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Comparison of Transthoracic Echocardiography With N-Terminal Pro-Brain Natriuretic Peptide as a Tool for Risk Stratification of Patients Undergoing Major Noncardiac Surgery

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ABSTRACT

Background and Objectives: The role of preoperative transthoracic echocardiography (TTE) for the risk stratification has not been well investigated yet. We compared the predictive power of TTE with N-terminal pro-brain natriuretic peptide (NT-proBNP), a representative biomarker that predicts perioperative cardiovascular risk, and investigated whether these tests have incremental value to the clinically determined risk. **Subjects and Methods:** We evaluated the Revised Cardiac Risk Index (RCRI), TTE, and NT-proBNP in 1,923 noncardiac surgery cases. The primary endpoint was a perioperative major cardiovascular event (PMCE), which was defined by any single or combined event of secondary endpoints including myocardial infarction, development of pulmonary edema, or primary cardiovascular death within 30 days after surgery. **Results:** All echocardiographic parameters including left ventricular ejection fraction, regional wall motion score index, and transmitral early diastolic velocity/tissue Doppler mitral annular early diastolic velocity (E/E') were predictive of PMCE (c-statistics=0.579±0.019 to 0.589±0.015), but none of these parameters were better than the clinically determined RCRI (c-statistics=0.594±0.019) and were inferior to NT-proBNP (c-statistics=0.748±0.019, p<0.001). The predictive power of RCRI {adjusted relative risk (RR)=1.4} could be improved by addition of echocardiographic parameters (adjusted RR=1.8, p<0.001), but not to that extent as by addition of NT-proBNP to RCRI (adjusted RR=3.7, p<0.001). **Conclusion:** TTE was modestly predictive of perioperative cardiovascular events but was not superior to NT-proBNP. Moreover, it did not have incremental value to the clinically determined risk. The results of our study did not support the use of routine echocardiography before noncardiac surgery. **(Korean Circ J 2011;41:505-511)**

KEY WORDS: Cardiovascular disease; Postoperative complications; Echocardiography; Natriuretic peptides.

Introduction

Most clinical cardiovascular risk indices are shown to have modest predictive power in patients undergoing major noncardiac surgery.[1)] Preoperative transthoracic echocardiography (TTE) is one of non-invasive cardiac evaluation tests that are frequently expected to increase the predictive power. Although poor left ventricular (LV) systolic or diastolic function is known to be predictive of postoperative heart failure or death,[2-4)] the routine use of preoperative echocardiography in clinically stable patients is not usually recommended by the current guidelines.[1)]

Recent studies have shown that natriuretic peptides can predict postoperative cardiovascular events.[5-8)] Currently, little data is available on the direct comparison of imaging- or biomarker-based predictors, or the incremental value of these predictors to the clinically determined risk. We compared directly the predictive power of N-terminal pro-brain natriuretic

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peptide (NT-proBNP) with TTE for the postoperative major cardiovascular events, and investigated whether additional evaluation of these risk predictors has incremental value to the clinical risk stratification.

Subjects and Methods

Study population

The study population was derived from our prospective, unselected, consecutive cohort of preoperative cardiac consultation for elective noncardiac surgery.[5] Of the 2,304 cohort patients, 1,923 (83.5%) patients had echocardiography within 2 weeks before surgery and constituted the study group (Fig. 1). Patients with moderate or severe valvular stenosis were not included in this study population. This study protocol was approved by the institutional review board of Samsung Medical Center.

Data collection

Clinical perioperative cardiovascular risk was assessed according to the Revised Cardiac Risk Index (RCRI) modified by Lee, a well-validated and widely used point score-based risk prediction index.[9,10] Briefly, RCRI calculates perioperative risk by sum of points. Each risk factor, including high-risk surgical procedures, history of ischemic heart disease, pulmonary edema, cerebrovascular disease, insulin-dependent diabetes and serum creatinine >2.0 mg/dL, is assigned one point. The risk of major cardiac event including myocardial infarction, pulmonary edema, primary cardiac arrest and complete heart block predicted by RCRI was known to be 0.4% to 11% according to an RCRI score of 0 to ≥3.

Basic laboratory tests including electrocardiography, chest X-ray, and NT-proBNP were evaluated within 2 weeks before surgery. Blood samples for NT-proBNP were collected into lithium heparin tubes and stored at -70°C until further analysis. Plasma NT-proBNP levels were measured using an Elecsys pro-BNP reagent kit (Roche Diagnostics, Indianapolis, In, USA) and an Elecsys 2010 analyzer (Roche Diagnostics, Indianapolis, IN, USA).

Transthoracic echocardiography

Two-dimensional (2-D) TTE was performed within 2 weeks before surgery at the discretion of the physician or if the patients had two or more of the following cardiovascular risk factors: diabetes mellitus, hypertension, aged 65 years or greater, current smoking status, or hypercholesterolemia. TTE was performed with a commercially available echocardiographic instrument (Vivid 7, GE Medical Systems, Milwaukee, WI, USA or Sequoia 512, Acuson, Mountain View, CA, USA). A standard M-mode, 2-D echocardiogram and echocardiographic Doppler study were performed. All TTE recordings were interpreted by staff cardiologists.

The routine standard echocardiographic examination included measurements of thickness of the ventricular septum and LV posterior wall, end-systolic and end-diastolic LV diameters from M-mode or 2-D imaging. Left atrial (LA) volume measurement and standard pulsed wave Doppler evaluation of diastolic function were carried out as previously described.[11] Both LV mass and LA volume were indexed to body surface area. Mitral inflow velocities were obtained by pulsed wave Doppler sample volume between the mitral leaflet tips during diastole and mitral annulus velocities were ob-

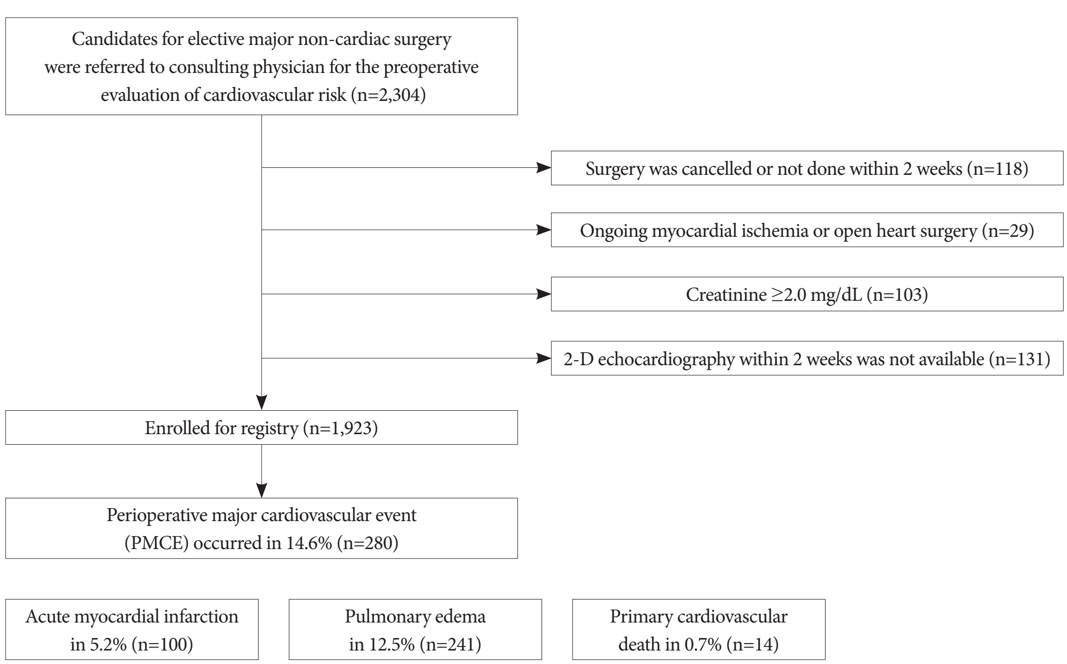

Fig. 1. Study flowchart.

tained from the septal portion of the mitral annulus by tissue Doppler imaging. All measurements were performed on 3 cardiac cycles and were then averaged.

Quantitative LV systolic ejection fraction (LVEF) and regional wall motion index (RWMI) was obtained from the digitally stored records. Diastolic dysfunction could be evaluated in a subgroup of 1,132 patients (58.9%) who were examined using tissue Doppler imaging with acceptable quality, and did not have non-sinus rhythm or left bundle branch block.

Clinical outcome

All patients were followed until discharge or up to 30 days of hospitalization after surgery. Primary endpoint was a perioperative major cardiovascular event (PMCE), which was defined by any single or combined event of secondary endpoints including myocardial infarction, development of pulmonary edema, or primary cardiovascular death. Individual patients may have had more than one event, and all events were counted as an incidence. Myocardial infarction was defined by a rise in postoperative troponin I above the 99th percentile of the upper reference limit (0.78 ng/mL, Roche Diagnostics, Switzerland), which was evaluated at the end of the day of surgery and 24 hours later. Pulmonary edema was diagnosed after a formal reading of the chest X-ray by a radiologist consistent with the complication. Primary cardiovascular death was defined by sudden death that could not be explained by any other non-cardiovascular postoperative complications.

Statistical analysis

Perioperative risk predictors including RCRI, NT-proBNP, and echocardiographic parameters were treated as continuous variables or ordered categorical variables. Receiver-operating characteristic (ROC) analysis was performed to calculate sensitivity, specificity, area under the curve (AUC), and the optimal cut-off value. The predictive power of each predictor was compared using Hanley and McNail method.[12] Independent predictors of PMCE in univariate analysis were categorized by optimal cut-off levels, and were used in multivariate logistic models.[13] The adjusted relative risk (RR) of each predictor and the combination of these predictors in an additive manner was evaluated. A $p<0.05$ (2-sided) was considered significant. SPSS version 13.0 was used mostly. ROC curves were compared using Medcalc version 9.6.

Results

Baseline characteristics

Preoperative clinical characteristics of the study population are shown in Table 1. 2-D TTE was performed within 2 weeks before surgery (10.8±8.2 days). NT-proBNP were evaluated within 2 weeks before surgery (7.4±7.2 days). Briefly,

Table 1. Clinical characteristics

	Frequency (%) or median with interquartile range
Age (years)	68 (61-73)
Male (sex)	1,185 (61.6)
Functional class III or IV	105 (5.5)
Diabetes*	341 (17.7)
Hypertension	1,162 (60.4)
Previous or current heart failure	62 (3.2)
Previous stroke	182 (9.5)
Angina	256 (13.3)
Previous myocardial infarction	163 (8.5)
Previous revascularization†	296 (15.4)
Pathological Q waves	105 (5.5)
Atrial fibrillation	162 (8.4)
Left bundle branch block	14 (0.7)
Preoperative noninvasive test‡	752 (39.1)
Overall positive result for ischemia	185 (9.6)
Preoperative invasive test	534 (27.8)
Significant coronary artery disease by invasive test	353 (18.4)
Any evidence of myocardial ischemia§	437 (22.7)
Creatinine (mg/dL)	0.90 (0.74-1.06)
NT-proBNP (ng/L)	113 (50-377)
Left ventricular ejection fraction	63 (58-68)
Left ventricular ejection fraction ≤40%	95 (4.9)
Abnormal left ventricular wall motion	407 (21.2)
E/E’	9.8 (7.6-12.4)
Left atrial volume index	25.4 (18.7-33.0)
RCRI (median, interquartile range)	1 (0-2)
High risk surgery by RCRI¶	813 (42.3)
Beta blocker	336 (17.5)
ACE inhibitor or ARB	468 (24.3)
Calcium channel blocker	478 (24.9)
Aspirin	496 (25.8)
Statin	290 (15.1)
Nitrate	80 (4.2)
IV inotropic agents	10 (0.5)

*Includes 68 (3.5%) patients with insulin-dependent diabetes, †Includes 215 (11.2%) cases of percutaneous coronary intervention and 81 (4.2%) cases of bypass surgery, ‡Includes 647 (33.6%) cases in which SPECT was performed, 138 (7.2%) cases in which treadmill test was performed, and 45 (2.3%) cases in which stress echocardiography was performed, §Any positive result of non-invasive test or significant (>50%) stenosis of major coronary artery by invasive test, ¶Defined as intraperitoneal, intrathoracic, or suprainguinal vascular surgery according to the Revised Cardiac Risk Index (RCRI modified by Lee). NT-proBNP: N-terminal pro-brain natriuretic peptide, ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker most patients had good functional status without overt heart failure (functional class I or II in 94.5% and no history of heart failure in 96.8%). Evidence of myocardial ischemia which was determined by positive non-invasive test or significant coronary artery stenosis was found in 22.7%. Percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) before surgery had been performed in 15.4%. Abnormal LV wall motion and LV systolic dysfunction defined by an ejection fraction of less than 40% was found in 21.2% of patients. Most patients received general anesthesia (97.5%). Patients who underwent urgent surgery within 24 hours after consultation because of altered clinical situation (4.4%) were not excluded from the analysis (Table 2).

Clinical outcomes

PMCE had developed in 280 patients (14.6%), including 100 (5.0%) acute myocardial infarction, 241 (12.5%) pulmonary edema, and 14 (0.7%) primary cardiovascular deaths caused by 3 (0.2%) acute myocardial infarction, 2 (0.1%) stress induced cardiomyopathy, 4 (0.2%) aortic aneurysm rupture or dissection, 1 (0.1%) stroke, and 4 (0.2%) sudden death of unknown cause (Fig, 1). There were 5 deaths caused by postoperative disease progression or surgical complication (0.3%). There were no differences in PMCE between the vascular surgery and non-vascular surgery groups in this study.

Table 2. Surgical procedure

	Frequency (%)
Vascular surgery	523 (27.2)
Aorta	158 (8.2)
Suprainguinal vascular	96 (5.0)
Infrainguinal vascular	156 (8.1)
Carotid endarterectomy	96 (5.0)
Other vascular	17 (0.9)
Non-vascular surgery	1,400 (72.8)
Thorax	85 (6.0)
Abdomen	474 (33.9)
Head and neck	154 (11)
Orthopedic	415 (29.6)
Prostate	78 (5.6)
Neurosurgery	36 (2.6)
Other surgery	158 (11.3)
General anesthesia	1,874 (97.5)
Urgent surgery	85 (4.4)

Receiver-operating characteristic analysis of perioperative risk predictors

ROC analysis using continuous variables showed that all

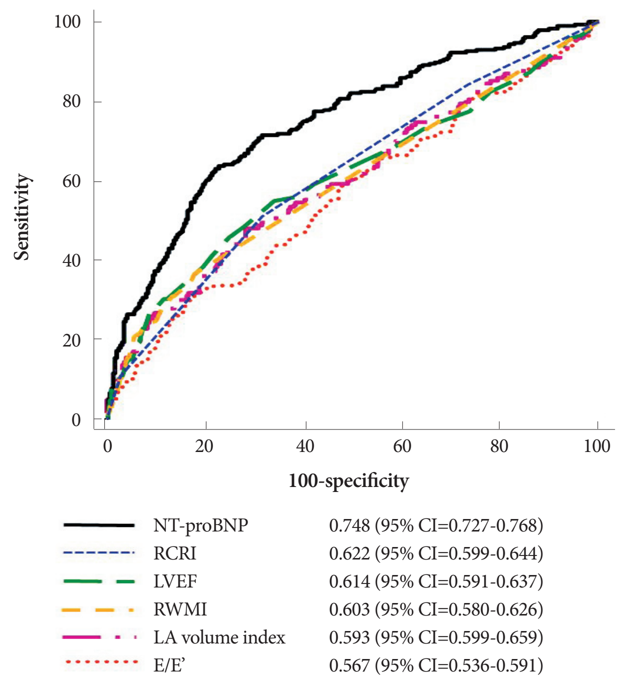

Fig. 2. Comparison of risk predictors. The predictive power of each risk predictors for the perioperative major cardiovascular event was investigated and compared to each other by area under curve (AUC) of ROC analysis. AUC with 95% confidence intervals (CIs) are shown. NT-proBNP: N-terminal pro-brain natriuretic peptide, RCRI: Revised Cardiac Risk Index, LVEF: left ventricular ejection fraction, RWMI: regional wall motion index, LA volume index: left atrial volume index, E/E': transmitral early diastolic velocity/tissue Doppler mitral annular early diastolic velocity. *$p<0.05$ by Hanley and McNeil method, ROC: receiver-operating characteristic.

Table 3. Diagnostic performance of risk predictors categorized using optimal cut-off values for the postoperative major cardiovascular event

Optimal cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value
NT-proBNP ≥301 ng/L	65.0 (59.1-70.6)	77.9 (75.8-79.8)	33.3 (29.4-37.5)	92.9 (91.4-94.2)
RCRI ≥2	49.6 (43.6-55.7)	69.2 (66.9-71.4)	21.6 (18.4-24.9)	89.0 (87.1-90.6)
LVEF <50%	22.9 (18.1-28.2)	92.9 (91.5-94.1)	35.4 (28.4-42.8)	87.6 (86.0-89.1)
E/E' ≥13	23.6 (18.7-29.0)	86.7 (84.9-88.3)	23.2 (18.4-28.5)	86.9 (85.2-88.5)
LA volume index ≥33	27.1 (22.0-32.8)	83.2 (81.3-85.0)	21.6 (17.4-26.3)	87.0 (85.3-88.6)
Any RWMA exists	36.4 (30.8-42.4)	81.4 (79.5-83.3)	25.1 (20.9-29.6)	88.3 (86.5-89.8)
Any abnormal echocardiographic parameters from the above	48.2 (42.2-54.2)	71.6 (69.3-73.7)	22.4 (19.2-26.0)	89.0 (87.2-90.7)

The sensitivity, specificity, positive predictive value, and negative predictive values of each categorized risk predictors are shown. Because these values depend on the cut-off levels, values at the point of optimal cut-off levels calculated from ROC analysis were presented. NT-proBNP: N-terminal pro-brain natriuretic peptide, RCRI: Revised Cardiac Risk Index, LVEF: left ventricular ejection fraction, LA: Left atrial, RWMA: regional wall notion abnormality echocardiographic parameters including systolic and diastolic parameters were modestly predictive of PMCE; LVEF [AUC=0.614 {95% confidence interval (CI)=0.591-0.637}], RWM score index {AUC=0.603 (0.580-0.626)}, LA volume index {AUC=0.593 (0.563-0.623)}, and E/E' {AUC=0.567 (0.536-0.597)} (p<0.05 for all). However, the predictive power of these parameters was not higher than RCRI {AUC=0.622 (0.599-0.644)} (p=0.020 between E/E', p=not significant between echocardiographic parameters) and was significantly lower than NT-proBNP {AUC=0.748 (0.727-0.768)} (p<0.001 between echocardiographic parameters) (Fig. 2).

To evaluate the incremental value of other risk predictors to clinical risk index, RR adjusted to age, sex, and traditional clinical factors were calculated using the parameters categorized by optimal cut-off levels. The RR of RCRI cut-off (≥2) increased 2.8-fold after addition of NT-proBNP cut-off (≥301 ng/L) {RR=1.4 (95% CI=1.0-1.8) to 3.7 (2.7-5.0), p<0.001}. Contrarily, the RR of RCRI cut-off (≥2) modestly increased after addition of LVEF cut-off (≤50%) {RR=1.4 (1.0-1.8) to 1.8 (1.4-2.4), p<0.001} and did not increase after addition of all the other echocardiographic parameters. Addition of both NT-proBNP and echocardiographic parameters did not result in a further increase in RR. The increase in RR by addition of NT-proBNP to RCRI was also evident in secondary endpoints including AMI and pulmonary edema (Table 4).

Discussion

To our knowledge, this is the first study to compare the predictive power of hemodynamic biomarker with that of imaging modality and investigated the incremental value of these modalities to the clinically determined risk. TTE, which is one of the widely used cardiovascular imaging modality, was inferior to NT-proBNP, a representative hemodynamic biomarker, for the prediction of perioperative cardiovascular risk in non high-risk patients for major noncardiac surgery. Moreover, TTE did not have incremental value to the clinically determined risk whereas NT-proBNP had incremental value to the clinically determined risk.

Most preoperative echocardiographic assessments have focused on the systolic function. Decreased LV ejection fraction has been repeatedly shown to be associated with perioperative cardiovascular morbidity.[2)3)14)15)] In our study, LVEF of less than 50% was significantly but modestly predictive of PMCE. Although diastolic dysfunction is not uncommon in patients undergoing noncardiac surgery, routine preoperative evaluation does not include evaluation of diastolic dysfunction for risk stratification. In our study, the presence of perioperative diastolic dysfunction was not related to the perioperative cardiovascular risk. The result of our study could be partially explained by the difference between a general cardiovascular biomarker and an imaging modality. NT-

Table 4. Clinical outcomes according to the risk predictors

	PMCE		AMI		CHF		CV Death	
	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
Optimal cut-off of each risk predictor								
RCRI ≥2	1.35 (1.02-1.76)	0.037	1.12 (0.69-1.82)	0.64	1.31 (0.96-1.82)	0.08	0.29 (0.06-1.43)	0.13
NT-proBNP ≥301 ng/L	3.94 (3.13-4.87)	<0.001	2.95 (1.91-4.50)	<0.001	4.72 (3.64-5.98)	<0.001	5.36 (1.53-18.28)	0.009
LVEF <50%	2.18 (1.61-2.86)	<0.001	1.63 (0.93-2.79)	0.08	2.31 (1.66-3.10)	<0.001	8.66 (2.63-26.59)	0.005
E/E' ≥13	1.61 (1.23-2.08)	0.008	1.40 (0.85-2.25)	0.18	1.73 (1.29-2.27)	0.003	0.35 (0.04-2.71)	0.32
LA volume index ≥33	1.45 (1.09-1.88)	0.010	1.26 (0.75-2.08)	0.38	1.48 (1.10-1.97)	0.011	1.64 (0.45 -5.83)	0.45
RWMA ≥1.04	1.70 (1.28-2.22)	<0.001	1.51 (0.93-2.41)	0.09	1.67 (1.23-2.23)	0.001	1.70 (0.45-6.21)	0.43
Any abnormal echocardiographic parameters	1.70 (1.33-2.14)	<0.001	1.61 (1.05-2.47)	0.03	1.75 (1.34-2.1258)	<0.001	1.13 (0.36- 3.54)	0.83
Combination of optimal cut-off of each predictors*								
RCRI ≥2 or LVEF <50%	1.82 (1.39-2.35)	<0.001	1.34 (0.81-2.18)	0.25	1.92 (1.43-2.54)	<0.001	1.69 (0.47-5.92)	0.42
RCRI ≥2 or NT-proBNP ≥301 ng/L	3.72 (2.73-4.96)	<0.001	3.37 (1.86-5.99)	<0.001	3.80 (2.70-5.25)	<0.001	3.15 (0.77-12.52)	0.10
RCRI ≥2 or NT-proBNP ≥301 ng/L or LVEF <50%	3.96 (2.88-5.33)	<0.001	3.80 (2.02-6.99)	<0.001	4.16 (2.92-5.81)	<0.001	5.32 (1.07-25.92)	0.041

The association of each risk predictor with clinical outcome is shown as adjusted relative risk (RR) with 95% confidence intervals (CIs). Significant univariate risk factors including significant univariate clinical factors-age, sex, functional status ≥3, diabetes, heart failure, stroke, evidence of ischemic heart disease or history of revascularization, emergency surgery, and vascular surgery; were included in multivariate logistic regression analysis. *Defined as at least one of three risk predictors is higher than cut-off values proBNP is one of best independent predictors of cardiovascular impairment as well as a marker of myocardial ischemia and heart failure, which might better reflect the complex pathophysiology of perioperative cardiovascular stress represented by a catecholamine surge with associated hemodynamic stress, systemic inflammation, and hypercoagulability.[16-18] On the other hand, E/E' is a specific marker for LV filling pressure which could be affected significantly by perioperative volume status.[19]

Integration of both NT-proBNP and echocardiographic parameters modestly improved the predictive power of the clinically determined risk, except for the risk of primary cardiovascular death {RR=5.3 (95% CI=1.1-25.9), p=0.041}. Therefore, these two risk predictors might provide complementary prediction in the high-risk event or death.[18] Investigation of the role of preoperative echocardiography in the high-risk group and comparison with biomarkers would be advisable in the near future.[16]

Our study is not free from its several limitations as described below. First, in our patient cohort, only 4.9% of patients had abnormal LV systolic function (LVEF <40%) and patient mean age was 68 years. All patients in our study were low-risk non high-risk patients for major noncardiac surgery. Therefore, these characteristics may limit the generalizability of our findings. Secondly, only patients who had undergone formal preoperative cardiovascular consultation were included. Thirdly, NT-proBNP and echocardiography were not evaluated on the same day. Fourthly, tissue Doppler study was done in only 59% of patients due to financial and clinical constraints. However, given the strength of our results, it is unlikely that enrollment of more patients or tissue Doppler study in more number of patients would have changed the main results of our study. Although it has been well validated and widely used in clinical practice, only the transmitral early diastolic velocity/tissue Doppler mitral annular early diastolic velocity (E/E') has been used for the evaluation of diastolic dysfunction. The recently developed new methods for the evaluation of diastolic dysfunction such as strain, strain rate and LV torsion have not been evaluated and would be of interest in future studies.

In conclusion, preoperative echocardiography was modestly predictive of perioperative cardiovascular events but was inferior to NT-proBNP. Moreover, it did not have incremental value to the clinically determined risk. Our results did not support the use of routine evaluation of echocardiography before noncardiac surgery. However, preoperative echocardiography before noncardiac surgery can provide independent information about the risk of postoperative cardiac complications in selected patients.

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