Prognostic Implications of Preoperative E/e′ Ratio in Patients with Off-pump Coronary Artery Surgery

Eun-Ho Lee, M.D.,* Sung-Cheol Yun, Ph.D.,† Ji-Hyun Chin, M.D.,‡ Dae-Kee Choi, M.D.,* Hyo-Jung Son, M.D.,§ Wook-Chong Kim, M.D.,* Seong-Soo Choi, M.D.,‖ Jun-Gol Song, M.D.,* Kyung-Don Hahm, M.D.,# Ji-Yeon Sim, M.D.,** In-Cheol Choi, M.D.††

ABSTRACT

Background: The ratio of early transmitral flow velocity to early diastolic velocity of the mitral annulus (E/e′) correlates with left ventricular (LV) filling pressure. In particular, an E/e′ ratio more than 15 is an excellent predictor of increased LV filling pressure. The authors evaluated the prognostic implications of preoperative estimated LV filling pressure, assessed by E/e′ ratio, in patients undergoing off-pump coronary artery bypass graft surgery.

Methods: This observational study investigated 1,048 consecutive adults undergoing elective off-pump coronary artery bypass graft surgery. The primary outcome was occurrence of major adverse cardiac events (MACE), defined as a composite of death, myocardial infarction, malignant ventricular arrhythmia, cardiac dysfunction, or need for new revascularization. Logistic regression and survival analyses were performed.

Results: An E/e′ ratio more than 15 was independently associated with 30-day MACE (odds ratio 2.4, 95% CI 1.4–3.9, $P = 0.001$) and 1-yr MACE (hazard ratio 2.1, 95% CI 1.4–3.1, $P = 0.001$), irrespective of underlying LV ejection fraction. MACE free 1-yr survival rate was significantly decreased in patients with E/e′ >15, irrespective of underlying LV ejection fraction.

Conclusions: Increased LV filling pressure, assessed by E/e′ ratio, is an independent predictor of 30-day and 1-yr MACE in patients who undergo elective off-pump coronary artery bypass graft surgery. These findings indicate that measurements of E/e′ may assist in preoperative risk stratification of these patients.

What We Already Know about This Topic

- The ratio of early transmitral flow velocity to early diastolic velocity of the mitral annulus (E/e′) correlates with left ventricular filling pressure
- The current study investigated whether an elevated left ventricular filling pressure, determined by a preoperative increased E/e′ (>15), would be associated with major adverse cardiac events after off-pump coronary artery bypass graft surgery

What This Article Tells Us That Is New

- Elevated left ventricular filling pressure, assessed by E/e′ ratio, is an independent predictor of 30-day and 1-yr major adverse cardiac events in patients who undergo elective off-pump coronary artery bypass graft surgery

DIASTOLIC dysfunction often occurs in patients undergoing surgery for coronary artery disease.[1,2] This dysfunction is related to abnormal left ventricular (LV) relaxation and filling during diastole, resulting in increased LV filling pressure and impairment of the ability of the heart to handle varying loading conditions.[3] Although increased LV filling pressure has been associated with higher morbidity and mortality after acute coronary syndrome[4,5] and cardiac surgery,[2,6,7] the prognostic implications of preoperatively increased LV filling pressure in patients undergoing coronary artery bypass surgery remain unclear.

During off-pump coronary artery bypass surgery (OPCAB), temporary occlusion of the coronary arteries during coronary anastomosis and displacement of the heart to expose the grafting site result in transient regional ischemia and hemodynamic deterioration.[8,9] Because these hemodynamic consequences are caused primarily by impaired filling and diastolic dysfunction of the right and left ventricles,[8,10] preexisting increased LV filling pressure may further aggra-

* Clinical Assistant Professor, Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea. † Assistant Professor, Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine. ‡ Clinical Fellow, Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine. § Clinical Fellow, Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, University of Ulsan College of Medicine. ‖ Resident, Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine. # Assistant Professor, Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine. ** Associate Professor, Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine. †† Professor, Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine.

Received from the Department of Anesthesiology and Pain Medicine and the Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea. Submitted for publication May 30, 2011. Accepted for publication October 21, 2011. Support was provided solely from institutional and/or departmental sources.

Address correspondence to Dr. Choi: Professor, Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, 388-1, Pungnap 2-dong, Songpa-gu, Seoul 138-736, Korea. icchoi@amc.seoul.kr. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

 Anesthesiology 2012; 116:362–71

vate intraoperative hemodynamic instability, resulting in poorer outcomes after surgery.[6]

Several echocardiographic indices, including transmitral flow patterns and deceleration time of early transmitral flow, are widely used for the noninvasive assessment of LV filling pressures.[11] Of these indices, the ratio of early transmitral flow velocity to early diastolic mitral annulus velocity (E/e′) has been shown to be the most accurate and relatively preload-independent noninvasive predictor of increased LV filling pressure.[12] This ratio has shown excellent reproducibility, with an E/e′ >15 found to be the best Doppler predictor of increased mean LV diastolic pressure and pulmonary artery wedge pressure.[12,13] In addition, an E/e′ >15 is a powerful predictor of poor survival after acute coronary syndrome and unoperated severe aortic stenosis[4,5,14] and is associated with significant hemodynamic derangement during grafting in OPCAB despite well-preserved LV systolic function.[6]

We therefore hypothesized that increased LV filling pressure, determined by a preoperative increased E/e′ (more than 15), would be associated with adverse outcomes after OPCAB. To test this hypothesis, we conducted an observational study to examine the relationship between preoperative E/e′ and the frequency of postoperative major adverse cardiac events (MACE) in patients undergoing OPCAB.

Materials and Methods

Study Population

This observational study, which was approved by our institutional ethics committee/review board (Seoul, Korea), included patients who had undergone primary OPCAB at a single institution between January 1, 2006, and September 30, 2009, and who had undergone both Doppler assessment of transmitral flow velocities and Doppler tissue imaging of the medial mitral valve annulus within 1 month before surgery. Patients who underwent emergency surgery or concomitant valvular or aortic surgery, and those who participated in another trial during that period were excluded, as were patients with grade ≥2/4 mitral regurgitation on echocardiography, those with a preoperative inotrope, intraaortic balloon pump or ventricular assist device support, and those with atrial fibrillation.

Clinical and Echocardiographic Data

Clinical data for all patients, including demographic data, comorbidities, laboratory data, medication use, anesthetic management, surgical techniques, postoperative management, and morbidity and mortality, were obtained from the Asan Medical Center Coronary Artery Bypass Surgery and Anesthesia Database and from a retrospective review of the computerized patient record system (Asan Medical Center Information System Electronic Medical Record). The Asan Medical Center Coronary Artery Bypass Surgery and Anesthesia Database was initiated in 2006 to provide continuous assessment and improvement of quality of care for all patients who undergo coronary artery bypass surgery at Asan Medical Center. This database contains comprehensive information on more than 100 variables, including demographic, clinical, laboratory, intraoperative, and outcome variables, collected prospectively by a research nurse who reviewed each patient's computerized medical records.

Transthoracic echocardiography was performed by experienced sonographers and reported by staff cardiologists with advanced training in echocardiography. Comprehensive two-dimensional and Doppler echocardiography, including Doppler tissue imaging, were performed using a Hewlett-Packard Sonos 2500 or 5500 imaging system equipped with a 2.5 MHz transducer (Hewlett-Packard, Andover, MA). LV end-systolic and end-diastolic volume and left ventricular ejection fraction (LVEF) were calculated by the biplane Simpson method.[15] Early transmitral inflow velocity (E), early deceleration time, and late transmitral inflow velocity were determined using conventional pulsed-wave Doppler echocardiography in the apical four-chamber view with 4-mm sample volume. Early diastolic mitral annular velocity (e′) was determined by pulsed wave Doppler tissue imaging from the same view, using a 4-mm sample volume located at the septal side of mitral annulus, and E/e′ ratio was acquired. Systolic pulmonary artery pressure was estimated as the sum of the right ventricular to right atrial pressure gradient during systole and the right atrial pressure, assigned a fixed value of 10 mmHg in this study. The right ventricular to right atrial peak systolic pressure gradient was estimated from the tricuspid regurgitation velocity by the modified Bernoulli equation.[16] Wall motion was assessed semiquantitatively by an experienced observer using a 16-segment, 4-point scale model of the LV, where 1 indicated normal motion; 2 indicated hypokinesia; 3 indicated akinesia; and 4 indicated dyskinesia.[15] Wall motion score index was assessed as the ratio between the sum of scores and the number of visualized segments.

As an E/e′ ratio more than 15 is usually considered indicative of increased LV filling pressure,[12,17] we performed analyses using this cutoff.

Intraoperative and Postoperative Management

General anesthesia was induced with a bolus IV injection of 0.2 mg/kg etomidate followed by 0.8 mg/kg rocuronium to facilitate orotracheal intubation and a continuous infusion of remifentanil and propofol using a target controlled infusion pump (Orchestra® Base Primea; Fresenius Kabi, Brezins, France). During the surgery, anesthesia was maintained with a continuous infusion of remifentanil and propofol, both of which were stopped at the end of surgery. Core temperature was kept above 36.0°C using a forced-air warming system. To maintain cardiac preload, intravascular volume was replaced with 0.9% saline or 6% hydroxyethyl starch 130/0.4 (Voluven®, Fresenius-Kabi, Bad Homburg, Germany). An agent such as phenylephrine, dopamine, or norepinephrine

was administered when mean arterial pressure and/or cardiac index decreased despite optimization of circulating blood volume. Packed erythrocytes were transfused when hemoglobin concentration was less than 8 g/dL. A cell salvage device (AUTOLOG, Medtronic Inc, Minneapolis, MN) was used in all patients, and salvaged blood was reinfused before the end of surgery. Heparin was administered at a dose of 150 IU/kg to achieve a target activated clotting time of 250–350 s before dissection of the internal mammary artery. Activated clotting time assessments were repeated every 30 min, with heparin added as required. On completion of all anastomoses, protamine was administered to reverse the effects of heparin and return the activated clotting time to preoperative levels. From the time of incision to chest closure, all patients received a continuous intravenous infusion of isosorbide dinitrate and a calcium channel blocker such as diltiazem.

Surgical procedures were performed by five experienced academic surgeons similarly competent in OPCAB surgery. Median sternotomy was performed in all patients. A commercially available stabilizing system (Guidant, Santa Clara, CA or Medtronic OPCAB system, Minneapolis, MN) was used to facilitate coronary anastomosis, and carbon dioxide was insufflated to enhance visualization during surgery. Whenever possible, the left internal thoracic artery was preferentially used to graft the left anterior descending artery and an intracoronary shunt was inserted into the coronary artery for each anastomosis, which was 1.5–2.5 mm in size according to the coronary artery lumens. Coronary artery bypass was achieved with either arterial or saphenous vein grafts, with complete myocardial revascularization being the primary surgical goal for each patient.

After surgery, all patients were transferred to the intensive care unit (ICU) and were ventilated with 60% O_2 in air with volume-controlled ventilation and a tidal volume of 10 ml/kg with 5 cm H_2O of positive end-expiratory pressure. The fractional inspired oxygen tension and respiratory rate of the ventilator were adjusted according to the results of blood gas analysis to maintain partial pressure of alveolar oxygen (Pa_{O_2}) between 80 and 100 mmHg and partial pressure of alveolar carbon dioxide (Pa_{CO_2}) between 35 and 40 mmHg. Patients were extubated when their hemodynamics were stable, there was no excessive bleeding (<100 ml/h), temperature was >36°C, they breathed spontaneously, and their blood gases were adequate (Pa_{O_2} >80 mmHg and Pa_{CO_2} <45 mmHg). Fluid management consisted of infusion of 5% dextrose with additional colloid solution or blood to maintain normovolemia and hemoglobin more than 9 g/dL and to correct blood coagulation. Electrolyte imbalances were promptly treated to within the normal ranges. Inotropic and vasopressor agents were used as necessary to maintain hemodynamics within the normal ranges. Patients were discharged from the ICU to the general ward when their clinical status became stabilized and further ICU monitoring and care were not required.

Clinical Outcome and Follow-up

Nonfatal major adverse cardiac events and death were recorded postoperatively during in-hospital stay and within 1 yr after surgery. Data were obtained until September 2010 during annual visits to the outpatient clinic and by a detailed review of all medical records or by telephone interviews. The last evaluation of patient survival status was performed in September 2010.

The primary endpoint of the study was the occurrence of MACE at 30 days and within 12 months after surgery because expected incidence for a single adverse cardiac event in our population is low. MACE was defined as the composite outcome of any one or more of the following: death, myocardial infarction, malignant ventricular arrhythmia, cardiac dysfunction, or need for new revascularization. A patient experiencing more than one single event was counted only once in the composite outcome.

Mortality was defined as death from any cause within 12 months of primary OPCAB surgery. Myocardial infarction was defined as increases in cardiac biomarkers (troponin I or creatinine kinase-MB) to more than five times the normal reference range, plus either new pathologic Q wave or new left bundle branch block, angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium during the first 72 h after OPCAB, and as increases of cardiac biomarkers with ≥1, together with either symptoms of ischemia, new ischemic electrocardiographic changes, or imaging evidence of new loss of myocardium within 12 months after surgery.[18] Malignant ventricular arrhythmia was defined as sustained ventricular tachycardia or fibrillation that occurred during the postoperative period and/or within 12 months after surgery. Sustained ventricular tachycardia was defined as consecutive premature ventricular contractions at a rate of more than 100/min, were sustained for more than 30 s and required treatment with cardioversion or antiarrhythmic agents. Ventricular fibrillation was defined by its characteristic electrocardiographic appearance. Cardiac dysfunction was defined as hemodynamic instability requiring conversion to cardiopulmonary bypass during surgery or new placement of an intraaortic balloon pump or ventricular assist device during the intraoperative or postoperative period and as clinical signs of congestive heart failure (fluid retention, oliguria, basilar rales, and persistent chest infiltration requiring diuretic agents) requiring rehospitalization within 12 months of surgery. The need for new revascularization was defined as coronary artery bypass grafting or percutaneous coronary intervention within 12 months of surgery. The presence or absence of MACE was judged by two experts who were blinded to echocardiographic data. In the case of disagreement, a third blinded expert participated in a discussion with the first two, and a consensus was reached.

For validation of complete follow-up data regarding mortality, information about vital status, dates, and causes of death were obtained from the National Population Registry of the Korea National Statistical Office using a unique personal identification number for each patient.

Statistical Analysis

Categorical variables are presented as frequencies and percentages, and continuous variables as mean ± SD or medians with ranges. Between-group differences in baseline clinical and surgical characteristics and postoperative outcomes were compared using independent Student *t* test or the Mann–Whitney rank-sum U test for continuous variables and the chi-square test or Fisher exact test for categorical variables, as appropriate.

Table 1. Baseline Demographic and Clinical Characteristics According to E/e′ Ratio

—	E/e′ ≤15	E/e′ >15	*P* Value
No.	744	304	
Demographics			
Age (yr)	63 [56–69]	67 [62–72.8]	<0.001
Female, n	143 (19.2)	115 (37.8)	<0.001
Clinical characteristics			
BMI (kg/m^2)	24.6 ± 2.7	24.9 ± 3.0	0.191
EuroSCORE (L)	1.7 [1.2–2.8]	2.8 [1.8–4.8]	<0.001
Laboratory data			
Hematocrit (%)	39.6 [36.0–42.2]	36.6 [32.9–40.2]	<0.001
Creatinine (mg/dl)	0.9 [0.8–1.1]	1.0 [0.8–1.3]	<0.001
Albumin (g/dl)	3.8 [3.6–4.1]	3.6 [3.3–4.0]	<0.001
C-reactive protein (mg/dl)*	0.2 [0.1–0.4]	0.2 [0.1–0.8]	0.006
Echocardiographic variables			—
LVEF (%)	60 [55–64]	58 [46–63]	<0.001
E/e′ ratio	11 [10–13]	19 [17–22]	<0.001
LA size (mm)	39 [36–42]	41 [38–44]	<0.001
LV end systolic volume (ml)	37 [29–50]	42 [29–62]	<0.001
LV end diastolic volume (ml)	95 [79–113]	98 [78–128]	0.005
LV mass index (g/m^2)	100.3 [86.6–117.9]	114.0 [93.1–136.7]	<0.001
Deceleration time (ms)*	217 [185–248]	215 [185–245]	0.472
E/A ratio*	0.83 [0.67–1.01]	0.81 [0.67–1.07]	0.403
sPAP (mmHg)*	31 [28–35]	35 [29–41]	<0.001
Wall motion score index	1.0 [1.0–1.4]	1.2 [1.0–1.7]	<0.001
Medical history			
Diabetes mellitus	299 (40.2)	189 (62.2)	<0.001
Hypertension	438 (58.9)	226 (74.3)	<0.001
Previous MI	124 (16.7)	59 (19.4)	0.289
Congestive heart failure	11 (1.5)	15 (4.9)	0.001
Cerebrovascular disease	120 (16.1)	78 (25.7)	<0.001
Peripheral vascular disease	19 (2.6)	13 (4.3)	0.141
COPD	51 (6.9)	16 (5.3)	0.339
s/p PTAC c stent	151 (20.3)	58 (19.1)	0.655
Hypercholesterolemia	572 (76.9)	235 (77.3)	0.883
Renal dysfunction	50 (6.7)	50 (16.4)	<0.001
Left main disease	162 (21.8)	61 (20.1)	0.539
Smoker, current	180 (24.2)	62 (20.4)	0.214
Medication			
ACEI or ARB	261 (35.1)	135 (44.4)	0.005
β-blocker	455 (61.2)	190 (62.5)	0.685
CCB	537 (72.2)	213 (70.1)	0.492
Diuretics	99 (13.3)	76 (25.0)	<0.001
Aspirin	519 (69.8)	207 (68.1)	0.596
Clopidogrel	386 (51.9)	161 (53.0)	0.751
Statins	453 (60.9)	189 (62.2)	0.751
Intraoperative data			—
Grafts per patients, n	3.1 ± 1.0	2.9 ± 1.0	0.012
Operation time (min)	230 [190–280]	220 [185–270]	0.597
Total crystalloid (L)	1.4 [1.1–1.8]	1.3 [1.0–1.7]	0.08
Total colloid (L)	1.1 [1.0–1.5]	1.0 [0.8–1.4]	<0.001
p-e (unit)	0 [0–2.0]	1.5 [0–2.0]	<0.001

Data are expressed as number of patients (%), mean ± SD, or median [first-third quartiles].

* C-reactive protein, deceleration time, E/A ratio, and systolic pulmonary artery pressure were available only in 1,001 (95.5%), 1,017 (97%), 1,030 (98.3%), and 825 (78.7%) patients, respectively.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CCB = calcium channel blocker; COPD = chronic obstructive pulmonary disease; E/A ratio = ratio of early to atrial inflow velocity; E/e′ = ratio of early transmitral flow velocity to early diastolic mitral annulus velocity; EuroSCORE (L) = logistic European System for Cardiac Operative Risk Evaluation; LA = left atrium; LV = left ventricle; LVEF = left ventricle ejection fraction; MI = myocardial infarction; p-e = packed erythrocyte; PTCA c stent = percutaneous transluminal catheter angioplasty with stent insertion; sPAP = systolic pulmonary artery pressure.

Between-group differences in 30-day and 1-yr outcomes were analyzed in all patients as well as in subgroups according to LVEF (*a priori*). Univariate and multivariable logistic regression analyses were performed to evaluate the effects of E/e′ ratio on 30-day MACE. All variables in table 1 were tested and variables with a P value ≤0.10 in univariate analyses (*i.e.*, age, sex, body mass index, smoking, hypercholesterolemia, peripheral vascular disease, renal dysfunction, EuroSCORE, left main disease, preoperative serum albumin level, LVEF, left atrial size, LV end-systolic volume, systolic pulmonary artery pressure, wall motion score index, use of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, use of β-blockers, number of grafted vessels, and surgery time) were included in the multivariable logistic model. Because history of congestive heart failure is a risk factor for perioperative morbidity and mortality, it was forced into the final model. A backward elimination process was used to develop the final multivariable model, and adjusted odds ratios (ORs) with 95% CIs were calculated.

In addition, multivariate Cox proportional hazards regression models were used to estimate adjusted hazard ratios for the association between E/e′ ratio and 1-yr MACE. Potential independent predictors of outcome were identified by univariate analyses. LV dysfunction categories and some important risk covariates (age, sex, body mass index, smoking, hypercholesterolemia, peripheral vascular disease, renal dysfunction, EuroSCORE, left main disease, preoperative serum albumin level, LVEF, left atrial size, systolic pulmonary artery pressure, wall motion score index, use of β-blockers, and number of grafted vessels), which were significantly ($P \leq 0.10$) associated with 1-yr MACE on univariate analysis, were candidates for the multivariable Cox proportional hazards models. History of congestive heart failure was also forced into the final model. A backward elimination process was used to develop the final multivariable model, and adjusted hazard ratios with 95% CIs were calculated. The proportional hazards assumption was confirmed by testing of partial (Schoenfeld) residuals, and no relevant violation were found. Cumulative MACE free 1-yr survival was calculated by the Kaplan–Meier method, and differences between curves were compared using the log-rank test.

To decrease the effect of potential confounding in this observational study, we also rigorously adjusted for significant differences in patient characteristics by using weighted logistic regression models and weighted Cox proportional hazards regression models with the inverse probability of treatment weighting.[19] Weights for patients with E/e′ ratio more than 15 were the inverse of 1— propensity score, and weights for patients with E/e′ ratio ≤15 were the inverse of propensity score. All propensity scores were estimated without regard to outcomes, using multiple logistic regression analysis. A full model included all variables in table 1. Model discrimination was assessed using the C statistic, and model calibration was evaluated using Hosmer-Lemeshow statistics. In overall data, the model was well calibrated (Hosmer-Lemeshow test; $P = 0.30$) with reasonable discrimination (C statistic = 0.93).

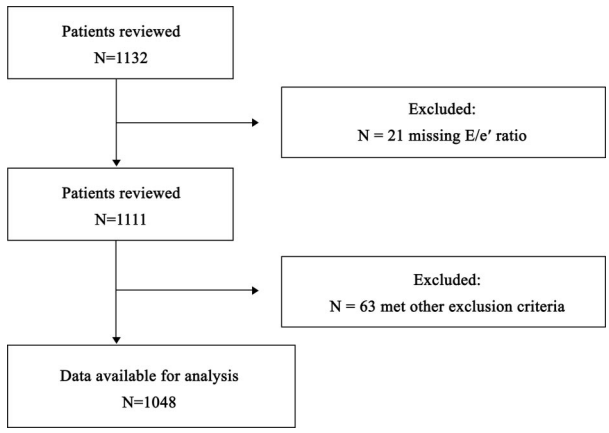

Fig. 1. Study inclusion/exclusion flow diagram.

All reported P values are two-sided, and values of $P < 0.05$ were considered statistically significant. Data manipulation and statistical analyses were performed using SAS® Version 9.1 (SAS Institute Inc., Cary, NC).

Results

A total of 1,132 patients underwent OPCAB during the 45-month study period. After excluding patients without preoperative E/e′ ratio data (n = 21), or who met any of the exclusion criteria (n = 63), we included data from the remaining 1,048 patients (fig. 1). These 1,048 patients consisted of 790 men (75%) and 258 women (25%) with a mean age of 63.5 ± 11.0 yr. Preoperative echocardiograms were obtained a mean 6.6 ± 5.3 days before surgery.

The baseline demographic, echocardiographic, and clinical characteristics of the study population categorized according to E/e′ ratio are shown in table 1. Of the 1,048 patients, 304 (29%) had an E/e′ ratio more than 15. These patients were older, more likely to be female, and had higher EuroSCORE than patients with an E/e′ ratio ≤15. Patients with an E/e′ ratio more than 15 were also more likely to have histories of diabetes, hypertension, cerebrovascular disease, and renal dysfunction. Compared with patients having an E/e′ ratio ≤15, those with an E/e′ ratio more than 15 were more likely to have a lower LVEF and a larger left atrial size, LV mass index, and LV end systolic and diastolic volume as well as higher systolic pulmonary artery pressure and wall motion score index. However, these differences, although statistically significant, were clinically irrelevant.

Postoperative outcomes are shown in table 2. Postoperative extubation time, ICU stay, and hospital stay were longer in patients with an E/e′ ratio more than 15 than in those with an E/e′ ratio ≤15. After 30 days, 80 patients (7.6%) had MACE, including 11 who died, 58 who had myocardial infarction, 10 who had malignant ventricular arrhythmia, 11 who had cardiac dysfunction, and 7 who needed new revas-

Table 2. Postoperative Outcomes Stratified by E/e′ Ratio

—	E/e′ ≤15	E/e′ >15	*P* Value
Extubation time (h)	8.0 [6.0–12.1]	9.1 [7.0–13.3]	<0.001
ICU stay (days)	2.3 ± 1.8	2.9 ± 5.0	0.003
Use of inotropes	609 (81.9)	251 (82.6)	0.854
Duration of inotropic support (h)	36.0 [10.0–47.0]	36.0 [8.3–50.0]	0.362
Hospital stay (days)	8.8 ± 6.9	11.4 ± 13.8	<0.001
Postoperative weight gain (%)	0.9 [0.1–1.8]	0.9 [0–1.8]	0.965
30-day			
MI	37 (5.0)	21 (6.9)	0.274
Ventricular arrhythmia	3 (0.4)	7 (2.3)	0.012
Cardiac dysfunction	6 (0.8)	5 (1.7)	0.382
New revascularization	5 (0.7)	2 (0.7)	0.697
Death	3 (0.4)	8 (2.6)	0.004
1-yr			
MI	41 (5.5)	24 (7.9)	0.190
Ventricular arrhythmia	3 (0.4)	7 (2.3)	0.012
Cardiac dysfunction	8 (1.1)	6 (2.0)	0.394
New revascularization	8 (1.1)	4 (1.3)	0.990
Death	10 (1.3)	11 (3.6)	0.032

Data are expressed as number of patients (%), mean ± SD, or median [first-third quartiles].
E/e′ = ratio of early transmitral flow velocity to early diastolic mitral annulus velocity; ICU = intensive care unit; MI = myocardial infarction.

cularization. In total, MACE occurred within 30 days in 43 patients (5.8%) with an E/e′ ratio ≤15 and in 37 patients (12.2%) with an E/e′ ratio more than 15 (table 3). Multivariable logistic regression analyses demonstrated that an E/e′ ratio more than 15 was independently associated with 30-day MACE (OR 2.4; 95% CI 1.4–3.9; $P = 0.001$). Other risk factors associated with 30-day MACE were body mass index (OR 0.9; 95% CI 0.8–0.9; $P = 0.011$), current smoking (OR 2.7; 95% CI 1.5–4.9; $P = 0.001$), left main disease (OR 2.7; 95% CI 1.6–4.5, $P = 0.001$), preoperative treatment with β-blockers (OR 2.3; 95% CI 1.3–4.0; $P = 0.005$), number of grafted vessels (OR 0.5; 95% CI 0.4–0.7; $P < 0.001$), and operation time (OR 1.01; 95% CI 1.004–1.010; $P < 0.001$).

At 1-yr follow up, 100 patients (9.5%) had MACE, including 21 who died, 65 who had myocardial infarction, 14 who had cardiac dysfunction, and 12 who required revascularization. In total, 1-yr MACE occurred in 55 patients (7.4%) with an E/e′ ratio ≤15 and 45 patients (14.8%) with an E/e′ ratio more than 15. Multivariable Cox proportional hazards regression analyses demonstrated that an E/e′ ratio more than 15 was independently associated with 1-yr MACE (HR 2.1; 95% CI 1.4–3.1; $P = 0.001$). Other risk factors associated with 1-yr MACE were peripheral vascular disease (HR 2.8; 95% CI 1.4–5.7; $P = 0.005$), left main disease (HR 2.2; 95% CI 1.5–3.4; $P = 0.001$), and number of grafted vessels (HR 0.7; 95% CI 0.6–0.9; $P = 0.001$).

After inverse probability of treatment weighting adjustment, patients with E/e′ ratio more than 15 continued to have significantly higher 30-day (OR 1.9; 95% CI 1.1–3.1; $P = 0.015$) and 1-yr (HR 1.9; 95% CI 1.2–3.2; $P = 0.013$) risks of MACE.

To determine whether these effects were due to abnormal LV systolic function, we separately assessed the prognostic effects of E/e′ ratio in patients with preserved (LVEF ≥50%) and reduced (LVEF less than 50%) LV systolic function. An E/e′ ratio more than 15 was independently related to both 30-day and 1-yr MACE, both in patients with LVEF ≥50% and less than 50% (table 3). Other risk factors associated with 30-day MACE in patients with preserved LV systolic function were left main disease (OR 2.6; 95% CI 1.5–4.7; $P = 0.001$), preoperative treatment with β-blockers (OR 2.3; 95% CI 1.2–4.5; $P = 0.016$), and number of grafted vessels (OR 0.7; 95% CI 0.5–0.9; $P = 0.004$). Other risk factors associated with 30-day MACE in patients with reduced LV systolic function were current smoking (OR 6.6; 95% CI 1.5–27.9; $P = 0.011$), left main disease (OR 5.2; 95% CI 1.6–17.3, $P = 0.007$), peripheral vascular disease (OR 9.3; 95% CI 1.4–62.5; $P = 0.021$), intraoperative transfusion of packed erythrocytes (OR 1.6; 95% CI 1.1–2.5; $P = 0.027$), and longer operation time (OR 1.01; 95% CI 1.003–1.016; $P = 0.003$). In addition to E/e′ ratio more than 15, other risk factors associated with 1-yr MACE in patients with preserved LV systolic function were peripheral vascular disease (HR 3.4; 95% CI 1.5–8.1; $P = 0.004$) and left main disease (HR 2.3; 95% CI 1.4–3.8; $P = 0.001$), and other risk factors associated with 1-yr MACE in patients with reduced LV systolic function were current smoking (HR 3.8; 95% CI 1.4–10.0; $P = 0.007$), peripheral vascular disease (HR 4.0; 95% CI 1.1–14.1; $P = 0.032$), and left main disease (HR 2.7; 95% CI 1.1–6.4; $P = 0.025$).

The 1-yr MACE free survival rate was significantly decreased in patients with E/e′ >15 than with E/e′ ≤15, both in patients with LVEF ≥50% ($P = 0.024$) and LVEF less than 50% ($P = 0.007$) (fig. 2).

Table 3. Association between E/e′ ratio and 30-day and 1-yr MACE

—	No. (%)						
—	E/e′ ≤15	E/e′ >15	Unadjusted	Multivariable Adjusted	*P* Value	IPTW Adjusted	*P* Value
30-day MACE	—	—	Odds ratio (95% CI)*		—	—	—
Overall	43/744 (5.8)	37/304 (12.2)	2.6 (1.4–3.6)	2.4 (1.4–3.9)	0.001	1.9 (1.1–3.1)	0.015
LVEF ≥50%	34/621 (5.5)	22/214 (10.3)	2.0 (1.1–3.5)	2.3 (1.3–4.3)	0.006	—	—
LVEF <50%	9/123 (7.3)	15/90 (16.7)	2.5 (1.1 – 6.1)	3.7 (1.1–11.9)	0.029	—	—
1-yr MACE	—	—	Hazard ratio (95% CI)†		—	—	—
Overall	55/744 (7.4)	45/304 (14.8)	2.1 (1.4–3.1)	2.1 (1.4–3.1)	0.001	1.9 (1.2–3.2)	0.013
LVEF ≥50%	45/621 (7.3)	26/214 (12.2)	1.7 (1.1–2.8)	1.5 (1.1–4.5)	0.013	—	—
LVEF <50%	10/123 (8.1)	19/90 (21.1)	2.7 (1.3–5.9)	2.3 (1.1–5.2)	0.046	—	—

Odds ratios and hazard ratios are for the E/e′ >15 group relative to the E/e′ ≤15 group.

* Odds ratios are adjusted for LVEF; body mass index, left main disease, smoking, preoperative medication (β-blocker), number of grafted vessels, and operation time. † Hazard ratios are adjusted for LVEF; peripheral vascular disease, left main disease, and number of grafted vessels.

CI = confidence interval; E/e′ = ratio of early transmitral flow velocity to early diastolic mitral annulus velocity; IPTW = inverse probability of treatment weighting; LVEF = left ventricular ejection fraction; MACE = major adverse cardiac event.

Discussion

This large observational study showed that increased preoperative LV filling pressure, defined as E/e′ >15, was associated with increased risks of 30-day and 1-yr MACE after OPCAB.

Increased LV filling pressure has been shown to be an independent risk factor for cardiovascular complications after major cardiovascular and vascular surgery.[2,6,20–24] Although LV filling pressure can be measured by placing a catheter in the LV (LV end-diastolic pressure) or pulmonary artery (pulmonary capillary wedge pressure), this invasive approach is not suitable for daily clinical practice. Doppler echocardiography is an established and widely available method for assessing LV filling pressure.[11] Although conventional Doppler techniques, including measurements of transmitral flow velocities and deceleration time of early transmitral flow, have been widely used for the noninvasive assessment of LV diastolic filling patterns, these measurements are greatly affected by loading conditions, heart rate, and rhythm disturbances.[25,26] E/e′ has been shown to be a good approximation of LV filling pressure under various conditions, including sinus tachycardia, preserved or depressed LV systolic function, mitral regurgitation secondary to ischemic or dilated cardiomyopathy, and LV hypertrophy.[11,12,27–31] Although E/e′ >15 is considered the best Doppler predictor of increased LV filling pressure,[12,13] few studies have assessed postoperative outcomes of patients with preoperatively increased E/e′.[6,7,24]

We have shown here that preoperative E/e′ >15 was associated with increased 30-day and 1-yr cardiovascular risks in patients undergoing OPCAB, even after adjustment for confounders. Postoperative extubation time, ICU stay, and hospital stay were longer in patients with E/e′ ratio more than 15 than in those with E/e′ ratio ≤15, results consistent with those of recent studies assessing the relationship between preoperative increased E/e′ and adverse outcomes of cardiac surgery.[6,7,24] For example, evaluation of the relationship between preoperative E/e′ value and intraoperative hemodynamic changes and postoperative outcomes in 50 patients with preserved systolic LV function undergoing OPCAB found that, compared with patients with

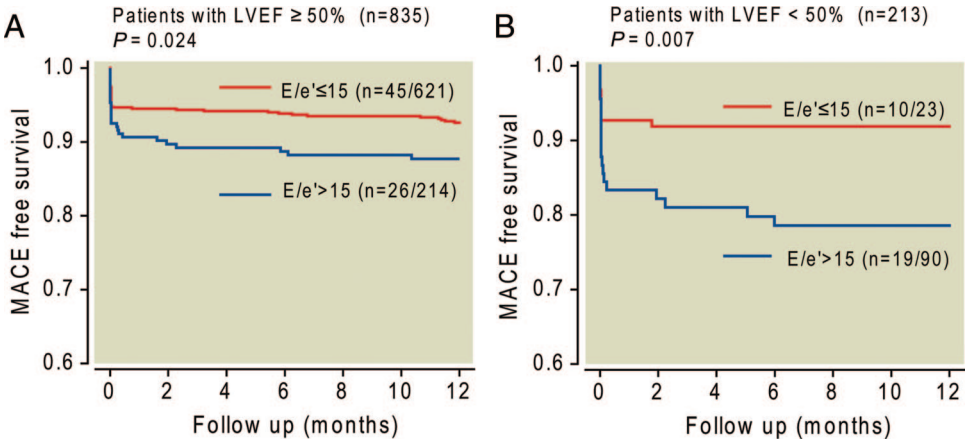

Fig. 2. One-year major adverse cardiac event (MACE) free survival in patients with left ventricular ejection fraction (LVEF) ≥ 50% and LVEF <50% undergone off-pump bypass graft as stratified by E/e′ cutoff of 15. There was significantly lower 1-yr MACE free survival rate in patients with E/e′ >15 compared with patients with E/e′ ≤15 among both subjects with LVEF ≥50% (*A*) and subjects with LVEF <50% (*B*).

E/e′ <8, patients with E/e′ >15 were more likely to develop a significant reduction in cardiac index and mixed venous oxygen saturation during grafting.[6] These values did not return to baseline levels after the completion of grafting and required significantly larger amounts of norepinephrine to maintain mean arterial pressure during surgery, a longer time to extubation, and a longer length of stay in the ICU.[6] Similarly, multivariate analysis of the relationship between preoperative E/e′ and postoperative adverse outcomes in 210 patients who underwent isolated aortic valve replacement showed that, after adjustment for confounders, E/e′ >12 was associated with an increase in midterm postoperative cardiovascular events, including heart failure, embolic cerebral infarction, and cardiac death (HR 40.8; 95% CI 39.0–41.68; $P < 0.001$).[7] Furthermore, multivariate analysis of the prognostic value of E/e′, obtained by transesophageal echocardiography before surgical repair, on early morbid events in 205 patients undergoing cardiac surgery found that, after adjusting for confounders, increased E/e′ (≥8) was significantly associated with prolonged ICU stay and the need for inotropic support.[24] Consistent with these findings, our results indicate that preoperatively increased E/e′ is an important risk factor for short- and intermediate-term cardiovascular complications in patients undergoing OPCAB.

LV systolic function is a major prognostic marker for adverse events after OPCAB, and patients with preserved LV systolic function are usually considered at low risk for these adverse events.[32] Our findings, however, suggest that E/e′ may provide additional prognostic information, especially in patients with preserved LV systolic function. This finding is consistent with those of previous studies, which found that, in patients with acute myocardial infarction and unoperated severe aortic stenosis, E/e′ was a significant predictor of adverse outcomes, independent of LVEF, and was the echocardiographic parameter most predictive of increased cardiac risk.[4,14]

In contrast to previous studies, which showed that perioperative treatment with β-blockers had a cardioprotective effect, we found that preoperative treatment with β-blockers was significantly associated with increased 30-day MACE.[33,34] The beneficial effects of β-blocker on postoperative outcomes, however, may depend on their pattern of perioperative administration or intraoperative hemoglobin concentration.[35,36] Perioperative withdrawal from β-blockers or surgical anemia in patients being treated with β-blockers may increase the risks of postoperative cardiac morbidity and mortality, thus explaining our finding that preoperative β-blocker therapy had harmful effects on 30-day cardiac morbidity and mortality. Unfortunately, however, our database contains no information on the pattern of use or dosage of perioperative β-blockers or on intraoperative hemoglobin concentration. Therefore, it is necessary to investigate the relationship among these confounding factors, preoperative β-blocker therapy, and postoperative outcomes.

Increased LV filling pressure, as shown by E/e′ >15, may predispose patients to MACE after OPCAB for several reasons. First, increased LV filling pressure is usually related to LV pressure overload, which predisposes to ventricular remodeling, cardiac neurohormonal activation, systemic inflammation, and increased excitability, all of which would be expected to adversely affect patient outcomes.[3,37–40]

Second, patients with increased LV filling pressure commonly have increased myocardial wall stress, which may precipitate energy imbalance and myocardial ischemia,[37] making these patients susceptible to perioperative myocardial damage. In addition, even if systolic function is normal, the cardiovascular systems of patients with increased LV filling pressure are more sensitive to acute changes in perioperative loading conditions. This may make them more prone to the development of hypovolemia, which can cause tachycardia with a concomitant reduction in coronary perfusion, leading to further myocardial damage during OPCAB.[41]

Third, exposure of the grafting site and facilitation of coronary anastomosis during OPCAB require displacement of the heart and compression of the myocardial wall, resulting in significant hemodynamic consequences due primarily to impaired filling and diastolic dysfunction of the right and left ventricles.[8,10] Although these hemodynamic disturbances are usually transient and well tolerated, patients with preexisting increased LV filling pressure are more likely to develop significant hemodynamic instabilities, which may further aggravate myocardial injury during grafting.[6]

This study had several limitations. First, it was a nonrandomized, observational study. We considered many variables thought to affect outcome because observational studies with adequate multivariate analysis can provide valuable information. Nevertheless, because multivariate analysis cannot consider all factors, other hidden factors in patients undergoing OPCAB may have influenced our results. In addition, although subgroup analyses can provide valuable information, this approach was associated with some caveats, such as the occurrence of false-positive or false-negative effects, chance differences in observed effects, lack of power to perform the analysis, and issues relating to multiple statistical testing.[42] These results therefore need to be interpreted with caution. Second, although we discussed a possible relationship between hemodynamic disturbances and increased LV filling pressure, the exact intraoperative hemodynamic information on our study population was not available. Therefore, further studies are warranted to determine whether increased LV filling pressure, as assessed by E/e′ ratio, is associated with intraoperative hemodynamic instability and whether E/e′ ratio can provide additional information to intraoperative hemodynamic variables. Third, all echocardiographic data were acquired by several sonographers and cardiologists. Thus, we cannot exclude some interobserver variability in echocardiographic data that may have confounded our results. Fourth, although e′ is associated with global LV diastolic filling pattern, it is a regional index. Therefore, the E/e′ ratio may be influenced by regional wall motion abnormalities at the Doppler sampling site. Because only septal mitral annular velocity has been routinely measured in our hospital, our Doppler tissue imaging measurements were limited, being only at the septal site. Thus, our results may not be generalized to Doppler tissue

imaging values obtained from the lateral mitral annulus, which may provide additional information.[31,43,44] Because e′ obtained from the lateral mitral annulus tends to be higher and lateral E/e′ tends to be lower than those from septal mitral annulus, different cutoff values need to be applied on the basis of e′ location.[11,12,43] In addition, we cannot exclude the possibility that the septal E/e′ ratio may have been affected by tethering to the right ventricle and other structures in the middle of the heart. Thus, these data should be interpreted with caution. Finally, like other Doppler, clinical, and hemodynamic variables, E/e′ reflects LV filling pressures at the time of measurement, which may be affected by a variety of factors, including administration of drug or loading condition during the perioperative period. In addition, although E/e′ is the Doppler parameter most prognostic in patients undergoing OPCAB, a single measurement alone may not provide maximal prognostic information.

Conclusions

We found that patients with E/e′ >15 were at significantly greater risk of 30-day and 1-yr MACE, independent of LVEF, than patients with E/e′ ≤15. Our findings suggest that E/e′ ratio may provide additional prognostic information over baseline systolic function in patients undergoing OPCAB. Therefore, measurements of E/e′ may assist in preoperative risk stratification of patients in this setting.

The authors thank Bo-Young Hwang, M.D., Clinical Fellow, Department of Anesthesiology and Pain Medicine, Asan Medical Center, Seoul, Korea, for valuable contributions to data collection.

References

1. Djaiani GN, McCreath BJ, Ti LK, Mackensen BG, Podgoreanu M, Phillips-Bute B, Mathew JP: Mitral flow propagation velocity identifies patients with abnormal diastolic function during coronary artery bypass graft surgery. Anesth Analg 2002; 95:524–30
2. Salem R, Denault AY, Couture P, Blisle S, Fortier A, Guertin MC, Carrier M, Martineau R: Left ventricular end-diastolic pressure is a predictor of mortality in cardiac surgery independently of left ventricular ejection fraction. Br J Anaesth 2006; 97:292–7
3. Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, Brosnihan B, Morgan TM, Stewart KP: Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA 2002; 288:2144–50
4. Hillis GS, Mller JE, Pellikka PA, Gersh BJ, Wright RS, Ommen SR, Reeder GS, Oh JK: Noninvasive estimation of left ventricular filling pressure by E/e' is a powerful predictor of survival after acute myocardial infarction. J Am Coll Cardiol 2004; 43:360–7
5. Richardson-Lobbedez M, Marchaux S, Bauters C, Darchis J, Auffray JL, Bauchart JJ, Aubert JM, LeJemtel TH, Lesenne M, Van Belle E, Goldstein P, Asseman P, Ennezat PV: Prognostic importance of tissue Doppler-derived diastolic function in patients presenting with acute coronary syndrome: A bedside echocardiographic study. Eur J Echocardiogr 2008; 9:594–8
6. Shim JK, Choi YS, Chun DH, Hong SW, Kim DH, Kwak YL: Relationship between echocardiographic index of ventricular filling pressure and intraoperative haemodynamic changes during off-pump coronary bypass surgery. Br J Anaesth 2009; 102:316–21
7. Chang SA, Park PW, Sung K, Lee SC, Park SW, Lee YT, Oh JK: Noninvasive estimate of left ventricular filling pressure correlated with early and midterm postoperative cardiovascular events after isolated aortic valve replacement in patients with severe aortic stenosis. J Thorac Cardiovasc Surg 2010; 140:1361–6
8. Mathison M, Edgerton JR, Horswell JL, Akin JJ, Mack MJ: Analysis of hemodynamic changes during beating heart surgical procedures. Ann Thorac Surg 2000; 70:1355–60; discussion 60–1
9. George SJ, Al-Ruzzeh S, Amrani M: Mitral annulus distortion during beating heart surgery: A potential cause for hemodynamic disturbance–a three-dimensional echocardiography reconstruction study. Ann Thorac Surg 2002; 73:1424–30
10. Chassot PG, van der Linden P, Zaugg M, Mueller XM, Spahn DR: Off-pump coronary artery bypass surgery: Physiology and anaesthetic management. Br J Anaesth 2004; 92:400–13
11. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A: Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009; 22:107–33
12. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, Tajik AJ: Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation 2000; 102: 1788–94
13. Talreja DR, Nishimura RA, Oh JK: Estimation of left ventricular filling pressure with exercise by Doppler echocardiography in patients with normal systolic function: A simultaneous echocardiographic-cardiac catheterization study. J Am Soc Echocardiogr 2007; 20:477–9
14. Biner S, Rafique AM, Goykhman P, Morrissey RP, Naghi J, Siegel RJ: Prognostic value of E/E' ratio in patients with unoperated severe aortic stenosis. JACC Cardiovasc Imaging 2010; 3:899–907
15. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I, et al: Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989; 2:358–67
16. Sorrell VL, Reeves WC: Noninvasive right and left heart catheterization: Taking the echo lab beyond an image-only laboratory. Echocardiography 2001; 18:31–41
17. Paulus WJ, Tschpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbly A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL: How to diagnose diastolic heart failure: A consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007; 28:2539–50
18. Thygesen K, Alpert JS, White HD, Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction, Jaffe AS, Apple FS, Galvani M, Katus HA, Newby LK, Ravkilde J, Chaitman B, Clemmensen PM, Dellborg M, Hod H, Porela P, Underwood R, Bax JJ, Beller GA, Bonow R, Van der Wall EE, Bassand JP, Wijns W, Ferguson TB, Steg PG, Uretsky BF, Williams DO, Armstrong PW, Antman EM, Fox KA, Hamm CW, Ohman EM, Simoons ML, Poole-Wilson PA, Gurfinkel EP, Lopez-Sendon JL, Pais P, Mendis S, Zhu JR, Wallentin LC, Fernndez-Avils F, Fox KM, Parkhomenko AN, Priori SG, Tendera M, Voipio-Pulkki LM, Vahanian A, Camm AJ, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber

S, Widimsky P, Zamorano JL, Morais J, Brener S, Harrington R, Morrow D, Lim M, Martinez-Rios MA, Steinhubl S, Levine GN, Gibler WB, Goff D, Tubaro M, Dudek D, Al-Attar N: Universal definition of myocardial infarction. Circulation 2007; 116:2634–53

19. Robins JM, Hernn MA, Brumback B: Marginal structural models and causal inference in epidemiology. Epidemiology 2000; 11:550–60
20. Bernard F, Denault A, Babin D, Goyer C, Couture P, Couturier A, Buithieu J: Diastolic dysfunction is predictive of difficult weaning from cardiopulmonary bypass. Anesth Analg 2001; 92:291–8
21. Vaskelyte J, Stoskute N, Kinduris S, Ereminiene E: Coronary artery bypass grafting in patients with severe left ventricular dysfunction: Predictive significance of left ventricular diastolic filling pattern. Eur J Echocardiogr 2001; 2:62–7
22. Matyal R, Hess PE, Subramaniam B, Mitchell J, Panzica PJ, Pomposelli F, Mahmood F: Perioperative diastolic dysfunction during vascular surgery and its association with postoperative outcome. J Vasc Surg 2009; 50:70–6
23. Flu WJ, van Kuijk JP, Hoeks SE, Kuiper R, Schouten O, Goei D, Elhendy A, Verhagen HJ, Thomson IR, Bax JJ, Fleisher LA, Poldermans D: Prognostic implications of asymptomatic left ventricular dysfunction in patients undergoing vascular surgery. ANESTHESIOLOGY 2010; 112:1316–24
24. Groban L, Sanders DM, Houle TT, Antonio BL, Ntuen EC, Zvara DA, Kon ND, Kincaid EH: Prognostic value of tissue Doppler-Derived E/e' on early morbid events after cardiac surgery. Echocardiography 2010; 27:131–8
25. Mller JE, Pellikka PA, Hillis GS, Oh JK: Prognostic importance of diastolic function and filling pressure in patients with acute myocardial infarction. Circulation 2006; 114:438–44
26. Garcia MJ, Smedira NG, Greenberg NL, Main M, Firstenberg MS, Odabashian J, Thomas JD: Color M-mode Doppler flow propagation velocity is a preload insensitive index of left ventricular relaxation: Animal and human validation. J Am Coll Cardiol 2000; 35:201–8
27. Nagueh SF, Mikati I, Kopelen HA, Middleton KJ, Quiones MA, Zoghbi WA: Doppler estimation of left ventricular filling pressure in sinus tachycardia. A new application of tissue doppler imaging. Circulation 1998; 98:1644–50
28. Nagueh SF, Lakkis NM, Middleton KJ, Spencer WH 3rd, Zoghbi WA, Quiones MA: Doppler estimation of left ventricular filling pressures in patients with hypertrophic cardiomyopathy. Circulation 1999; 99:254–61
29. Bruch C, Stypmann J, Gradaus R, Breithardt G, Wichter T: Usefulness of tissue Doppler imaging for estimation of filling pressures in patients with primary or secondary pure mitral regurgitation. Am J Cardiol 2004; 93:324–8
30. Bruch C, Stypmann J, Grude M, Gradaus R, Breithardt G, Wichter T: Tissue Doppler imaging in patients with moderate to severe aortic valve stenosis: Clinical usefulness and diagnostic accuracy. Am Heart J 2004; 148:696–702
31. Kasner M, Westermann D, Steendijk P, Gaub R, Wilkenshoff U, Weitmann K, Hoffmann W, Poller W, Schultheiss HP, Pauschinger M, Tschpe C: Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: A comparative Doppler-conductance catheterization study. Circulation 2007; 116:637–47
32. Arom KV, Emery RW, Flavin TF, Kshettry VR, Petersen RJ: OPCAB surgery: A critical review of two different categories of pre-operative ejection fraction. Eur J Cardiothorac Surg 2001; 20:533–7
33. Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM: Perioperative beta-blocker therapy and mortality after major noncardiac surgery. N Engl J Med 2005; 353:349–61
34. Wiesbauer F, Schlager O, Domanovits H, Wildner B, Maurer G, Muellner M, Blessberger H, Schillinger M: Perioperative beta-blockers for preventing surgery-related mortality and morbidity: A systematic review and meta-analysis. Anesth Analg 2007; 104:27–41
35. Beattie WS, Wijeysundera DN, Karkouti K, McCluskey S, Tait G, Mitsakakis N, Hare GM: Acute surgical anemia influences the cardioprotective effects of beta-blockade: A single-center, propensity-matched cohort study. ANESTHESIOLOGY 2010; 112:25–33
36. Wallace AW, Au S, Cason BA: Association of the pattern of use of perioperative -blockade and postoperative mortality. ANESTHESIOLOGY 2010; 113:794–805
37. Cohn JN, Ferrari R, Sharpe N: Cardiac remodeling–concepts and clinical implications: A consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol 2000; 35:569–82
38. Kosmala W, Derzhko R, Przewlocka-Kosmala M, Orda A, Mazurek W: Plasma levels of TNF-alpha, IL-6, and IL-10 and their relationship with left ventricular diastolic function in patients with stable angina pectoris and preserved left ventricular systolic performance. Coron Artery Dis 2008; 19: 375–82
39. Williams ES, Shah SJ, Ali S, Na BY, Schiller NB, Whooley MA: C-reactive protein, diastolic dysfunction, and risk of heart failure in patients with coronary disease: Heart and Soul Study. Eur J Heart Fail 2008; 10:63–9
40. Jin H, Chemaly ER, Lee A, Kho C, Hadri L, Hajjar RJ, Akar FG: Mechanoelectrical remodeling and arrhythmias during progression of hypertrophy. FASEB J 2010; 24:451–63
41. Apostolakis EE, Baikoussis NG, Parissis H, Siminelakis SN, Papadopoulos GS: Left ventricular diastolic dysfunction of the cardiac surgery patient; a point of view for the cardiac surgeon and cardio-anesthesiologist. J Cardiothorac Surg 2009; 4:67
42. Vandenbroucke JP, von Elm E, Altman DG, Gtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M, STROBE Initiative: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. Epidemiology 2007; 18:805–35
43. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiones MA: Doppler tissue imaging: A noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997; 30:1527–33
44. Rivas-Gotz C, Manolios M, Thohan V, Nagueh SF: Impact of left ventricular ejection fraction on estimation of left ventricular filling pressures using tissue Doppler and flow propagation velocity. Am J Cardiol 2003; 91:780–4