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Detection of Myocardial Injury by CMR After Transcatheter Aortic Valve Replacement

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ABSTRACT

BACKGROUND Myocardial injury after transcatheter aortic valve replacement (TAVR) is common, but its cause and relationship to the extent of myocardial tissue loss remain unclear.

OBJECTIVES This study sought to examine the incidence and degree of ischemic myocardial damage using cardiac magnetic resonance imaging and myocardial biomarkers in patients undergoing TAVR.

METHODS Patients with severe aortic stenosis (n = 61) underwent cardiac magnetic resonance imaging before and after TAVR for the assessment of new myocardial injury. High-sensitivity cardiac troponin T and creatine kinase-myocardial band were measured before and at 24, 48, and 72 h after TAVR.

RESULTS After TAVR, new myocardial late enhancement (LE) with an ischemic pattern occurred in 11 patients (18%), with a mean mass of 3.7 g (interquartile range: 1.2 to 6 g) or 1.8% (interquartile range: 1.3% to 4.1%) of the left ventricular mass. Patients with new LE had a decreased left ventricular function (ejection fraction: pre, 55.5 ± 14.1% vs. post, 45.3 ± 14.9%; p = 0.001). In patients without new LE, no differences were observed (ejection fraction: pre, 53.9 ± 17.3% vs. post, 54.6 ± 16.3%; p = NS) after TAVR.

CONCLUSIONS New ischemic-type myocardial LE after TAVR can be observed in a notable proportion of patients and is assumed to be of embolic origin. Patients with new LE feature a significant decrease in left ventricular function at discharge. (J Am Coll Cardiol 2014;64:349–57) © 2014 by the American College of Cardiology Foundation

Transcatheter aortic valve replacement (TAVR) has evolved into standard procedure for patients with aortic stenosis who are at high risk for conventional surgery (1). The interventional approach has been shown to be more effective than standard medical treatment in high-risk patients, but it is nonetheless associated with relatively high mortality and morbidity (2). Periprocedural myocardial injury has been identified as a predictor of unfavorable outcome after TAVR (3), and various hypotheses exist concerning the underlying mechanisms of myocardial damage, including global myocardial ischemia due to extreme hypotension, direct trauma during balloon inflation or prosthesis placement, and coronary embolization of aortic valve debris (3,4). Hereof, an obstruction of the coronary ostia by the valve prosthesis or leaflets has to be distinguished (5). However, the cause of myocardial injury in patients undergoing TAVR is not well-described, and the extent of myocardial tissue loss has not yet been investigated. For this purpose, cardiac magnetic resonance (CMR) imaging—being the gold standard for detection and quantification of

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ABBREVIATIONS AND ACRONYMS

CK-MB = creatine kinase-myocardial band

CMR = cardiac magnetic resonance

EF = ejection fraction

hs-cTnT = high-sensitivity cardiac troponin T

LV = left ventricular

MI = myocardial infarction

PCI = percutaneous coronary intervention

TA = transapical

TAVR = transcatheter aortic valve replacement

TF = transfemoral

myocardial infarction (MI)—may be considered the most appropriate method (6). In the setting of percutaneous coronary intervention (PCI), a close association has been described between infarct size determined by CMR, left ventricular ejection fraction (LVEF), and biomarker release (7,8); however, such data on TAVR are currently lacking.

The objectives of our study were to examine the prevalence and degree of new areas of late enhancement (LE) as a measure of myocardial damage in patients undergoing TAVR and to correlate it with the periprocedural rise of myocardial biomarkers.

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METHODS

PATIENT SELECTION AND PROCEDURAL DATA. From January 2011 to September 2013, patients with severe aortic stenosis scheduled for TAVR were enrolled in the study. Exclusion criteria were as follows: contraindication for CMR, concomitant PCI, the presence of intracardiac thrombi, conversion to open heart surgery, major complications associated with myocardial injury, and the need for cardiopulmonary resuscitation or extracorporeal circulation.

TABLE 1 Baseline Characteristics

Characteristics	All Patients (n = 61)	TA (n = 26)	TF (n = 35)
Demographics			
Age, yrs	81.9 ± 5.3	81.9 ± 5.9	81.9 ± 4.8
Female	32 (52.5)	15 (57.7)	14 (40.0)
Cardiac measures			
Logistic EuroSCORE, %	24.0 ± 9.6	24.8 ± 11.2	23.4 ± 8.4
STS PROM score, %	6.3 ± 4.5	6.6 ± 4.8	6.2 ± 4.3
EF, %	53.5 ± 13.8	53.6 ± 13.3	53.5 ± 14.4
Mean AV gradient, mm Hg	43.4 ± 17.3	44.7 ± 15.6	42.4 ± 18.8
AV area, cm^2	0.7 ± 0.2	0.7 ± 0.3	0.6 ± 0.2
GFR, ml/min	68.6 ± 24.6	69.7 ± 25.2	67.8 ± 24.5
Comorbidities			
Hypertension	58 (95.1)	26 (100)	32 (91.4)
CAD	40 (68.9)	18 (69.2)	22 (62.9)
Hyperlipidemia	35 (57.4)	18 (69.2)	17 (48.6)
Atrial fibrillation	22 (36.1)	11 (42.3)	11 (31.4)
MI history	16 (26.3)	9 (37.6)	7 (20.0)
Diabetes	17 (27.9)	9 (34.6)	8 (22.9)
CABG	10 (16.4)	6 (23.1)	4 (11.4)
Stroke history	7 (11.5)	4 (15.4)	3 (8.6)

Values are mean ± SD or n (%). None of the differences between the 2 subgroups were statistically significant.

AV = aortic valve; CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; GFR = glomerular filtration rate; MI = myocardial infarction; STS PROM = Society of Thoracic Surgeons Prediction of Mortality; TA = transapical; TF = transfemoral.

The ethics committee of the University of Giessen, Germany approved the study protocol. Written informed consent was obtained from all patients. Baseline examinations including the protocol for multislice computed tomography are described in the Online Appendix.

Implantations were performed as previously reported (1,9). In brief, for the transapical (TA) route, balloon-expandable prostheses (Sapien XT 23, 26, and 29 mm; Edwards Lifesciences, Irvine, California) were implanted. For the transfemoral (TF) route, either balloon-expandable prostheses (Sapien XT 23, 26, and 29 mm) or self-expandable prostheses (Corevalve revalving system 26, 29, and 31 mm; Medtronic, Minneapolis, Minnesota) were used. Before intervention, patients received acetylsalicylic acid 100 mg/d. During the procedure, heparin was administered intravenously at a dose that maintained an activated clotting time of >250 s. Immediately after a successful procedure, patients began to receive clopidogrel 75 mg/day for 3 months, with an initial loading dose of 600 mg.

CMR IMAGING. Baseline CMR was performed as part of the pre-interventional evaluation process on a 1.5-T scanner (Sonata, Siemens Medical Solutions, Erlangen, Germany). The post-interventional scan was conducted during the hospital stay, as soon as patients were appropriately stable. All CMR studies were evaluated by 2 experienced cardiologists who were consensus-blinded to the clinical data using customized software (CAAS, MRV 3.3, Pie Medical Imaging BV, Maastricht, the Netherlands). Further details are provided in the Online Appendix.

CARDIAC BIOMARKERS. Venous blood samples for the determination of high-sensitivity cardiac troponin T (hs-cTnT) and creatine kinase-myocardial band (CK-MB) were drawn before and at 24, 48, and 72 h after TAVR. Serum was processed immediately and frozen at -80°C until assay. cTnT was measured in serum with the high-sensitivity electrochemiluminescence immunoassay (Elecsys Analyzer 2010 hs-cTnT assay, Roche Diagnostics, Mannheim, Germany), as described previously (10).

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD or as median (interquartile range [IQR]); categorical data are presented as n (%). Continuous data were compared by use of the Mann-Whitney signed rank test for paired data and the Mann-Whitney *U* test for unpaired data. For categorical data, the 2-sided Fisher exact test was applied. Correlation between discrete variables was assessed with the Pearson product moment correlation. The receiver operating characteristic curve was analyzed for discrimination of new MIs with biomarkers; the threshold for hs-cTnT was calculated using the Youden index. All statistical data were

TABLE 2 Comparison of Patients With New Versus Those Without New LE After TAVR

	LE⁺ (n = 11)	LE⁻ (n = 50)	p Value
Demographics			
Age, yrs	82.8 ± 5.6	81.7 ± 5.3	NS
Female	7 (63.6)	25 (50.0)	NS
Cardiac measures			
Logistic EuroSCORE, %	26.1 ± 9.6	23.5 ± 9.7	NS
STS PROM score, %	6.8 ± 4.5	6.2 ± 4.5	NS
EF, %	52.6 ± 15.3	53.7 ± 13.7	NS
Mean AV gradient, mm Hg	40.5 ± 23.1	44.0 ± 16.1	NS
AV area, cm^2	0.6 ± 0.2	0.7 ± 0.2	NS
GFR, ml/min	47.3 ± 18.5	69.9 ± 17.0	0.01
Comorbidities			
Hypertension	10 (90.9)	48 (96.0)	NS
Diabetes	5 (45.5)	12 (24.0)	NS
Hyperlipidemia	4 (36.4)	31 (62.0)	NS
Stroke history	2 (18.2)	5 (10.0)	NS
MI history	4 (36.4)	12 (24.0)	NS
Atrial fibrillation	3 (27.3)	17 (34.0)	NS
CAD	5 (45.5)	35 (70.0)	NS
Treatment history			
Prior PCI	4 (36.4)	20 (40.0)	NS
Prior CABG	0	10 (20.0)	NS
Statin	9 (81.8)	43 (86.0)	NS
Beta-blocker	10 (90.9)	37 (74.0)	NS
Arterial characteristics			
Dense spontaneous echo	2 (18.2)	6 (12.0)	NS
LAA flow velocity, cm/s	31.6 ± 12.3	33.8 ± 11.1	NS
Annulus, mm	23.6 ± 1.8	23.3 ± 2.3	NS
MSCT			
Calcium score AV	2502.4 ± 1480.3	3023.7 ± 1741.9	NS
Calcium score coronary arteries	368.7 ± 430.3	796.8 ± 739.5	NS
Distance, annulus-LCA, mm	12.6 ± 2.2	14.1 ± 3.1	0.09
Distance, annulus-RCA, mm	14.6 ± 2.5	15.1 ± 3.0	NS
CMR			
Scan, days			
Baseline	3 (IQR 1-7)	2 (IQR 1-5)	NS
After TAVR	7 (IQR 4-7)	6 (IQR 6-7.3)	NS
EF, %	55.5 ± 14.1	53.9 ± 17.3	NS
Baseline			
After TAVR	45.3 ± 14.9	54.6 ± 16.3	0.08
LV mass, g	142.2 ± 30.3	147.8 ± 46.2	NS
Scar mass, g			
Baseline	3.3 (1.7-7.7)	7.0 (0-19.1)	NS
% of LV mass	2.9 (1.6-4.5)	4.7 (0-10.4)	NS
After TAVR	3.7 (1.2-6.0)	0	<0.001
% of LV mass	1.8 (1.3-4.1)	0	<0.001
EDD, mm	50.6 ± 5.7	48.8 ± 7.9	NS
ESD, mm	32.9 ± 8.7	31.0 ± 10.7	NS
EDV, ml	127.9 ± 37.9	136.5 ± 51.6	NS
ESV, ml	60.1 ± 36.6	68.3 ± 46.7	NS
Biomarkers			
hs-cTnT, ng/l			
Baseline	25.6 (20.4-59.1)	23.7 (9.5-50.9)	NS
Maximal	447 (212-562)	254 (128-504)	NS
CK-MB, U/l			
Baseline	10.0 (9.0-13.0)	11.0 (9.0-16.0)	NS
Maximal	18.0 (14.0-34.0)	21.0 (12.0-34.3)	NS
Procedural data			
Femoral access	7 (63.6)	28 (56.0)	NS
Apical access	4 (36.4)	22 (44.0)	NS
Corevalve	4 (36.4)	13 (26.0)	NS
Sapien XT	7 (63.6)	37 (74.0)	NS
Prosthesis/annulus ratio	1.12 ± 0.13	1.14 ± 0.09	NS
Balloon/annulus ratio	0.94 ± 0.14	0.95 ± 0.07	NS
Need for post-dilation	4 (36.4)	9 (18.0)	NS
Procedure duration, min	53.0 (42.0-65.0)	45.0 (36.8-63.3)	NS
Fluoroscopy time, min	10.9 (5.7-20.8)	9.4 (5.4-12.9)	NS
Contrast agent, ml	96.8 ± 37.5	84.3 ± 34.6	NS

Continued in the next column

Values are mean ± SD, n (%), or median (interquartile range).

CK-MB = creatine kinase-myocardial band; EDD = end-diastolic diameter; EDV = end-diastolic volume; ESD = end-systolic diameter; ESV = end-systolic volume; hs-cTnT = high-sensitivity cardiac troponin T; LAA = left atrial appendage; LCA = left coronary artery; LE = late enhancement; MCST = multislice computed tomography; NS = not significant; PCI = percutaneous coronary intervention; RCA = right coronary artery; TAVR = transcatheter aortic valve replacement; other abbreviations as in Table 1.

analyzed with SPSS version 18.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York).

RESULTS

PATIENTS AND PROCEDURAL RESULTS. Eighty-seven patients who met all of the inclusion criteria were enrolled, and a baseline CMR was acquired. In 26 cases, post-procedural CMR was not available for several reasons: 12 patients required pacemaker implantation, 6 were in unstable condition, death occurred in 5 cases (emergency conversion in 3 patients, 1 case of major stroke, and 1 case of annular rupture), and 3 patients refused the post-procedural examination. Therefore, the study protocol was completed in 61 patients (TF: Sapien XT, n = 18; Corevalve, n = 17; TA: Sapien XT, n = 26). Baseline characteristics were similar between the groups with TA and TF access (Table 1). None of the patients reported symptoms indicative of MI.

COMPARISON OF PATIENTS WITH NEW LE VERSUS PATIENTS WITHOUT NEW LE. Except for reduced renal function in the group with new LE (LE⁺), there were no further significant differences in baseline

and procedural parameters between the LE^+ group and the group without new LE (LE^-), including findings on electrocardiography (Table 2, Online Fig. 1).

CMR imaging. The time intervals of baseline CMR to procedure and from procedure to post-interventional scans were similar between the LE^+ and LE^- groups (Table 2). Image quality overall was appropriate, and the implanted prostheses did not produce artefacts that would have interfered with any of the analyses performed.

The results of the CMR volumetric analyses are summarized in Table 2. Baseline CMR revealed pre-existing myocardial ischemic scars in 42 patients (68.8%), with an average mass of 10.9 g (IQR: 5.1 to 21.9 g) or 7.4% (IQR: 3.9 to 11.7 g) of total LV mass. Among these patients, 9 of 42 (21.4%) had no relevant coronary artery disease, and 28 of 42 (66.7%) had no history of MI. There was no relevant difference in baseline infarct size between the LE^+ and LE^- groups (Table 2).

New hyperenhancement after TAVR was observed in 11 patients (18%) featuring a primarily subendocardial or intramural localization (Fig. 1, Online Table 1). The mean mass of new LE was 3.7 g (IQR: 1.2 to 6 g), or 1.8% (IQR: 1.3 to 4.1 g) of total LV mass. The transmural extents ranged from 25% to <50% in 2 patients, 50% to <75% in 4 patients, and 75% to 100% in 1 patient. Four patients (36.4%) had intramural lesions with a viable endocardial rim. The affected coronary territory involved the left anterior descending artery in 4 patients, the left circumflex artery in 3 patients, and the right coronary artery in 3 patients. One patient demonstrated 1 lesion each in the left anterior descending artery and the left circumflex artery.

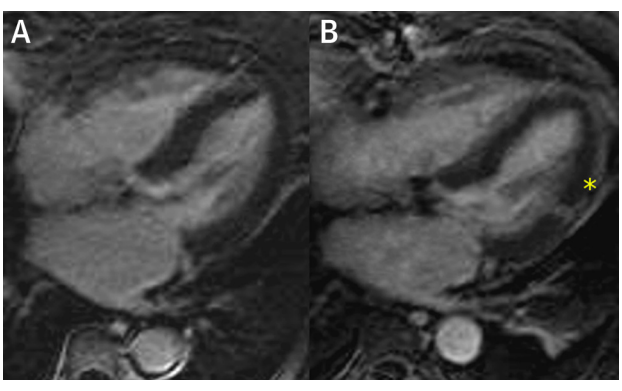

FIGURE 1 New Myocardial LE After TAVR

Late enhancement (LE) images before **(A)** and after **(B)** transcatheter aortic valve replacement (TAVR). The **asterisk** indicates new myocardial hyperenhancement.

There were no significant differences with respect to infarct size, change in EF, and increase in biomarker levels between the group with a viable endocardial rim and that without (Online Table 2).

Prior PCI/MI with known coronary artery disease was present in 5 cases. Four patients had coronary stenosis of >50% before TAVR, without the need for revascularization. In only 1 patient with residual stenosis (>50%) of the right coronary artery, new myocardial scarring was present in the same coronary territory, whereas in all of the other patients, there was no correlation between pre-existing stenosis and localization of new infarctions.

Whereas LVEF remained similar in the LE^- group (pre, 53.9 ± 17.3% vs. post, 54.6 ± 16.3%; p = NS), LE^+ patients revealed a significant post-procedural decrease in LVEF (pre, 55.5 ± 14.1% vs. post, 45.3 ± 14.9%; p = 0.001) (Fig. 2). There was no significant correlation between the mass of new LE and the decrease in LVEF (R = 0.28; p = NS).

Cardiac biomarkers. The baseline hs-cTnT concentration was 24.9 ng/l (IQR: 11.2 to 51.9) and was above the 99th percentile (14 ng/l) in 46 cases (75.4%). After the TAVR procedure, there was an increase in hs-cTnT levels above the 99th percentile in all patients. The maximum concentration of hs-cTnT within 72 h after the procedure was 307.3 ng/l (IQR: 141.2 to 533.8 ng/l), and a 15-fold rise was observed in 61 patients (55.7%) (TF, 10 of 35 [28.5%] vs. TA, 24 of 26 [92.3%]; p < 0.001). The CK-MB concentration at baseline was 11 U/l (IQR: 9 to 15 U/l) and increased to a maximum value of 21 U/l (IQR: 13.5 to 34 U/l) after the procedure, with a 5-fold rise in 26.2% of the population.

Neither baseline values nor post-operative maximum concentrations of hs-cTnT and CK-MB were significantly different between the LE^+ and LE^- groups (Table 2).

The results of the subgroup analysis according to the chosen access are depicted in Figures 3 and 4. Within the TF group, the LE^+ subgroup had significantly higher maximum concentrations of hs-cTnT compared with that in the LE^- subgroup (242.9 ng/l [IQR: 167.4 to 457 ng/l] vs. 141.2 ng/l [IQR: 85.9 to 205.9 ng/l]; p = 0.03). In contrast, CK-MB levels were almost identical between the 2 groups (15 U/l [IQR: 13 to 18 U/l] vs. 14 U/l [IQR: 11 to 20.8 U/l]; p = NS). The receiver operating characteristic curve of hs-cTnT maximum values for the detection of new LE after TAVR revealed an area under the curve of 0.76 (95% confidence interval [CI]: 0.57 to 0.96; p = 0.03). A threshold of 209 ng/l yielded a sensitivity of 71.4% and a specificity of 78.8% (Fig. 5). The area under the curve for a relative increase in the concentration of

hs-cTnT within the TF group was not significant (0.683; p = 0.26).

Within the TA group, the LE$^+$ subgroup also had a higher maximum increase in hs-cTnT levels after the procedure, but the difference was not significant (LE$^+$, 686.4 ng/l [IQR: 475.4 to 871.6 ng/l] vs. LE$^-$, 473.7 ng/l [IQR: 379 to 784.2 ng/l]; p = NS). Likewise, maximum values for CK-MB were not significantly different (LE$^+$, 36.5 U/l [IQR: 32.5 to 46.5 U/l] vs. LE$^-$, 31 U/l [IQR: 25 to 42.3 U/l]; p = NS).

DISCUSSION

In the present study, we demonstrated that new ischemic-type hyperenhancement detected by CMR occurs in a notable proportion of patients undergoing TAVR (**Central Illustration**). The small size, subendocardial or intramural localization, and multifocal distribution of the lesions are findings that suggest an embolic origin. Furthermore, the prevalence of such lesions, which in most cases were considered not definitely related to a relevant coronary stenosis or coronary artery calcium, argues in favor of an embolic cause and at the same time makes other potential causes, such as global or regional hypoperfusion, rather unlikely. Experimental data derived from balloon valvuloplasty of calcified porcine aortic valves provide evidence for embolization of multiple, small particles in both coronary arteries and thereby support our hypothesis (11). This suggested mechanism corresponds well to the previously described finding that cerebral embolism occurs in up to 84% of patients after TAVR (12).

CMR is acknowledged to be the most appropriate method for the detection and quantification of infarct size (6). Its value has been described for the imaging of periprocedural myocardial necrosis after PCI (7,8). Ricciardi et al. (8) reported a median mass of myocardial lesions after PCI of 2 g or 1.5% of left ventricular mass, which is within a range similar to that in our observations. The minimally detectable masses of 0.7 g or 0.8 g in these studies and 0.5 g in our own results indicate a very high sensitivity of this method. By contrast, clinical or electrocardiographic parameters were of limited value for the diagnosis of MI in our study. Therefore, CMR proves to be a useful imaging modality for the description of ischemic lesions and should be considered a complementary method for future studies on myocardial alterations after TAVR.

To our knowledge, this is the first publication showing that TAVR is associated with visible, localized damage of the myocardium. Two recently published studies describe CMR performed before and 6 months after TAVR, with evidence of new hyperenhancement in 1 patient each at 6 months, but due to the long follow-up interval, these lesions could not be attributed to the procedure (13,14). A direct comparison

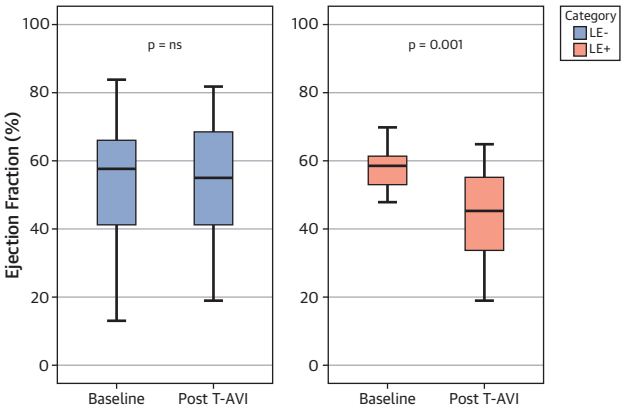

FIGURE 2 Comparison of EF Between the LE$^+$ and LE$^-$ Groups

After TAVR, the mean ejection fraction (EF) remained unchanged from baseline in the LE$^-$ group **(left)**, whereas in the LE$^+$ group it was significantly decreased **(right)**. Abbreviations as in Figure 1.

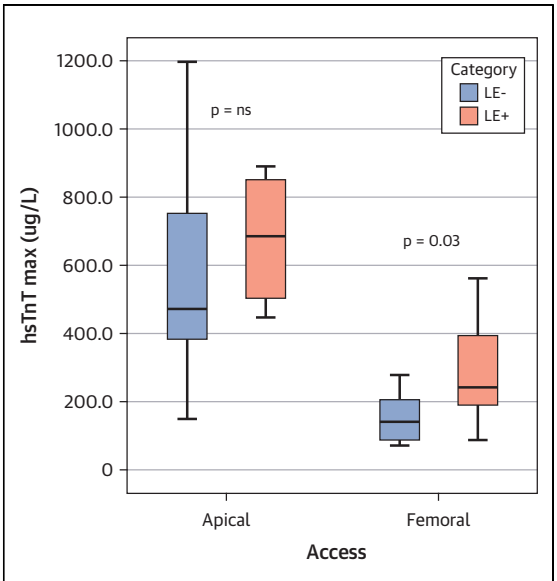

FIGURE 3 Post-Procedural hs-cTnT Maximal Values

Maximum values of high-sensitivity cardiac troponin T ($hs\text{-}cTnT_{max}$) after TAVR are higher in the transapical group. Within both the femoral and apical subgroups, hs-cTnT concentrations were higher in the LE$^+$ patients, but the difference was significant only within the transfemoral group (p = 0.03). Abbreviations as in Figure 1.

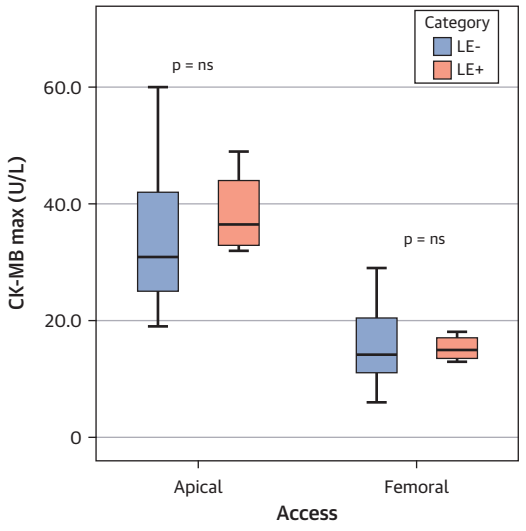

FIGURE 4 Post-Procedural CK-MB Maximal Values

Maximal values of creatine kinase-myocardial band ($CK\text{-}MB_{max}$) after TAVR were higher in the transapical group. Within both the apical and femoral subgroups, CK-MB concentrations were numerically but not statistically significantly higher in the LE^+ patients. Abbreviations as in Figure 1.

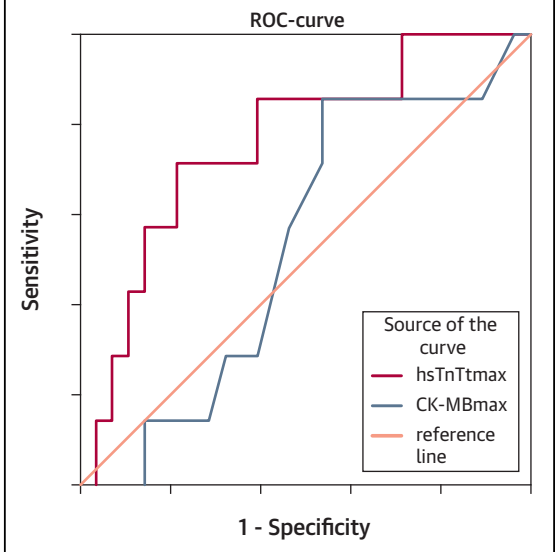

FIGURE 5 hs-cTnT for Detection of Myocardial Infarction After TAVR

The receiver operating characteristic (ROC) curve of hs-cTnT maximal values for the detection of new LE after transfemoral TAVR revealed an area under the curve of 0.76. A threshold of 209.0 ng/l yielded a sensitivity of 71.4% and a specificity of 78.8%. MI = myocardial infarction; other abbreviations as in Figures 1, 3, and 4.

with our results is difficult because these studies focused on various key aspects and had a different patient population with a lesser age, minor-risk profile, and smaller patient numbers. Furthermore, infarcted areas may shrink considerably over time and might become subsequently unnoticeable.

CARDIAC BIOMARKERS. A post-procedural elevation of cardiac biomarker levels was observed in all patients, indicating that myocardial damage commonly occurs to varying degrees. We further noted a lack of correlation between the level of cardiac biomarkers and the mass of new myocardial hyperenhancement detected by CMR; this is in contrast to the setting of PCI, in which such an association has been described to be common (7,8). Myocardial damage after PCI can mostly be attributed to distal embolization, whereas in TAVR multiple underlying mechanisms may be assumed.

Myocardial biomarker concentrations did not discriminate between patients with new LE and those without. Only the subgroup analysis revealed significantly higher concentrations of hs-cTnT in the TF group with new LE than in those without. In the TA group, patients with new hyperenhancement also had numerically higher levels of hs-cTnT, but the difference was not significant; this finding can be ascribed to the overall higher values caused by the apical trauma. In addition, despite significantly higher biomarker concentrations in the LE^+ patients, there was no linear correlation between hs-cTnT concentration and the mass of new myocardial lesions. However, due to the small patient numbers, this subgroup analysis is of limited statistical validity.

The inverse relationship between reduced renal function and higher troponin levels is well-known, and we cannot fully exclude that increased troponin concentrations in the LE^+ group may be ascribed to some extent to the differences in renal function. Nonetheless, despite lower GFR in LE^+ patients, biomarker levels at baseline were similar between these 2 groups, so at the least, the initial conditions were comparable.

We assume that the TAVR procedure is associated with multiple confounding factors that contribute to myocardial damage. Elevated cardiac biomarkers certainly indicate myocardial injury, but an explicit attribution to a definite cause is difficult.

IMPACT ON LV FUNCTION. In our study population, LE^+ patients had a significant decrease in LVEF after TAVR, whereas LVEF in the LE^- group remained unchanged. The relatively small mean lesion size of

2.6% of LV mass certainly would not explain this considerable decrease in LVEF. Accordingly, a CMR study in patients with troponin elevation after PCI and evidence of new hyperenhancement with a mean of even 5% of LV mass demonstrated no change in LVEF (7). Several experimental studies may help to understand this observation. It has been demonstrated that brief episodes of myocardial ischemia may cause prolonged impairment of contractile function on reperfusion (15), which can last up to 1 week and even longer in cases of repetitive myocardial ischemia (16). Experimental animal models with coronary microembolization have indicated that an inflammatory reaction may play a crucial role in the development of contractile dysfunction, independent of infarct size (17). With respect to TAVR, we assume that the evidence of new myocardial lesions probably indicates a relevant exposure to microemboli but does not allow for a hypothesis on the exact amount and size of the embolic load. Studies with coronary protection devices have revealed that nearly all coronary interventions are associated with distal embolization of small particles, but an elevation of myocardial biomarkers is found in only 5% to 40% (18). This finding leads to the hypothesis that embolized particles do not always cause measurable necrosis of myocytes and also might partially explain why new myocardial hyperenhancement was not evident in all patients after TAVR. Rather, those lesions might represent only the visible proportion of the true coronary embolic load, essentially the "tip of the iceberg."

The transapical access inevitably causes a localized defect of the apex. An echocardiographic study has demonstrated that post-operative apical dysfunction developed in 28% of patients and completely resolved in half of those patients (19). However, global LV function has been shown to be unaffected by these localized and often transient wall-motion abnormalities and seems to rather improve over time (20). Therefore, we presume that the impact of the apical approach on global LV function can be neglected.

CLINICAL IMPLICATIONS. According to the revised Valve Academic Research Consortium (VARC II) criteria, 36 patients (59%) had a periprocedural MI, which is in clear contrast to our CMR results showing proof of MI in only 18% (21). The 25 subjects (41%) without morphological evidence of a localized myocardial lesion as revealed by CMR had a TA approach in most cases (88%), which explains the relevant increase in hs-cTnT. Therefore, we conclude that the biomarker-based VARC II criteria fail to sufficiently discriminate patients with MI—especially in cases of the TA approach. Given the lack of an apical trauma, the diagnostic use of cardiac biomarkers for the detection of MI might at best be considered in TF patients, which in our study yielded a sensitivity of 71.4% and a specificity of 78.8% for an hs-cTnT level of 209 ng/l. Interestingly, these values approximately correspond to the threshold of a 15-fold rise of hs-cTnT as defined by VARC II. In this regard, it may be of reasonable interest whether this subset of patients might benefit from dual-antiplatelet therapy for 12 months, as recommended in current guidelines (22). Thus far, there is no evidence supporting the present practice of administering acetylsalicylic acid

Mechanisms of peri-procedural myocardial injury in cardiac interventional procedures

Cardiac interventional procedure	Mechanisms of peri-procedural myocardial injury	Clinical implications
TAVR	**Coronary embolism** caused by detachment of multiple fragments from calcified aortic valve leaflets **Global hypoperfusion** due to rapid pacing or hypotension **Apical access** **Direct trauma** during balloon valvuloplasty or prothesis deployment	Omit pre-ballooning, appropriate sizing of balloon and device, keep rapid pacing periods short or implantation without rapid pacing (only feasible with some devices), avoid unnecessary manipulation within the aortic valve, ensure complete revascularization prior to TAVI, optimal anesthetic (drug and volume) management
PCI	**Distal embolization** **Side branch occlusion** **Dissection** **Acute stent thrombosis** **Coronary perforation**	Direct stenting, prevention of side branch occlusion, antithrombotic and antiplatelet drugs, distal protection devices, statins, ischemic preconditioning
Ablation	**Catheter application** (radiofrequency, cryoballoon, laser) **Coronary embolism** (air, thrombi, charcoaling) **Mechanical irritation and perforation** (catheter manipulation) **Transseptal puncture** **Accelerated or rapid ventricular stimulation**	Use of irrigated tip catheter, careful aspiration of air and consistent flushing of the catheters with saline, effective peri-procedural anticoagulation, shortening procedure time

CENTRAL ILLUSTRATION Mechanisms of Periprocedural Myocardial Injury in Cardiac Interventional Procedures

This table summarizes various mechanisms of myocardial damage and their clinical implications in selected cardiac interventions. The described patterns may be subdivided into classic myocardial infarction (types 2 and 4) and miscellaneous forms including procedure-related injury (e.g., apical access, trans-septal puncture) or mechanical irritation (e.g., balloon valvuloplasty, catheter manipulation). Notably, coronary embolism is a complication that is common to many interventional procedures. PCI = percutaneous coronary intervention; TAVR = transcatheter aortic valve replacement.

100 mg/d and clopidogrel 75 mg/d for 3 to 6 months after TAVR. The development of coronary protective devices or valve prostheses and delivery systems with protective features should be the subject of future investigations.

STUDY LIMITATIONS. Our hypothesis cannot be definitively proven with the methods applied in our study. Our data did not point out clinical or procedural predictors expected to be associated with new-onset LE, including the need for post-dilation, procedural duration, extent of aortic valve calcification, and the chosen access (**Table 2**). Only renal function was significantly decreased in the LE^{+} group, which might indicate an unhealthier population more prone to myocardial damage. Further limitations of our study were the rather small sample size from a single center and the inhomogeneity of the patient cohort due to different TAVR approaches and various valve types implanted; thus, the presented rate of patients with new myocardial injury should be interpreted with caution. At the least, an access-related bias seems to be of minor relevance, given the similar baseline characteristics between the TA and TF groups.

CONCLUSIONS

New ischemic-type myocardial LE after TAVR was observed in a notable proportion of patients and is assumed to be of embolic origin. These patients featured a significant decrease in LV function at discharge. Although elevation of cardiac biomarkers is common after TAVR, it cannot be clearly related to the myocardial alterations measured with CMR due to the multifactorial causes of periprocedural myocardial injury.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Ischemic myocardial hyperenhancement detected by CMR imaging develops in some patients after TAVR and may be a more specific diagnostic marker of myocardial injury after TAVR than clinical, electrocardiographic, or biomarker criteria, which are often inconclusive.

TRANSLATIONAL OUTLOOK 1: Additional observational and prospective studies are warranted to correlate biomarker and serial CMR studies and establish the prognostic implications of myocardial injury detected by the various methods in patients undergoing TAVR.

TRANSLATIONAL OUTLOOK 2: Myocardial injury detected by CMR may be caused by embolism related to catheter manipulations in patients undergoing TAVR, and more research is needed to confirm this mechanism and to develop improved valve prostheses, delivery systems, and myocardial protection strategies.

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APPENDIX For supplemental materials, please see the online version of this article.