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Original Research

Change in Dicrotic Notch Index Predicts Outcomes in Patients Undergoing Transcatheter Edge-to-Edge Repair for Mitral Regurgitation

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ABSTRACT

Background: Changes in the dicrotic notch characteristics in the aortic pressure waveform have not been adequately studied with mitral transcatheter edge-to-edge repair (M-TEER). In this study, we sought to determine the changes in the dicrotic notch index (DNI) with M-TEER and identify their significance in determining procedural success.
Methods: We retrospectively analyzed patients undergoing M-TEER between 2019 and 2022 at our institution. DNI ([systolic-dicrotic pressure]/[systolic-diastolic pressure]) was calculated from invasive ascending aortic pressure waveforms. The cut point for change in DNI was determined and used to compare differences in composite clinical outcomes of mortality and heart failure hospitalization. To identify the determinants of change in DNI, variables including post-M-TEER MR and change in forward stroke volume (FSV) were measured.
Results: Of the 145 patients included in the study cohort, DNI significantly increased after M-TEER (0.49 $\pm$ 0.11 to 0.52 $\pm$ 0.11, $p < 0.001$). A cut point of 2.71% change in DNI identified higher probability of event-free survival at 1 year. Using this cut point, change in DNI was an independent predictor of event-free survival (hazard ratio: 0.45 [95% CI: 0.21-0.99], $p = 0.01$). Of the studied variables, change in FSV was the only predictor of change in DNI (hazard ratio: 0.187 [95% CI: 0.072-0.302], $p = 0.002$) with significant correlation ($r = 0.30$, $p < 0.001$).
Conclusions: DNI increases after M-TEER, and the magnitude of increase in DNI is associated with better clinical outcomes. Further, increase in FSV correlates with increase in DNI. DNI measured during M-TEER procedure provides an additional simple measure of procedural success.

ABBREVIATIONS

DNI, dicrotic notch index; FSV, forward stroke volume; LA, left atrial; LV, left ventricular; LVOT, left ventricular outflow track; MR, mitral regurgitation; M-TEER, mitral transcatheter edge-to-edge repair; PMR, primary MR; SEP, systolic ejection period; SMR, secondary MR.

Introduction

In recent years, mitral transcatheter edge-to-edge repair (M-TEER) has become an important treatment option for high-surgical-risk patients with primary mitral regurgitation (MR) and symptomatic patients with secondary MR despite guideline-directed medical therapy.[1–5] The success of the M-TEER procedure is traditionally defined by a reduction in MR without generating significant mitral stenosis.[6,7] To date, the change in forward stroke volume (FSV) has not been used as an indicator of the success of M-TEER. Although it is reasonable to assume that FSV would increase with the correction of MR, this has not been shown conclusively in large part due to the infrequent usage of right heart catheterization during M-TEER.

Most patients undergoing M-TEER have arterial pressure monitoring as the procedure is performed under general anesthesia.[8] Many centers, including ours, use aortic pressure monitoring with a pigtail catheter in the aortic root, which provides a landmark for transseptal puncture as well as the monitoring of left ventricular (LV) pressure when needed. However,

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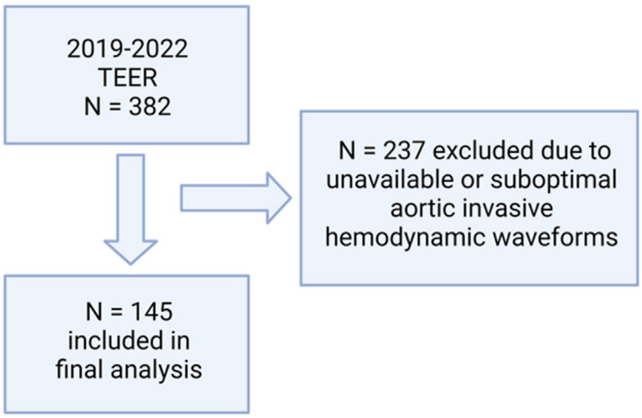

Figure 1. Consort flow diagram.
Abbreviation: TEER, transcatheter edge-to-edge repair.

more granular investigations of the pressure tracing itself have not been conducted. For instance, the changes in the dicrotic notch in the aortic pressure waveform have not been adequately investigated during valvular interventions. We have previously reported the importance of the dicrotic notch index (DNI) during the transcatheter aortic valve replacement procedure, especially to understand residual aortic regurgitation.[9] However, the changes in DNI during M-TEER have not been previously studied.

In this study, we sought to determine whether patient outcomes after the M-TEER procedure are predicted by changes in DNI and if the changes in DNI correlate with changes in FSV.

Materials and Methods

Patient Population

This retrospective study identified patients who underwent M-TEER between 2019 and 2022 at our institution. High-risk surgical patients with primary MR and secondary MR patients with persistent symptoms despite guideline-directed medical therapy were considered candidates for M-TEER. Patients with interpretable aortic invasive hemodynamic waveforms during M-TEER were included in the study. Baseline clinical variables and follow-up information were obtained from electronic medical records. This study was approved by the Cleveland Clinic Institutional Review Board.

Measurements

Invasive aortic pressure waveforms were retrieved from SyngoDynamics software (Siemens Medical Solutions Inc). The measurements of systolic, diastolic, and dicrotic notch pressures were obtained from aortic waveforms. DNI was calculated from systolic, diastolic, and pulse pressure as: (systolic pressure − dicrotic notch pressure)/(systolic pressure − diastolic pressure). Mean left atrial (LA) pressure was obtained from invasive LA pressure waveforms during M-TEER. Transthoracic echocardiography was used to measure FSV before and after the procedure. FSV was calculated using left ventricular outflow track (LVOT) velocity time integral multiplied by LVOT area. LVOT area was calculated from LVOT diameter, which was measured in the parasternal long-axis view. The systolic ejection period (SEP) was measured from the time of aortic valve opening to its closure. Changes in DNI and FSV were defined as [(postprocedure − preprocedure) /(preprocedure)]* 100. Other echocardiographic variables were obtained from echocardiographic reports before and after M-TEER. The median time to pre-M-TEER transthoracic echo was 46.4 days (25th-75th percentile range: 14-85 days). The post-M-TEER median time to a complete transthoracic echo was 35.6 days (25th-75th percentile range: 0.5-50.6 days).

Patient Outcomes

The primary clinical outcome was the composite of all-cause mortality and heart failure hospitalization. These data were obtained from electronic medical chart review.

Statistical Analysis

All continuous variables were described as mean ± SD. All discrete variables were described as n (%). Two-tailed paired t-test was used to determine the significance of change in continuous variables. Two-tailed unpaired t-test was used to compare differences between primary MR (PMR) and secondary (SMR) MR. Chi-squared test was performed to compare discrete variables. Multivariate linear regression was performed to identify predictors of change in DNI using change in FSV, LA pressure, and MR severity as independent variables. Correlation between FSV and DNI was tested using Pearson's test. The optimal cutoff for categorizing patients into higher and lower DNI change post-M-TEER was identified using the *"surv_cutpoint"* function in the *survminer* R package. Kaplan-Meier estimates, generated to compare event-free survival between the

Table 1
Baseline patient characteristics in M-TEER patients

	Overall (N = 145, 100%)	Primary MR (N = 91, 63%)	Secondary MR (N = 54, 37%)	*p*-Value
Clinical variables				
Age, y, median (IQR)	79 (71-85)	81 (75-86)	72 (65-80)	**<0.001**
Female, %	54 (37)	36 (40)	18 (33)	0.45
BMI	27.14 ± 5.8	25.84 ± 4.8	29.33 ± 6.7	**0.001**
STS risk score	6.52 ± 6.26	5.92 ± 6.45	7.61 ± 5.81	0.14
Hypertension	123 (85)	72 (79)	51 (94)	**0.01**
Diabetes mellitus	34 (23)	19 (21)	15 (28)	0.34
Coronary artery disease	103 (71)	63 (69)	40 (74)	0.53
ESRD	3 (2)	0	3 (6)	0.05
Atrial fibrillation	102 (70)	62 (68)	40 (74)	0.45
Echocardiographic variables				
EF, %	51.07 ± 14.22	57.69 ± 9.46	40.37 ± 14.16	**<0.001**
LV internal diameter diastole, cm	5.42 ± 0.85	5.09 ± 0.73	5.91 ± 0.78	**<0.001**
LV internal diameter systole, cm	4.02 ± 1.15	3.46 ± 0.74	4.84 ± 1.15	**<0.001**
FSV, ml	61.01 ± 21.16	59.94 ± 20.43	62.86 ± 22.47	0.44
MR severity, %				
Mild	3 (2)	1 (1)	2 (4)	0.27
Moderate	20 (14)	10 (11)	10 (18)	
Severe	119 (82)	77 (88)	42 (78)	

Values are n (%), median (IQR), or mean ± SD.
Abbreviations: BMI, body mass index; EF, ejection fraction; ESRD, end-stage renal disease; FSV, forward stroke volume; IQR, interquartile range; LV, left ventricular; MR, mitral regurgitation; M-TEER, mitral transcatheter edge-to-edge repair; STS, Society of Thoracic Surgeons.

Table 2
Echocardiographic characteristics pre-M-TEER and post-M-TEER

	Overall (N = 145, 100%)		*p*-Value	Primary MR (N = 91, 63%)		*p*-Value	Secondary MR (N = 54, 37%)		*p*-Value
	Pre-M-TEER	Post-M-TEER		Pre-M-TEER	Post-M-TEER		Pre-M-TEER	Post-M-TEER	
EF, %	50.96 ± 14.34	49.00 ± 12.99	**0.016**	57.64 ± 9.50	53.30 ± 8.61	**<0.001**	39.86 ± 14.20	41.86 ± 15.71	0.121
FSV, ml	61.01 ± 21.16	71.64 ± 23.15	**<0.001**	59.94 ± 20.43	71.63 ± 24.09	**<0.001**	62.86 ± 22.47	71.65 ± 21.67	**<0.001**
SVI, ml/m^2	31.32 ± 9.83	37.59 ± 11.46	**<0.001**	31.55 ± 9.73	38.55 ± 12.00	**<0.001**	30.94 ± 10.07	35.98 ± 10.41	**<0.001**
LV internal diameter diastole, cm	5.41 ± 0.86	5.24 ± 1.03	**0.005**	5.08 ± 0.72	4.87 ± 0.79	**0.005**	5.96 ± 0.80	5.85 ± 1.09	0.310
LV internal diameter systole, cm	4.00 ± 1.12	3.92 ± 1.16	0.173	3.48 ± 0.74	3.47 ± 0.74	0.818	4.86 ± 1.15	4.68 ± 1.33	0.084
RV systolic pressure, mmHg	53.41 ± 20.06	46.25 ± 14.23	**<0.001**	54.28 ± 20.00	44.03 ± 11.76	**<0.001**	52.35 ± 20.30	48.94 ± 16.47	0.201
MR severity, %									
Mild	3 (2)	95 (66)	**<0.001**	1 (1)	60 (66)	**<0.001**	2 (4)	35 (65)	**<0.001**
Moderate	20 (14)	38 (26)		10 (11)	24 (26)		10 (18)	14 (26)	
Severe	119 (82)	12 (8)		77 (88)	7 (8)		42 (78)	5 (9)	

Values are n (%) or mean ± SD.
Abbreviations: EF, ejection fraction; FSV, forward stroke volume; LV, left ventricular; M-TEER, mitral transcatheter edge-to-edge repair; MR, mitral regurgitatio; RV, right ventricularn; SVI, stroke volume index.

two DNI groups, utilized the log-rank test and the *survminer* package in R. The optimal cut point identification was done using the maximally selected rank statistics from R software version 4.3.2 (R Core Team, Vienna, Austria). This cut point was used to compare differences in clinical outcomes. Data analysis was performed using SPSS software version 27 (IBM, Chicago, Illinois).

Results

Patient Population

Of the 382 patients who underwent M-TEER between 2019 and 2022, 145 were included in the final analysis, while 237 were excluded due to unavailable or suboptimal aortic waveforms (Figure 1). Of the 145 included patients, 91 (63%) had PMR and 54 (37%) had SMR. The median age of the study population was 79 (interquartile range, 71 to 85 years), and 37% of the patients were female. The mean Society of Thoracic Surgeons risk score was 6.52 ± 6.26. Patients with PMR were significantly older than those with SMR (81 vs. 72 years, $p < 0.001$). SMR patients had a significantly higher body mass index (29.33 ± 6.7 vs. 25.84 ± 4.8, $p = 0.001$). A significantly higher percentage of SMR patients had hypertension compared to PMR patients (94 vs. 79%, $p = 0.01$). As expected, the ejection fraction was significantly lower in SMR patients compared to PMR patients (40.37% ± 14.16% vs. 57.69% ± 9.46%, $p < 0.001$), and the LV diastolic and systolic internal diameters were significantly higher in SMR patients (Table 1).

Hemodynamic Changes With M-TEER

In the overall study population, FSV and stroke volume index increased after M-TEER, whereas LV internal diastolic diameter, ejection

$$\text{DNI} = \frac{\text{Systolic Pressure} - \text{DN Pressure}}{\text{Systolic Pressure} - \text{Diastolic Pressure}}$$

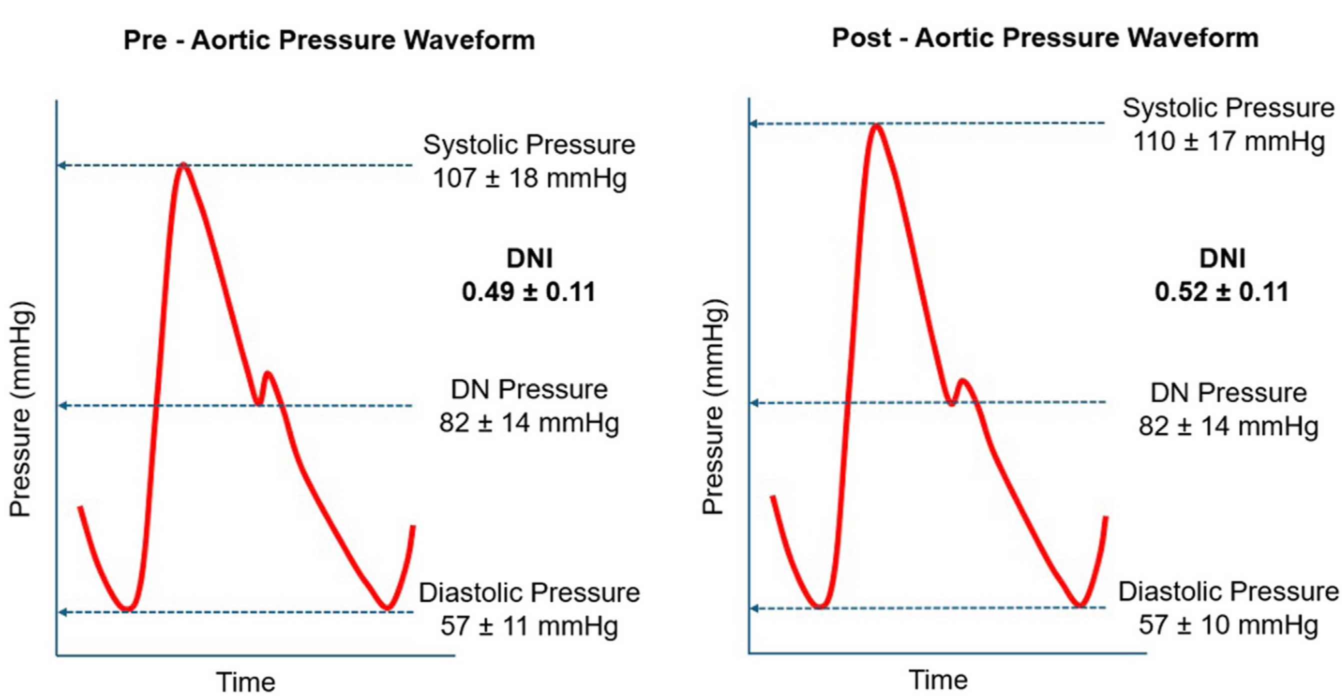

Figure 2. Aortic tracings showing DNI calculation before and after M-TEER with mean hemodynamic parameters.
Abbreviations: DN, dicrotic notch; DNI, dicrotic notch index; M-TEER, mitral transcatheter edge-to-edge repair.

Table 3
Dicrotic notch waveform characteristics

	Overall (N = 145, 100%)		*p*-Value	Primary MR (N = 91, 63%)		*p*-Value	Secondary MR (N = 54, 37%)		*p*-Value
	Pre-M-TEER	Post-M-TEER		Pre-M-TEER	Post-M-TEER		Pre-M-TEER	Post-M-TEER	
DN pressure, mmHg	82.14 ± 13.87	82.28 ± 13.79	0.9	82.07 ± 14.49	82.79 ± 14.53	0.63	82.27 ± 12.88	81.44 ± 12.51	0.56
DN amplitude, mmHg	2.72 ± 2.60	3.65 ± 3.09	**<0.001**	2.38 ± 2.50	3.41 ± 3.14	**<0.001**	3.30 ± 2.67	4.05 ± 2.98	**0.02**
DN duration, s	0.07 ± 0.03	0.08 ± 0.03	**0.003**	0.07 ± 0.03	0.08 ± 0.03	**0.004**	0.07 ± 0.03	0.08 ± 0.03	0.29
DNI	0.49 ± 0.11	0.52 ± 0.11	**<0.001**	0.49 ± 0.11	0.53 ± 0.11	**<0.001**	0.50 ± 0.11	0.52 ± 0.11	**0.002**
SBP, mmHg	107.01 ± 17.70	110.35 ± 17.48	**0.03**	107.28 ± 17.09	112.34 ± 18.27	**0.02**	106.57 ± 18.84	107.00 ± 15.67	0.83
DBP, mmHg	57.10 ± 10.97	56.86 ± 9.80	0.75	56.30 ± 10.63	56.26 ± 9.21	0.97	58.44 ± 11.50	57.86 ± 10.72	0.61
SEP, s	3.00 ± 0.44	3.16 ± 0.44	**<0.001**	3.05 ± 0.43	3.22 ± 0.47	**<0.001**	2.90 ± 0.43	3.05 ± 0.35	**0.002**
Mean LA pressure	19.94 ± 7.47	15.13 ± 6.29	**<0.001**	18.86 ± 7.54	14.05 ± 5.55	**<0.001**	21.93 ± 7.01	17.13 ± 7.12	**<0.001**

Values are mean ± SD. Bolded values signify statistical significance.
Abbreviations: DBP, diastolic blood pressure; DN, dicrotic notch; DNI, dicrotic notch index; LA, left atrial; MR, mitral regurgitation; M-TEER, mitral transcatheter edge-to-edge repair; SBP, systolic blood pressure; SEP, systolic ejection period.

fraction, and right ventricular systolic pressure decreased (Table 2). PMR patients demonstrated a significant reduction in LV diastolic diameter and ejection fraction, while SMR patients did not. In both PMR and SMR patients, MR was significantly reduced, with more than 90% of patients having moderate or less MR after M-TEER (Table 2).

Systolic blood pressure increased after M-TEER in the overall study population, particularly in PMR patients (107.28 ± 17.09 to 112.34 ± 18.27, $p = 0.02$). DNI and SEP also increased significantly in both PMR and SMR patients (Figure 2). Mean LA pressure decreased significantly (Table 3).

Predictors of Change in DNI

The change in FSV correlated positively with the change in DNI after M-TEER ($r = 0.30$, $p < 0.001$) (Figure 3). In a multivariate linear regression analysis to identify the factors that predict change in DNI using the change in FSV, MR severity, and LA pressure as independent variables, the change in FSV was the only independent predictor (hazard ratio: 0.187 [95% CI: 0.072-0.302]).

Patient Outcomes

The cut point of 2.71% change in DNI was found using maximally selected rank statistics (Figure 4). Kaplan-Meier survival curves indicated that patients with a relative change in DNI >2.71% had better overall survival than did patients with ≤2.71% increase in DNI ($p = 0.01$; Figure 5). In a multivariate analysis using post-M-TEER MR severity, post-M-TEER mean gradient, mechanism of MR, change in LA mean pressure, and change in DNI as covariates, the change in DNI was the only independent predictor of mortality and heart failure hospitalization (hazard ratio: 0.45 [95% CI: 0.21-0.99]).

Discussion

There are three main findings of this study: (1) DNI significantly increased after the M-TEER procedure; (2) the increase in DNI correlated with the increase in FSV; and (3) an increase in DNI after M-TEER was associated with a lower mortality and heart failure hospitalization at 1 year after the procedure.

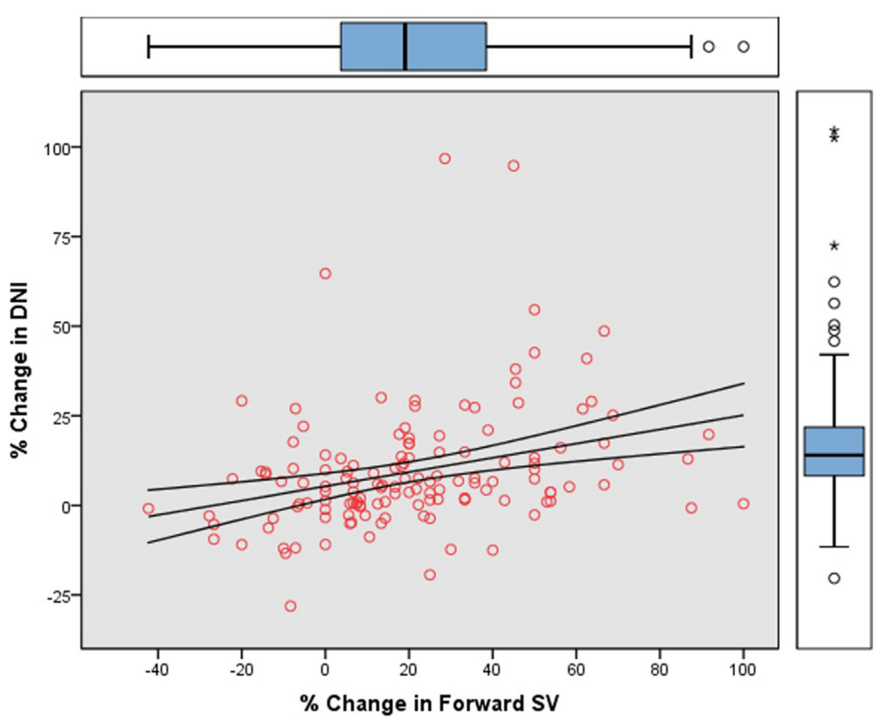

Figure 3. Correlation between change in FSV and DNI.
Abbreviations: DNI, dicrotic notch index; FSV, forward stroke volume; SV, stroke volume.

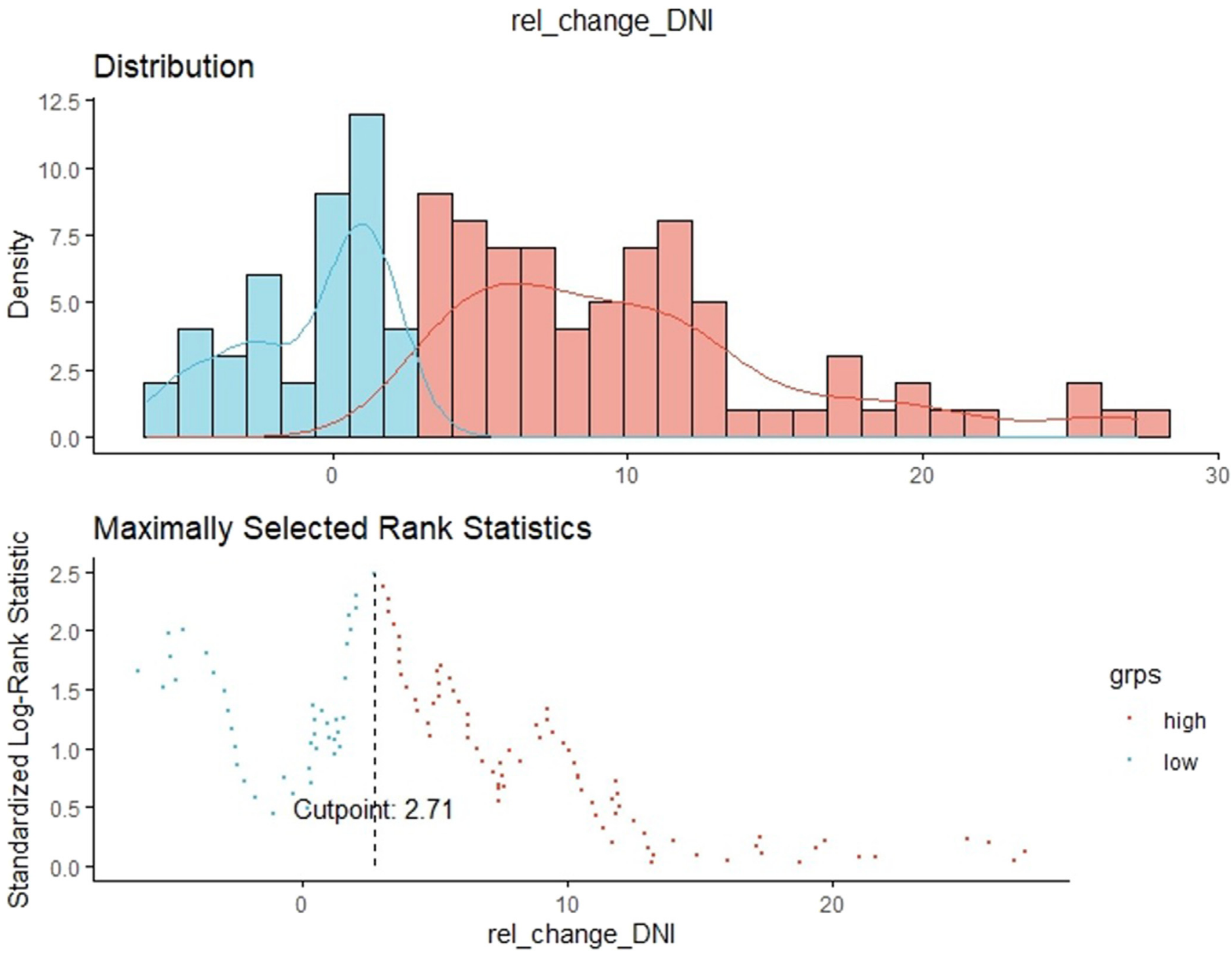

Figure 4. Cut point determination of change in DNI.
Abbreviation: DNI, dicrotic notch index.

While the dicrotic notch has not yet been studied as a hemodynamic parameter in patients undergoing M-TEER, patient outcomes after M-TEER have been shown to correlate with other echocardiographic and hemodynamic measurements including reduction in MR and decrease in LA pressure. In a study by Makkar et al.,[10] lower mortality was observed in primary MR patients with mild or less residual MR after M-TEER compared to those with moderate or severe residual MR. Similarly, in secondary MR patients, reduction in MR after M-TEER was also shown to be associated with lower mortality and a better quality of life at 5-year follow-up.[8,11] Additionally, the severity of residual MR correlated with clinical outcomes.[11]

While MR grade in M-TEER patients may be an accurate predictor of clinical outcomes, MR grade can sometimes be difficult to determine by echocardiography after M-TEER device placement due to limitations in quantification as a result of shadowing from the device and distortion of regurgitant jets.[12,13] More recently, the degree of LA pressure reduction was also shown to correlate with degree of MR improvement in M-TEER patients. In a study by Maor et al.,[14] a decrease in LA pressure in patients following M-TEER was associated with clinical improvement as measured by the 6-minute walk test. However, data for the significance of LA pressure on other clinical outcomes, such as heart failure hospitalization, are limited.[15]

The current study provides a novel method for measuring the hemodynamic response to M-TEER using changes in DNI. This measurement is simple and readily available from invasive aortic pressure measurements during the procedure. The current study investigated the mechanism of the increase in DNI by correlating it with the increase in FSV. There are four potential mechanisms by which FSV can increase. First, an increase in cardiac contractility could directly increase FSV, but contractility should not change after M-TEER is performed. Second, an increase in preload could increase FSV, but the correction of MR should reduce preload due to reduced regurgitant volume. Third, a decrease in afterload could increase FSV, but afterload has been shown to increase with M-TEER.[16] Finally, an increase in SEP leads to an increase in FSV, and we have shown that SEP increases after M-TEER. With a longer SEP, the aortic valve remains open longer, allowing more blood to be ejected. This increased FSV results in the dicrotic notch moving closer to the diastolic pressure, thereby increasing DNI and providing the basis for the relationship between DNI and outcomes as suggested by the current analysis.

FSV measurements are not commonly performed during M-TEER procedures, as they may require right heart catheterization. Transesophageal echocardiographic measurement of FSV is also rarely performed during the procedure. Therefore, the measurement of the change in DNI provides a simple and practical approach as an additional determinant for the efficacy of M-TEER.

There are many determinants of clinical outcomes after the M-TEER procedure. The current study identified change in DNI (>2.71%) to be an independent predictor for clinical outcomes. This association provides

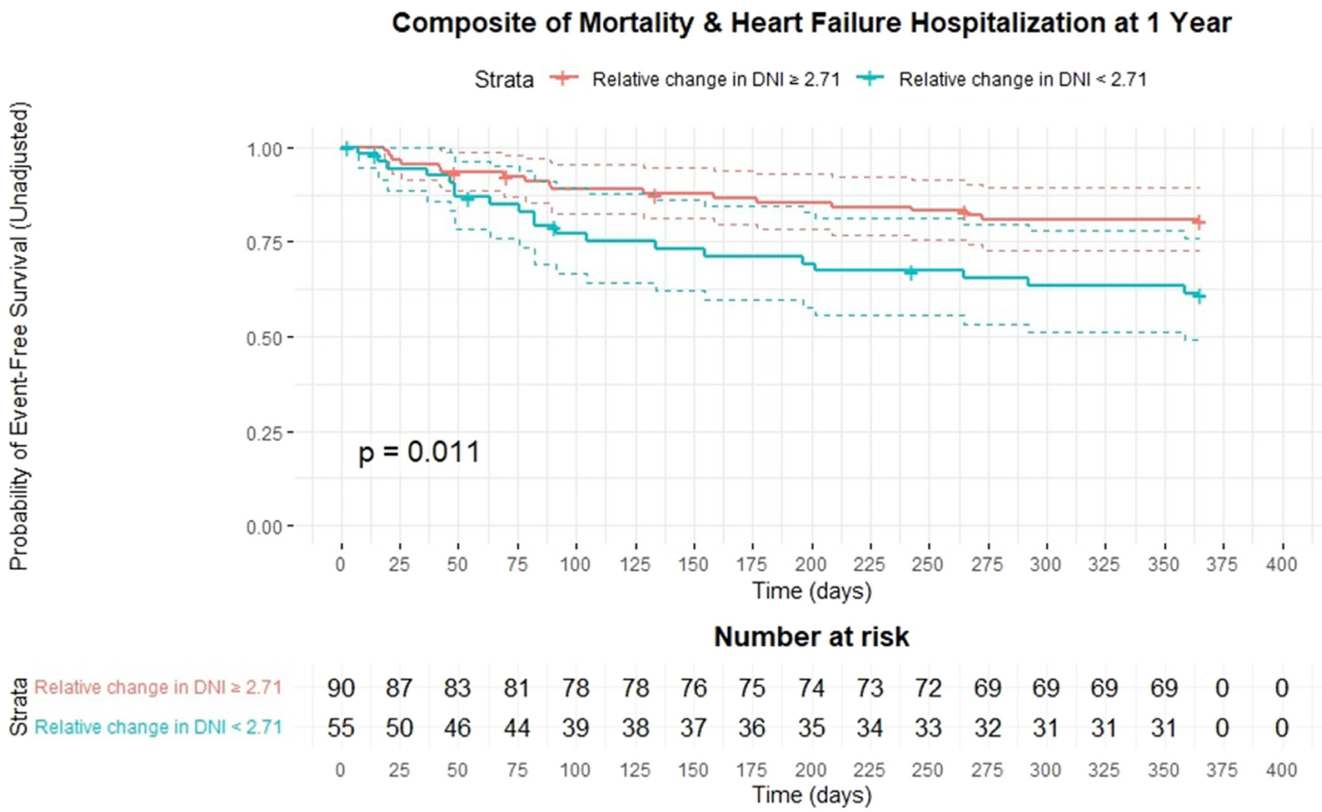

Figure 5. Change in DNI predicting mortality and heart failure hospitalization 1 year after M-TEER.
Abbreviations: DNI, dicrotic notch index; M-TEER, mitral transcatheter edge-to-edge repair.

rationale for the use of DNI as one of the measures of the clinical success of M-TEER. The change in DNI was an independent predictor even after adjusting for the magnitude of MR reduction, the post-M-TEER mean mitral valve gradient, the mechanism of MR, and the change in LA mean pressure. Taken together, DNI can be used as a novel measure to evaluate procedural success.

There were some limitations to this study. First, this was a single-center study from a high-volume tertiary center. Second, this was a retrospective study, which requires prospective validation in a future multicenter investigation. Third, the measurement of stroke volume was not simultaneously performed with DNI measurement. Therefore, the correlation of change in DNI with increase in stroke volume is hypothesis-generating. Finally, while manual calculation of DNI as performed in this study is not practical at the procedural bedside, this value could easily be generated by the hemodynamic software if it is ultimately found to be a beneficial outcome measure. Further, we used the central aortic waveform recordings, but potentially peripheral arterial tracings can be used to calculate similar DNI. However, this needs further validation from future studies.

Conclusions

The DNI increases with reduction in MR after M-TEER, and this increase correlates with an increase in FSV. The increase in DNI provides a novel and simple measure of the clinical success of M-TEER and correlates to 1-year clinical outcomes. Future multicenter prospective studies are needed to validate this novel measurement.

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Ethics Statement

As a restrospective chart-based analysis of de-identified patient data, this study represents minimal risk and was processed under expedited review by the Institutional Review Board of Cleveland Clinic.

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Disclosure Statement

The authors report no conflict of interest.

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