up to date, several studies have been conducted related to factors affecting the development of CIN in patients with TAVI. However, the importance of the CV/GFR ratio in predicting the development of CIN has not yet been investigated in detail. The importance of the CV/GFR ratio in the prediction of CIN development and in determining the amount of contrast medium that can be applied safely to TAVI patients was evaluated in this study.

Methods

Study Population and Data Collection

For this study, 72 patients who underwent aortic valve replacement with the TAVI method at our center were evaluated between June 2013 and August 2014. Patients who were considered appropriate for the TAVI method by our heart team were included in the study because they were inoperable or at high risk for surgical aortic valve replacement. The operative risks of patients were calculated with the logistic European System for Cardiac Operative Risk Evaluation (Logistic EuroSCORE) and the Society of Thoracic Surgeons Predictive Risk of Mortality (STS) scores. Patients with a logistic EuroSCORE $>20\%$ or a STS score $>10\%$ were considered high-risk patients [15]. These cases underwent dialysis before TAVI, and those with a creatinine value >2.5 mg/dl and with permanent pacemakers were not included in the study. Clinical data, patient characteristics, echocardiographic data, processual variables, morbidity and mortality rates were prospectively followed up for 6 months. Controls at the second week, first, third, and sixth month after patient discharge were performed at our center.

Study Protocol

Severe AS was diagnosed with echocardiographic methods. An average aortic gradient >40 mm Hg, an aortic valve area <1 cm², and a valve area index (valve area/body surface area) <0.6 cm² were considered to

indicate severe AS [15]. A balloon-expandable Edwards Sapien XT valve (Edwards Lifesciences, Irvine, Calif., USA) was used for the TAVI process. A vascular occlusion device (ProStar XL; Abbott Laboratories, North Chicago, Ill., USA) was used in eligible patients for femoral artery diameter and anatomical measurements. The surgical cutdown method was applied to patients who were unsuitable for the iliac and femoral artery anatomy vascular closure device. Transesophageal echocardiography and multislice CT tests were done to determine the diameter of the implanted aortic bioprosthesis. In all patients, clopidogrel 75 mg, acetylsalicylic acid 100 mg, and intravenous antibiotherapy was started before the operation. Iohexol (Omnipaque; GE Healthcare), a nonionic, low-osmolar, and monomeric contrast medium, was used as opaque material. The amount of contrast medium used was recorded during TAVI. Examinations such as CT and coronary angiography that required the administration of contrast medium except for the TAVI procedures were performed at least 72 h previously. The daily renal functions of all patients were monitored from admission to discharge. Creatinine levels were checked in the second week, the first, third, and sixth month after the operation (COBAS Integra 400 plus; Roche Diagnostics).

Estimated GFR was calculated with the Modification of Diet in Renal Disease formula: GFR (expressed in $ml/min/1.73 m^2$) = $186 \times SCr^{1.154} \times age^{0.203} (\times 0.742 \text{ female gender})$. Before TAVI, 1 ml/kg/h of 0.9% NaCl solution was administered for 24 h to the patients with a $GFR < 50 ml/min/1.73 m^2$; 48–72 h after the TAVI operation, 0.5 mg/dl or a 25% increase compared to the basal creatinine value was defined as CIN [11, 15–20]. Our study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the local ethics committee.

Statistical Analysis

Analysis was performed with SPSS 17.0 software (SPSS, Chicago, Ill., USA). To test the distribution pattern, the Kolmogorov-Smirnov method was used. Continuous variables were expressed as the mean $\pm$ SD, and the categorical variables were expressed as percentages. To identify the correlations between CIN and the clinical or laboratory parameters, a univariate analysis was performed using an unpaired t test or Mann-Whitney U test for the continuous variables and the χ^2 test for the categorical variables, respectively. A multivariate logistic regression analysis was used to assess the correlation among the parameters, whose statistical significance was demonstrated on a univariate analysis level of $p < 0.05$ and through well-known risk factors. Models were developed with stepwise techniques, for which the results were expressed as odds ratios with 95% confidence intervals (CIs). An exploratory evaluation for additional cut points of different variables was performed using the receiver operating characteristic (ROC) curve analysis. Significant difference was defined as $p < 0.05$.

Results

General Characteristics of Patients

Seventy-two patients (aged 78.6 ± 11.6 years; 38 females) were included in our study. No significant differences between the groups in terms of demographic, laboratory, and echocardiographic characteristics were found. The mean STS score in the CIN+ group was higher ($p = 0.028$) compared to that in the CIN– group. When the risk factors were evaluated, a difference between the groups in terms of coronary artery disease, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, and peripheral arterial disease was not ascertained (tables 1, 2).

Procedure

A balloon-expandable Edwards Sapien XT valve via transfemoral access was implanted in all patients. The average radiation time was 8.2 ± 3.1 min. The average CV and the average extubation times were 191.4 ± 33.2 and 204 ± 43.1 min, respectively. The length of stay in the intensive care unit and the length of stay at the hospital were 1.47 ± 0.9 and 4.44 ± 3.1 days, respectively.

CIN after TAVI was observed in a total of 16 patients (22.2%). The CIN group's length of stay in the intensive care unit and the length of stay at the hospital were 1.6 ± 1.4 and

Table 1. Demographic and operation characteristics of the patients

Variables	CIN+ (n = 16)	CIN- (n = 56)	p value
Age, years	78.6±6.1	76.3±7.9	0.218
Females	11 (68.8)	27 (48.2)	0.121
Body mass index	29.2±9.4	27.7±4.1	0.091
Previous cardiac operation (n = 12, 16.7%)	1 (6.3)	11 (19.6)	0.191
Previous PCI (n = 19, 26.4%)	2 (12.5)	17 (30.4)	0.132
Coronary artery disease (n = 44, 61.1%)	10 (62.5)	34 (60.7)	0.569
Permanent pacemaker	0	0	n.s.
Diabetes mellitus (n = 30, 41.7%)	9 (56.3)	21 (37.5)	0.146
Arterial hypertension (n = 48, 66.7%)	12 (75.0)	36 (64.3)	0.314
Chronic obstructive pulmonary disease (n = 46, 63.9%)	10 (62.5)	36 (64.3)	0.559
GFR, ml/min/1.73 m ²	54.3±17.9	62.7±21.8	0.162
Logistic EuroSCORE, %	37.1±10.9	36.4±15.5	0.303
STS score, %	16.5±9.7	12.8±4.1	0.028
CV, ml	203.4±41.3	170.2±30.9	<0.001
CV/GFR ratio	4.6±1.5	3.7±1.7	0.001
Intensive care unit stay, days	1.6±1.1	1.4±0.9	0.679
Total hospital stay, days	4.8±1.6	4.3±1.4	0.250
Mortality, in hospital (n = 2, 2.8%)	1 (6.3)	1 (1.8)	0.925
Mortality, 1–6 months (n = 3, 4.1%)	2 (12.5)	1 (1.8)	0.108
Total mortality (n = 5, 6.9%)	3 (18.8)	2 (2.8)	0.038
Stroke	0	0	n.s.
Major bleeding (n = 6, 8.3%)	2 (12.5)	4 (7.1)	0.401
Minor bleeding (n = 15, 20.8%)	3 (18.8)	12 (21.4)	0.561

Data are presented as mean ± SD or number (%). n.s. = Not significant.

Table 2. Laboratory data and echocardiographic findings

Variables	CIN+	CIN-	p value
Baseline creatinine, mg/dl	1.20±0.64	1.11±0.29	0.689
Urea, mg/dl	51.4±22.9	48.2±18.2	0.666
Potassium, mmol/l	5.12±1.41	4.51±0.53	0.716
Brain natriuretic peptide, pg/ml	7,880.6±4,687.4	7,044.8±3,968.5	0.125
High-sensitive troponin T	22.8±17.5	20.3±18.9	0.920
Low-density lipoprotein, mg/dl	128.9±45.7	109.0±34.5	0.126
Hemoglobin, g/dl	11.2±1.85	11.4±1.85	0.832
Platelets, ×10 ³ /μl	255.2±73.7	261.9±125.5	0.129
White blood cells, ×10 ³ /μl	13.6±8.7	7.6±2.8	0.257
C-reactive protein, mg/l	4.0±3.0	2.9±2.6	0.657
Left ventricular ejection fraction, %	41.5±11.1	44.3±9.3	0.263
Aortic valve area (before TAVI), cm ²	0.63±0.08	0.62±0.09	0.968
Aortic valve area (6 months after TAVI), cm ²	1.75±0.24	1.81±0.42	0.762
Mean aortic gradient (before TAVI), mm Hg	49.9±9.4	51.4±11.3	0.604
Mean aortic gradient (6 months after TAVI), mm Hg	8.4±2.4	7.9±1.8	0.425
Postaortic regurgitation grade ≥2	1 (6.3)	4 (7.1)	0.987
sPAP (before TAVI), mm Hg	48.5±10.8	43.9±7.6	0.179

Data are presented as mean ± SD or number (%). sPAP = Systolic pulmonary artery pressure.

Table 3. Univariate and multivariate analysis of risk factors determining CIN

Variables	Univariate analysis		Multivariate analysis	
	odds ratio	p value	odds ratio	p value
Age	1.1 (0.8–1.4)	0.057	–	–
Diabetes mellitus	1.6 (0.8–2.6)	0.092	–	–
Coronary artery disease	1.8 (0.8–3.5)	0.062	–	–
STS score	1.2 (0.9–1.4)	0.017	1.2 (0.9–1.5)	0.079
Logistic EuroSCORE	1.1 (0.9–1.3)	0.087	–	–
Ejection fraction	1.0 (0.8–1.3)	0.154	–	–
Creatinine	2.0 (1.1–3.1)	0.011	1.9 (1.2–2.7)	0.032
GFR	3.1 (1.4–7.2)	<0.001	2.3 (1.2–4.2)	0.005
CV	8.9 (4.7–15.3)	<0.001	3.9 (1.7–8.5)	<0.001
CV/GFR ratio	10.9 (4.9–23.1)	<0.001	4.9 (1.9–12.2)	<0.001
Mehran score	2.5 (1.5–3.1)	<0.001	2.0 (1.2–3.0)	0.024
Hemoglobin	0.9 (0.7–1.1)	0.108	–	–

Figures in parentheses are 95% CIs.

4.8 ± 1.6 days, respectively. After TAVI, none of the patients needed permanent pacemaker implantation due to atrioventricular conduction block. Vascular injuries occurred in 12 patients; 4 of these patients were in the CIN+ group ($p = 0.254$). Urgent surgical intervention was required for 4 patients with vascular complications (5.6%). Three of them were in the CIN+ group (5.4%). A differentiation between the groups in terms of stroke and bleeding complications was not ascertained. The amount of applied CV was higher in the CIN+ group ($p < 0.001$). Five patients died during the study period, and 2 of them passed away in the first month (1 CIN+ patient and 1 CIN– patient; $p = 0.925$). Between the first and the sixth month of follow-up, another 3 patients passed away (2 CIN+ patients and 1 CIN– patient; $p = 0.108$). It has been ascertained that the total mortality in the CIN+ group was higher compared to that in the CIN– group (18.8 vs. 2.8%; $p = 0.038$) (table 1).

CIN Predictors

In univariate analysis, which was conducted to determine CIN predictors after TAVI, it had been ascertained that statistically significant p values of the STS score, basal creatinine, basal GFR, CV, Mehran score, and CV/GFR ratio were <0.05 . Multivariate regression analysis was performed with these variables. We have detected that other variables apart from the STS score can predict the development of CIN (table 3). A ROC analysis of the variables determined as significant with multivariate regression analysis was performed. As a result of this ROC analysis, the CV/GFR ratio which may predict the development of CIN was determined as 3.9 [area under the curve (AUC) 0.773, 95% CI 0.604–0.906, sensitivity 71%, specificity 80%] (fig. 1, 2; table 4).

Discussion

According to the results of our study, the CV/GFR ratio can be used to predict the development of CIN in patients undergoing TAVI. It has been shown that a CV/GFR ratio >3.9 is a critical limit in predicting the development of CIN.

After invasive cardiovascular procedures, the mechanisms of kidney damage caused by contrast medium are not exactly clarified. It has been thought that toxicity resulting from the

Fig. 1. ROC curve for the predictors of CIN using baseline creatinine, CV, baseline GFR, Mehran score, and CV/GFR ratio.

Fig. 2. ROC curve for the predictors of CIN using GFR. The AUC for predicting CIN using GFR was 0.625 (sensitivity 57%, specificity 75%, 95% CI 0.477–0.773, cutoff 50.5 ml/min/1.73 m²).

Table 4. ROC results for the prediction of CIN using baseline creatinine, baseline GFR, Mehran score, CV, and CV/GFR ratio

	Cutoff	AUC	Sensitivity, %	Specificity, %	95% CI
CV/GFR ratio	3.91	0.773	71	80	0.640–0.906
CV	197.5	0.808	79	69	0.692–0.925
Mehran score	16.5	0.684	50	80	0.509–0.859
Basal GFR	50.5	0.625	57	75	0.477–0.773
Basal creatinine	1.17	0.577	50	71	0.416–0.737

characteristics of the contrast medium and the resultant degree of renal ischemia played a role in the development of CIN. On the other hand, there are many factors which can facilitate CIN development. These can be divided into two groups depending on patient characteristics and invasive surgery. The prominent facilitating characteristics of patients are: age, diabetes mellitus, cardiac insufficiency, and impaired basic renal functions [21, 22]. However, these variables do not differ among the groups in our study (tables 1, 2). With regard to surgery, factors that facilitate CIN development are: increase in the amount of contrast medium, hemodynamic irregularities, and hypotension [12–21]. During TAVI operation in particular, hypotensive periods may occur, thus increasing CIN probability.

According to Nash et al. [10], CIN is one of the most significant causes of hospital-acquired renal insufficiency. CIN ratios after TAVI are reported to be 10–30% [23–25]. In our study, CIN was detected in 16 patients (22.2%), which is similar to those ratios mentioned above. A significant increase in morbidity has been reported in earlier studies when cardiovascular pathology coexists with renal dysfunction. Similarly, the development of renal insufficiencies after aortic valve implementations increases mortality [10, 26]. However, in our study, in the first 6 months of follow-up, no statistically significant difference was observed in terms of morbidities. When complications were evaluated separately, the rates in the CIN+ group were higher but statistically not significant. This situation was attributed to the low number of patients. Bagur et al. [27] reported that mortality was 7% in aortic valve implementation without kidney injury, whereas with kidney injury, the rate was 15%. In our study, mortality rates during the 6 months of follow-up are remarkably higher for those who presented CIN (18.8 vs. 2.8%; $p = 0.038$). Even if the deterioration in basal kidney functions which might lead to CIN development cannot be totally cured, it is a risk factor which can be modified by the amount of CV used. So far, many studies have been conducted on renal functions of patients who have undergone TAVI, but the ratio of CV to creatinine clearance (CV/CCR) which can provide a prediction of CIN development has been determined earlier. Worasuwannarak et al. [28] noted that a CV/CCR >2.6 after PCI could predict CIN development. Yamamoto et al. [16] showed that in TAVI patients, a CV/CCR >3.7 is related with AKI. However, for increased levels of serum creatinine, GFR must be approximately 50% decreased. Thus, by the Cockcroft-Gault formula, creatinine clearance might be calculated higher than it should be. The accuracy of GFR calculation is higher for impaired or normal kidneys. For the evaluation of CIN development, the CV/GFR ratio can be assumed as a more reliable parameter than the CV/CCR. Nozue et al. [29] remarked that the CV/GFR ratio is one of the predictors of CIN development in patients who receive elective PCI. Wang et al. [14] have found the CV/GFR ratio which could predict CIN development after PCI to be 3.1 (AUC 0.736, 95% CI 0.631–0.841, $p = 0.001$, sensitivity 71%, specificity 70%) in diabetic patients with ST elevation myocardial infarction. According to the results of our study, CV, baseline creatinine, Mehran score, baseline GFR, and CV/GFR are fundamental variables which may lead to CIN after TAVI. According to the results of the statistical analyses, it is ascertained that the most important variables which directly affect CIN development after TAVI are CV and CV/GFR. According to ROC analysis, the CV/GFR ratio predicting CIN development is 3.9 (AUC 0.773, 95% CI 0.604–0.906, sensitivity 71%, specificity 80%).

Limitations

The basic limitations to our study are the low number of patients and that it was managed from a single center. Therefore, although the number of patients in the CIN+ group which experiences complications is huge, it may not have statistical significance. The main reasons (radiotoxic, nephrotoxic, ischemic) of CIN development were not put forth in depth because renal biopsy was not carried out. We feel that as the duration of follow-up rises, statistical differences will become clear.

Conclusion

In conclusion, it was determined that even if morbidity and mortality rates are low, the CV/GFR ratio – as in PCI procedures – is one of the predictors of CIN development also in TAVI. However, it is not a set rule. Regarding the basal GFR of the patients, the maximum amount of contrast medium to be used can be calculated in advance. We determine that before TAVI, the CV amount to be given should be calculated to provide a CV/GFR ratio <3.9 in order that renal complications might possibly be reduced.

Disclosure Statement

The authors declare no conflicts of interest.

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