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Prognostic value of a tissue Doppler-derived index of left ventricular filling pressure on composite morbidity after off-pump coronary artery bypass surgery

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Editor's key points

- There are few data on risk factors for patients undergoing off-pump coronary artery bypass surgery (OPCAB).
- An *E*/*e*′ ratio assessed by pulsed-wave Doppler is an established marker of diastolic dysfunction.
- In over 500 patients undergoing OPCAB, an *E*/*e*′ ratio >15 and high diastolic filling pressures were associated with postoperative morbidity.
- The *E*/*e*′ ratio may be useful to predict outcome after OPCAB, but more data are needed.

Background. The ratio of early transmitral flow velocity to early diastolic velocity of the mitral annulus (*E*/*e*′) is an indicator of diastolic function that correlates well with left ventricular (LV) filling pressure and is relatively independent of systolic function and rhythm abnormalities. We prospectively evaluated the predictive value of *E*/*e*′ for postoperative outcome in patients undergoing off-pump coronary artery bypass graft surgery (OPCAB).

Methods. Patients undergoing OPCAB were classified into three groups according to their *E*/*e*′ ratio: (i) normal *E*/*e*′ <8; (ii) undetermined *E*/*e*′ ≥8 and ≤15; and (iii) elevated *E*/*e*′ >15. Among those with *E*/*e*′ between 8 and 15, patients with elevated LV filling pressure were further identified by comprehensive Doppler examination. These patients were classified as having a high LV filling pressure, together with patients who had *E*/*e*′ ratios >15. Univariate and multivariate regression analyses were used to evaluate the relationship between preoperative variables and composite endpoints for morbidity.

Results. In univariate analysis, diabetes mellitus, recent myocardial infarction, chronic obstructive pulmonary disease, serum creatinine (sCr) concentration, *E*/*e*′ >15, high LV filling pressure, LV ejection fraction, New York Heart Association class III and IV, and use of diuretics were significant risk factors for postoperative morbidity. In multivariate regression analysis of these variables, only sCr (odds ratio 1.4) and *E*/*e*′ >15 (odds ratio 2.4) or high LV filling pressure (odds ratio 2.8) remained as independent risk factors.

Conclusions. *E*/*e*′ ratio >15 was a significant predictor of composite endpoints of postoperative morbidity. We suggest that *E*/*e*′ ratio should be included in the routine preoperative assessment of patients presenting for OPCAB.

Keywords: diastolic dysfunction; *E*/*e*′ value; LV filling pressure; off-pump coronary artery bypass

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Diastolic dysfunction involves abnormalities in cardiac filling, which result from a combination of slowed left ventricular (LV) relaxation and increased stiffness, reducing the ability of LV to adapt promptly to changes in loading conditions typical of the perioperative period.[1] As it is one of the first signs of myocardial ischaemia, diastolic dysfunction has received renewed interest in patients undergoing coronary artery bypass graft surgery (CABG) and relatively accurate, non-invasive surrogate measures of LV filling pressure are available.[2–4]

Among the available echocardiographic measures of diastolic function, the ratio of early transmitral flow velocity to early diastolic velocity of the mitral annulus (*E*/*e*′) correlates well with LV filling pressure; it is relatively independent of systolic function, rhythm abnormalities, LV hypertrophy, and functional mitral regurgitation compared with conventional measurements with Doppler techniques.[5–8] Furthermore, an *E*/*e*′ ratio >15, which accurately predicts elevated LV filling pressure, is associated with increased morbidity and mortality after myocardial infarction (MI).[9 10]

There is increasing evidence of the benefits of off-pump CABG (OPCAB) compared with on-pump CABG in particular subgroups of high-risk patients,[11–13] suggesting that different risk factors may be important. *E*/*e*′ >15 is also associated with more severe haemodynamic derangements during the period of heart displacement, longer time to extubation, and length of stay (LOS) in the intensive care unit (ICU) in patients with preserved LV ejection fraction (LVEF) undergoing OPCAB.[14] However, there are no comprehensive data on the prognostic importance of diastolic dysfunction as

measured by E/e' in patients undergoing OPCAB. Therefore, we evaluated the predictive value of preoperative risk factors for postoperative morbidity and mortality including the E/e' ratio in patients undergoing elective, isolated, and multivessel OPCAB in a prospective and observational trial.

Methods

Patient population and assessed risk factors

After Institutional Review Board approval, 510 consecutive patients undergoing elective, isolated, and multivessel OPCAB at Severance Hospital between March 2006 and December 2009 were prospectively studied. The need to obtain written consent from patients was waived by the Institutional Review Board.

Preoperative characteristics including age, gender, BMI, New York Heart Association Functional Classification (NYHA), history of recent MI within 1 month, chronic obstructive pulmonary disease, diabetes mellitus, vascular disease, hypertension, grade of mitral regurgitation, serum creatinine (sCr) concentration, and medications were assessed. Preoperative transthoracic echocardiography was performed 1 day before surgery by cardiologists unaware of this study. LVEF and E/e' were assessed. Briefly, early transmitral inflow velocity E was assessed by pulsed-wave Doppler from the apical four-chamber view with 1–2 mm sample volume. Early diastolic velocity of the mitral annulus (e') was assessed by pulsed-wave Doppler tissue imaging of the septal mitral annulus from the same view with 2–4 mm sample volume. LV filling pressures as measured by E/e' were classified into three groups: (i) normal $E/e' < 8$; (ii) undetermined $E/e' \geq 8$ and ≤ 15; and (iii) severely elevated $E/e' > 15$.[2] Since considerable variability exists in LV filling pressure in patients with E/e' value between 8 and 15, these patients were classified further as having either normal or elevated LV filling pressure by comprehensive Doppler examination[15]: raised LV filling pressure was diagnosed if the E/A ratio decreased by more than 0.5 during the Valsalva manoeuvre, or the pulmonary venous A-wave duration exceeded the mitral a-wave duration by at least 30 ms. Patients who were found to fulfil these criteria were classified together with patients who already demonstrated $E/e' > 15$ as having high LV filling pressure (diastolic dysfunction).

Perioperative management

All patients received standardized perioperative care. Standard monitoring included a pulmonary artery catheter (Swan-Ganz CCombo CCO/Sv_{O_2}; Edwards Lifesciences, Irvine, CA, USA) inserted via the right internal jugular vein and transoesophageal echocardiography. Anaesthesia comprised sufentanil with sevoflurane and rocuronium for neuromuscular block. All surgical procedures were performed by a single surgical team through median sternotomy, and the heart was displaced using a posterior pericardial stitch, large gauze (12×70 cm) swabs, and a tissue stabilizer (Octopus Tissue Stabilization System, Medtronic Inc., USA). Revascularization was carried out using a single or both internal thoracic arteries connected with an additional graft using the radial artery, saphenous vein, or both in a Y-configuration. The mean systemic arterial pressure during distal anastomosis was maintained between 70 and 80 mm Hg either with a 10–20° Trendelenburg position, norepinephrine infusion, or both. Also, milrinone was infused in patients with mixed venous oxygen saturation (Sv_{O_2}) <60% for >10 min despite optimization of preload and haematocrit and/or development of mitral regurgitation ≥grade 3 with a concomitant increase in mean pulmonary arterial pressure >30 mm Hg during grafting. In all cases, a cell salvage device was used and the salvaged blood re-infused to each patient. Indication for packed allogeneic red blood transfusion throughout the study period was haematocrit concentration <25%. After surgery, all patients were transferred to ICU. In the postoperative period, milrinone was infused when cardiac index was <2.0 litre min^{-1} m^{-2} or Sv_{O_2} <60% after optimization of other determinants of cardiac output including preload. An intra-aortic balloon pump (IABP) was inserted when cardiac index <2.0 litre min^{-1} m^{-2} and Sv_{O_2} <60% persisted with worsening acidaemia despite aggressive treatment.

Composite morbidity endpoints

Major endpoints of morbidity included acute renal failure (ARF), cardiovascular failure, stroke, mediastinitis, and need for ventilator support for >48 h as described previously.[16] ARF was defined as postoperative sCr concentration >177 μmol $litre^{-1}$ plus an increase in the sCr concentration >80 μmol $litre^{-1}$ from preoperative to maximum postoperative values if preoperative sCr <177 μmol $litre^{-1}$; or a new requirement for dialysis. Cardiovascular failure was defined as acute MI, IABP insertion, or cardiac arrest. MI was defined as the occurrence of increase in troponin-T >0.5 ng ml^{-1} (five times above the upper normal limit) and the development of new pathological Q-waves or new left bundle branch block.[17]

The endpoint of composite postoperative morbidity was defined as the presence of any of the major morbidity endpoints and/or in-hospital death and was assessed during the postoperative hospital stay. Our primary aim was to assess the association between E/e' >15 or high LV filling pressure and composite postoperative morbidity.

Statistical analysis

Statistical analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are shown as mean (SD), and categorical variables as number (%). Comparisons were made with Student's t-test/Mann–Whitney U-test or χ^2/Fisher's exact tests as appropriate.

To identify the independent predictors of composite postoperative morbidity, a logistic regression model was used. First, univariate logistic regression analysis was performed with the following variables: (i) variables with $P<0.05$ by intergroup comparisons between patients allocated into

two groups according to the presence of composite morbidity endpoints, (ii) potential confounding factors for analysis were selected on the basis of a literature review including age, gender, BMI, NYHA class, diabetes mellitus, hypertension, acute coronary syndrome, and preoperative sCr. All of the variables that had a *P*-value of <0.05 in univariate logistic regression were further introduced to a multivariate logistic regression analysis. Odds ratios and associated 95% confidence intervals were estimated. Model fit was assessed with the Hosmer–Lemeshow goodness-of-fit test.

Results

OPCAB was performed successfully in 500 patients and the remaining 10 patients required emergency conversion to on-pump CABG. The two most common complications were ARF and MI (Table 1). Overall, the number of patients allocated to the control and morbidity groups was 397 and 103, respectively.

The percentage of patients with diabetes, recent MI, or chronic obstructive pulmonary disease was greater in the morbidity group (Table 2). Higher sCr concentrations were observed in patients from the morbidity group with greater NYHA grade and lower LVEF. The overall incidence of patients having E/e' >15 and diastolic dysfunction was 39% and 47.4%, respectively. The percentage of patients with E/e' >15 and diastolic dysfunction was significantly higher in the morbidity group, with more frequent use of diuretics than the control group (Table 2).

The independent risk factors in univariate analysis for composite morbidity were diabetes mellitus, recent MI, chronic obstructive pulmonary disease, sCr concentrations, high LV filling pressure, E/e' value, E/e' >15, preoperative LVEF, NYHA class III and IV and the use of diuretics (Table 3).

In multivariate logistic regression analysis of these variables, only E/e' >15 and sCr concentrations remained as independent risk factors composite morbidity (Table 4). When diastolic dysfunction was introduced instead of E/e' >15, similar results were obtained with minimal changes in the odds ratios.

Table 1 Postoperative complications. Values are number of patients (%)

	Complications ($n=103$)
Acute renal failure	46 (9.2)
Dialysis	18 (3.6)
Cardiovascular failure	35 (7)
Myocardial infarction	35 (7)
Cardiac arrest	6 (1.2)
Stroke	3 (0.6)
Reoperation	8 (1.6)
Mediastinitis	17 (3.4)
Intubation >48 h	15 (3)
Death	6 (1.2)

Discussion

In this prospective study of the prognostic value of tissue Doppler-derived E/e' ratio on composite morbidity after OPCAB, E/e' >15 (odds ratio 2.4) and elevated preoperative sCr concentrations (odds ratio 1.4) were identified as independent risk factors. Furthermore, the presence of high LV filling pressure, which was diagnosed based on the E/e' value in conjunction with comprehensive Doppler examination, was also identified as an independent risk factor (odds ratio 2.8).

Table 2 Patient characteristics and preoperative clinical data. Data are expressed as mean (range), mean (SD) or number of patients (%). Control group, patients without any morbidity complications; morbidity group, patients with five major postoperative morbidity complications (cerebrovascular accident, mediastinitis, ARF, cardiovascular failure, and respiratory failure). MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association Functional Classification. *$P<0.05$, **$P<0.005$, and †$P<0.001$ compared with the control group

	Control group ($n=397$)	Morbidity group ($n=103$)
Age (yr)	64 (30–80)	66 (41–85)
Female gender	123 (31.0)	35 (34.0)
Body mass index (kg m^{-2})	24.1 (2.9)	24.1 (2.9)
Diabetes mellitus**	155 (39.0)	58 (56.3)
Vascular disease	32 (8.1)	5 (4.9)
Hypertension	253 (63.7)	75 (72.8)
COPD*	46 (11.6)	20 (19.4)
Recent MI (<1 month)†	65 (16.4)	31 (30.1)
Acute coronary syndrome	177 (44.6)	44 (42.7)
Left main disease	129 (32.5)	34 (33.3)
Triple vessel disease	259 (65.2)	77 (74.8)
Serum creatinine concentration (μmol litre^{-1})†	88 (80)	159 (195)
NYHA**		
I–II	363 (91.4)	84 (81.6)
III–IV	34 (8.6)	19 (18.4)
Mitral regurgitation (grade)		
0–I	307 (77.3)	80 (77.7)
II–IV	90 (22.7)	23 (22.3)
Left ventricular ejection fraction (%)†	56 (13)	49 (14)
E/e' value†		
<8	38 (9.6)	8 (7.8)
8–15	229 (57.7)	30 (29.1)
>15	130 (32.7)	65 (63.1)
Diastolic dysfunction**	163 (41.7)	74 (71.8)
Medications		
Nitrates	44 (11.1)	17 (16.5)
β-Blockers	258 (65.0)	69 (67.0)
Calcium channel blockers	177 (44.6)	43 (41.7)
Renin–angiotensin system antagonist	138 (34.8)	42 (40.8)
Diuretics**	58 (14.6)	30 (29.1)

Table 3 Univariate logistic regression analysis for predictors of composite morbidity. MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association Functional Classification; *E*/*e*′, ratio of mitral velocity to early diastolic velocity of the mitral annulus. *$P<0.05$, **$P<0.005$, and †$P<0.001$

	Odds ratio (95% confidence interval)
Age	1.02 (1.00–1.05)
Female gender	0.87 (0.55–1.38)
Body mass index	1.00 (0.93–1.08)
Diabetes mellitus**	2.01 (1.30–3.12)
Hypertension	1.53 (0.94–2.46)
COPD*	1.84 (1.03–3.27)
Recent MI (<1 month)**	2.44 (1.47–4.05)
Acute coronary syndrome	1.08 (0.70–1.67)
Serum creatinine level†	1.83 (1.37–2.44)
NYHA III–IV	2.42 (1.31–4.44)
Left ventricular ejection fraction†	0.97 (0.95–0.97)
E/*e*′ >15†	3.51 (2.24–5.52)
Diastolic dysfunction†	3.79 (2.35–6.12)
Diuretics**	2.40 (1.45–3.99)

Table 4 Multivariate logistic regression analysis for predictors of composite morbidity. MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; *E*/*e*′, ratio of mitral velocity to early diastolic velocity of the mitral annulus; NYHA, New York Heart Association Functional Classification. *$P<0.05$, **$P<0.005$, †$P<0.001$

	Odds ratio (95% confidence interval)
Diabetes mellitus	1.23 (0.73–2.05)
COPD	1.57 (0.80–3.10)
Recent MI (<1 month)	1.50 (0.81–2.77)
Serum creatinine level*	1.41 (1.11–1.79)
NYHA III–IV	1.68 (0.81–3.48)
Left ventricular ejection fraction	1.00 (0.98–1.02)
E/*e*′ >15**	2.42 (1.42–4.14)
Diastolic dysfunction†	2.80 (1.63–4.93)
Diuretics	1.41 (0.77–2.61)

Diastolic function is an active process requiring adenosine triphosphate (ATP)-dependent uptake of intracellular calcium into the sarcoplasmic reticulum. Diastolic dysfunction usually refers to a preclinical status involving abnormalities in cardiac filling, which result from a combination of slowed LV relaxation and increased stiffness. Diastolic dysfunction is one of the first signs of myocardial ischaemia and its prevalence ranges widely between 44% and 75% in patients undergoing CABG.[18 19] Studies using conventional Doppler measurements have shown that diastolic dysfunction is associated with increased morbidity and difficulty in weaning from cardiopulmonary bypass (CPB) in cardiac surgery.[2–4 20] However, though they were more accurate in predicting adverse outcome and mortality after CABG than EuroSCORE,[3] the conventional transmitral and pulmonary vein flow patterns are influenced by heart rate and rhythm, loading conditions and other factors.[5]

Alternatively, tissue Doppler-derived *e*′ is the early diastolic velocity of the mitral annulus representing the intrinsic speed of myocardial relaxation that is less affected by loading conditions.[5 21] Thus, combining the mitral inflow with the mitral annular velocity into a ratio *E*/*e*′ can accurately predict LV filling pressure for all degrees of LVEF and even in patients with sinus tachycardia, atrial fibrillation, and hypertrophic cardiomyopathy. Elevated filling pressure is almost always associated with a structural or functional abnormalities of the heart and, haemodynamically is a unifying feature for heart failure.[22] The *E*/*e*′ ratio is associated with increased morbidity and mortality after acute MI, using a cut-off value of >15.[9 10] Interestingly, directly measured LV end-diastolic pressure after MI was not identified as an independent risk factor for heart failure and worse survival, reinforcing the clinical significance of this simple and non-invasive tissue Doppler-derived surrogate measure of LV filling pressure and diastolic dysfunction.[23] In the surgical setting, only a single retrospective study delineated the significance of *E*/*e*′ >15 as a useful indicator for predicting increased LOS in ICU and need for inotropic support after cardiac surgeries using CPB and further evidence is needed.[2]

OPCAB is an important technique for coronary revascularization which has better outcomes than on-pump CABG, in particular high-risk patients.[11–13] However, mechanical heart displacement during grafting in OPCAB results in impaired filling and diastolic dysfunction of both ventricles leading to various degrees of haemodynamic derangement.[24 25] Although these haemodynamic derangements were thought to be transient and confined to the period of heart displacement, a recent study depicted the persistence of decreased cardiac index and mixed venous oxygen saturation in patients with *E*/*e*′ >15, despite having an LVEF of >50%.[14] In that study, patients with *E*/*e*′ >15 also required longer mechanical ventilation time and LOS in ICU, supporting our findings that *E*/*e*′ might have prognostic significance in patients undergoing OPCAB.

As the results of the current study indicate, only *E*/*e*′ >15 and preoperative sCr remained as independent risk factors of composite morbidity endpoints after OPCAB. Of note, patients with *E*/*e*′ >15 had 2.4-fold increased risk of composite morbidity endpoints after OPCAB, whereas the odds ratio of sCr was 1.4. These results clearly support the prognostic value of *E*/*e*′ >15, considering the close relationship between preoperative sCr and postoperative renal dysfunction and that ARF was the most frequent complication observed here.[26] Traditionally, LVEF representing the systolic heart function has been considered as an important risk factor and it is included in many risk-scoring systems. However, its association with postoperative outcome seems to diminish when diastolic function is assessed concurrently.[3 4] In previous studies, only diastolic dysfunction was associated

with adverse outcome and mortality, whereas the predictive power of EuroSCORE, Parsonnet's score, and LVEF were lost in the presence of diastolic dysfunction.[3 4] This is not surprising considering that diastolic function is also an active process requiring ATP and that diastolic dysfunction is one of the earliest signs of myocardial ischaemia, with a substantial incidence among patients undergoing CABG.

Another novel finding of this study is the data from patients with *E*/*e*′ between 8 and 15. Clear cut-off values of *E*/*e*′ exist based on validation studies. *E*/*e*′ <8 and >15 accurately predicted normal and increased mean LV diastolic pressure, respectively, whereas *E*/*e*′ between 8 and 15 demonstrated a poor correlation.[14] Undoubtedly, the prognostic value of *E*/*e*′ >15 has been clearly depicted in clinical studies involving patients with coronary artery disease including the current study, yet a substantial number of patients exhibit *E*/*e*′ between 8 and 15. We, therefore classified the patients further by aid of proposed Doppler examination to either having normal or increased LV filling pressure.[15] Thus, all of the patients were classified as either having high LV filling pressure or not, and when the prognostic value of this variable was evaluated, similar results could be observed. The presence of high LV filling pressure was associated with 2.8-fold increased risk of composite morbidity endpoints, whereas the odds ratio for sCr remained 1.4.

Patients with diastolic dysfunction need an increased preload to maintain adequate cardiac output. At the same time, the reduced ability to quickly adapt to the varying loading conditions, which is frequently encountered during the perioperative period, makes the patients more vulnerable to reduced cardiac output or abrupt increase in pulmonary venous pressure and consequent pulmonary oedema.[1] During OPCAB, haemodynamic derangement is accentuated in patients with *E*/*e*′ >15 as a consequence of mechanical heart displacement and often not restored to baseline values.[24 25] All these features would be plausible explanations for our results. The mainstay of diastolic dysfunction management undoubtedly begins with prompt recognition. Thus, the results of the current study should alert the importance of *E*/*e*′ >15 as a predictor of adverse events after OPCAB and the need to assess them before operation for comprehensive risk stratification and to improve patients' outcome and quality of life. Also, when a simple measurement of tissue Doppler-derived echocardiography parameter *E*/*e*′ demonstrates inconclusive range (8–15), further stratification should be sought by aid of other proposed Doppler examination to accurately assess the patients' risk before OPCAB.[15]

The limitations of this study are that although *E*/*e*′ is less affected by other interrelated factors than conventional Doppler, the presence of severe mitral regurgitation could have influenced its measurement and thus confounded the results.[27] However, *E*/*e*′ has been shown to be reliable in patients with secondary mitral regurgitation, and this is the most frequent type of mitral regurgitation encountered in patients with coronary artery disease.[8]

In conclusion, along with preoperative sCr concentrations, *E*/*e*′ >15 or diastolic dysfunction diagnosed based on the *E*/*e*′ ratio by further evaluation of Doppler examinations was identified as an independent risk factor for composite morbidity after OPCAB. As some of the unique features of OPCAB are closely related to diastolic dysfunction, the current trial demonstrates the prognostic importance of the *E*/*e*′ ratio and we suggest that it should be incorporated into a routine preoperative assessment for more comprehensive and accurate risk stratification in patients presenting for OPCAB.

Conflict of interest

None declared.

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