Combined impact of elevated arterial stiffness and left ventricular filling pressure on outcomes after off-pump coronary artery bypass grafting

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Abstract

Background: Brachial-ankle pulse wave velocity (baPWV) and early diastolic transmitral flow velocity to mitral annular tissue velocity (E/e'), markers of arterial stiffness and left ventricular (LV) filling pressure, respectively, have been associated with morbidity and mortality. We investigated their combined impact on postoperative complications and long-term survival of patients undergoing off-pump coronary artery bypass grafting (OPCAB).

Methods: A cohort of 164 patients were divided into four groups: baPWV≤19m/s and E/e'≤15 (reference), baPWV>19m/s and E/e'≤15 (high-PWV-only), baPWV≤19m/s and E/e'>15 (high-E/e'-only), and baPWV>19 m/s and E/e'>15 (high-PWV-and-E/e'). Each group was compared with the reference group to analyze the odds ratios of postoperative complications and the Kaplan-Meier survival curves, and to identify the group representing an independent prognostic predictor.

Results: The median age and follow-up duration were 66.2 years and 57.2 months, respectively. Postoperative acute kidney injury (POAKI) was higher in the high-PWV-only group and substantially higher in high-PWV-and-E/e' group (adjusted odds ratio (OR)=4.8; 95% confidence interval (CI), 1.3-17.1; p=0.016 vs. OR=22.6; CI, 5.9–86.1; p<0.001). ORs of postoperative atrial fibrillation (POAF) and postoperative stroke/delirium (POSD) were significantly higher only in the high-PWV-and-E/e' group. The 7-year survival rates differed across the groups (p<0.001). The high-E/e'-only and high-PWV-and-E/e' groups showed significantly lower survival rates than the reference group (75.6% and 53.5% vs. 93.9%). After adjustment for covariates, however, only the high-PWV-and-E/e' group turned out to be an independent predictor group for all-cause mortality.

Conclusion: Concurrent elevation in PWV and E/e' may independently affect not only the rates of POAKI, POAF, and POSD but also long-term survival after OPCAB.

Background

Pulse wave velocity (PWV) is now widely accepted as an index of arterial stiffness [1]. The ratio of the early transmitral blood flow velocity to early diastolic velocity of the mitral annulus (E/e') is a marker of left ventricular (LV) filling pressure and has been used to estimate the diastolic function [2]. E/e' is currently almost routinely evaluated during echocardiographic testing before cardiac surgery. The measurement of PWV is a simple and noninvasive procedure, which can be easily performed before surgery. In addition, several studies report that both elevated PWV and E/e' are associated with a higher risk of cardiovascular events and deaths in various patient populations [3, 4]. However, the association of PWV or E/e' with cardiac surgical outcome is rarely reported.

We reported earlier that elevated brachial-ankle PWV (baPWV) was an independent predictor of postoperative acute kidney injury (POAKI) and associated with the composite rate of stroke and/or delirium as well as the duration of ventilatory support [5]. Our team demonstrated that high PWV value was significantly correlated with elevated E/e' [6]. Considering the reported negative impact of diastolic

dysfunction on post-cardiovascular surgery outcomes [7], we hypothesized that the combined impact of elevated PWV and E/e' is greater than the impact of isolated elevation of either PWV or E/e'. Furthermore, we speculated that this concurrent elevation of PWV and E/e might be a more reliable predictor of long-term survival.

The aim of this study was to investigate whether significant elevation in both PWV and E/e' affect postoperative complications and long-term overall survival after off-pump coronary artery bypass grafting (OPCAB).

Materials And Methods

Patient selection

This study cohort is similar to our previous one with similar inclusion and exclusion criteria [5]. On-pump coronary artery bypass grafting cases were excluded in order to avoid bias due to cardiopulmonary bypass. The study excluded 79 patients from a total of 243 patients undergoing OPCAB between April 2013 and July 2019. The exclusion criteria were: 1) absence of PWV measurements, 2) insertion of aorto-iliac or renal stents (grafts), 3) patients with oliguria or already undergoing dialysis, 4) combination with any other cardiac procedure, and 5) uncontrolled and severe hypertension (blood pressure > 160/100 mmHg).

The study protocol was approved by the Seoul Metropolitan Government - Seoul National University Hospital's institutional review board (IRB No. 10-2021-140), and the requirement for informed consent was waived because this retrospective review of medical records did not adversely affect the rights or welfare of the subjects.

Measurement of baPWV and E/e'

The vast majority of the patients, who were referred for CABG from the cardiology department, underwent PWV measurements prospectively before surgery because several prospective studies related to PWV involved patients with coronary artery disease. The measurement was simple and noninvasive. Wrapping cuffs around both brachialis and ankles, the pulse volume waveform, blood pressure, phonogram, and heart rate were recorded simultaneously using a volume-plethysmographic apparatus (VP-1000, Colin Co. Ltd.; Komaki, Japan). Higher PWV value suggests stiffer arterial system. The mean values between the left and right baPWVs were used for analysis. We have already reported the calculation of baPWV previously [5]. Accordingly, high baPWV was defined as baPWV > 19 m/s, which was an independent predictor of POAKI following OPCAB.

Transthoracic echocardiography (Sequoia, Siemens Medical Solutions or Vivid 7, GE Medical Systems) with tissue Doppler analysis was routinely performed before surgery. The peak early transmitral filling velocity during early diastole (E) was imaged and early diastolic velocity at the septal mitral annulus (e') was determined in the apical four-chamber view, under pulsed-wave Doppler examination of the mitral

inflow, as well as tissue Doppler imaging of the mitral annulus. Although we intended to exclude cases where e' and E/e' may not provide a reliable estimate of LV filling pressure due to valve pathogenesis including significant mitral annular calcification and moderate-to-severe mitral regurgitation, no case was excluded. Based on the 2016 American Society of Echocardiography (ASE) recommendations for the evaluation of LV diastolic function using echocardiography [8] and studies investigating E/e' [9], an E/e' ratio greater than 15 at septal side was defined as high E/e'.

Surgical techniques

Our OPCAB strategy has already been described previously in the study investigating the association between baPWV and POAKI [5]. In brief, we first fabricated the composite graft by attaching the saphenous vein (SV) harvested from the lower leg to the *in situ* left internal thoracic artery (LITA) in a Y-shaped configuration. Next, the LITA was anastomosed to left anterior descending coronary artery, followed by SV sequential anastomoses to the other target coronary arteries. However, when a single inflow source was not appropriate due to flow competition, the proximal end of the SV graft was attached to the proximal ascending aorta via partial clamping or using a Heatstring III proximal seal system (Maquet holding B.V. & Co., Rastatt, Germany). A total arterial bypass was occasionally performed using the right internal thoracic artery or radial artery in patients younger than 60 years of age.

Definitions of postoperative and long-term outcomes

Operative mortality was defined as the number of death within 30 days of surgery. Perioperative myocardial infarction was defined by an elevation of biomarkers including either creatine kinase (CK-MB) concentration > 40 ng/mL or peak troponin I levels > 15 ng/mL at 12 hours postoperatively and the presence of new pathological Q waves or left bundle branch block. Renal function was assessed by measuring the levels of serum creatinine and determining the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) equation. Postoperative GFR was defined as the lowest eGFR within 7 postoperative days (PODs). According to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Foundation consensus statement [10], POAKI was defined as stage 1 or higher based on any of the following criteria: urine output < 0.5 mL/kg/h for 6 hours or longer; elevation of serum creatinine within 2 PODs > 0.3 mg/dL; and a serum creatinine increase > 1.5-fold relative to the baseline value within 7 PODs. Postoperative stroke/delirium (POSD) was a composite variable consisting of isolated stroke and isolated delirium, and a combination thereof. Stroke was defined as cerebral infarction of ischemic or hemorrhagic etiology, or transient ischemic attack based on brain imaging studies and consulting neurologists. Delirium was defined based on the criteria of the fifth edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-5) and the diagnosis was established in consultation with neuropsychiatrists. Postoperative pneumonia was defined as a lower respiratory tract infection with accompanying consolidation detected on chest x-ray.

Late mortality was defined as all-cause mortalities after 30 days of operation. Patients were identified as still living on October 31, 2021. The median follow-up duration was 57.2 months (range, 40.0–84.0 months) and none of the patients were lost to follow-up.

Statistical analysis

For descriptive statistics, categorical variables are expressed as counts and percentages. Values for continuous variables are expressed as mean ± standard deviation (SD) or median (interquartile range, IQR) when the data are not equally distributed. The baseline characteristics and postoperative complications were descriptively analyzed and compared across the four independent groups. One-way analysis of variance (ANOVA) or the Kruskal-Wallis test was used to test differences across the groups assuming a normal distribution, which was analyzed with the Kolmogorov–Smirnov test. Post-hoc analysis was also performed using Bonferroni's t-test or Dunn's test. For categorical variables, the Pearson $\chi 2$ test or the Fisher's exact test was used. Any trends of continuous variables associated with postoperative complication including ventilator support duration across the groups were confirmed using the Jonckheere-Terpstra test.

Multivariable logistic regression models adjusted for baseline characteristics including preexisting comorbidities were used to compare odds ratios of each group with those of the reference group to analyze the several important postoperative complications. Survival rate was estimated using Kaplan–Meier methods and between-group comparisons were performed using the log-rank test. Univariable and multivariable Cox proportional-hazards models were used in order to evaluate the impact of the risk factors on overall survival. The covariates included in the multivariable models were selected based on statistical evidence of a significant univariable association with long-term mortality. A p-value < 0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

The median age of this study population was 66.2 years and 79.9% of the patients had triple-vessel disease, with a median left ventricular ejection fraction (LVEF) of 57.3% and a median EuroSCORE II value of 1.6. In order to assess the effect of each group on the outcomes, the patients were divided into four groups: 1) elevation in baPWV alone (baPWV > 19 m/s and E/e ≤ 15, high-PWV-only group), 2) elevation in E/e' alone (baPWV ≤ 19 m/s and E/e > 15, high-E/e'-only group), 3) elevation in both baPWV and E/e' (baPWV > 19 m/s and E/e > 15, high-PWV-and-E/e' group), and elevation in neither baPWV nor E/e' (baPWV ≤ 19 m/s and E/e ≤ 15, reference group). The parameters of age, sex, diabetes, LVEF, eGFR, advanced chronic kidney disease (CKD stage ≥ 4), EuroSCORE II, and CHA2DS2-VAScSCORE differed across the four groups (Table 1). Compared with the reference group, the high-PWV-and-E/e' group showed the highest CHA2DS2-VAScSCORE value and rates of old age (> 75 y), male patients, and diabetes prevalence. LVEF was the lowest and EuroSCORE II value was the highest in the high-E/e'-only group. Estimated GFR was the lowest in the high-PWV-and-E/e' group. However, the groups did not show differences in the frequencies of cerebrovascular accidents, peripheral arteriopathy, acute myocardial

infarction, extent of coronary vessel involvement including left main disease, and previous coronary intervention.

Table 1
Patient characteristics

	Total	*Reference	High-PWV-only	High-E/e'-only	High-PWV-and-E/e'	†p value
N	164	89	28	29	18	
Age, years	69.0 (60.0-73.8)	63.0 (56.0–70.0)	71.0 (66.0–77.0)	70.0 (61.0-75.8)	72.5 (69.3–79.0)	< 0.001
age > 75years, n(%)	27 (16.5)	4 (4.5)	7 (25.0)	8 (27.6)	8 (44.4)	< 0.001
Female, n(%)	116 (70.7)	72 (80.9)	18 (64.3)	19 (65.5)	7 (38.9)	0.003
Body mass index,, kg/m2	24.18 ± 3.23	24.74 ± 3.00	23.79 ± 3.12	22.92 ± 3.44	24.03 ± 3.71	0.056
Hypertension, n(%)	117 (71.3)	58 (65.2)	21 (75.0)	21 (72.4)	17 (94.4)	0.087
Diabetes, n(%)	87 (53.0)	35 (39.3)	23 (82.1)	14 (48.3)	15 (83.3)	< 0.001
under insulin therapy, n(%)	*24 (14.6)*	4 (4.5)	11 (39.3)	5 (17.2)	4 (22.2)	< 0.001
Dyslipidemia, n(%)	54 (32.9)	28 (31.5)	13 (46.4)	7 (24.1)	6 (33.3)	0.332
COPD, n (%)	10 (6.1)	4 (4.5)	1 (3.6)	3 (10.3)	2 (11.1)	0.450
CVA, n (%)	26 (15.9)	9 (10.1)	4 (14.3)	8 (27.6)	5 (27.8)	0.059
Peripheral arteriopathy, n (%)	45 (27.4)	21 (23.6)	9 (32.1)	8 (27.6)	7 (38.9)	0.502
AMI, n(%)	24 (14.6)	12 (13.5)	4 (14.3)	5 (17.2)	3 (16.7)	0.933
Triple-vessel disease, n(%)	131 (79.9)	71 (79.8)	20 (71.4)	26 (89.7)	14 (77.8)	0.377
Left main disease, n(%)	56 (34.1)	29 (32.6)	11 (39.3)	11 (37.9)	5 (27.8)	0.817
Previous PCI, n (%)	22 (13.4)	13 (14.6)	5 (17.9)	2 (6.9)	2 (11.1)	0.638

A:late diastolic mitral inflow velocity; AMI: acute myocardial infarction; baPWV: brachial-ankle pulse wave velocity; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; E: early diastolic mitral inflow velocity; e': early diastolic mitral annular tissue velocity; GFR: glomerular filtration rate.

*Reference: neither high PWV nor high E/e'.

†One-way ANOVA, the Kruskal-Wallis test, and the $\chi 2$ test were used to test differences across groups for normally distributed, non-normally distributed, and categorical variables, respectively.

	Total	*Reference	High-PWV-only	High-E/e'-only	High-PWV-and-E/e'	†p value
Atrial fibrillation, n(%)	2 (1.2)	0 (0.0)	0 (0.0)	1 (3.4)	1 (5.6)	0.147
Left ventricular EF	61.0 (51.0-66.6)	61.7 (56.7–66.5)	62.1 (57.0-67.5)	47.2 (30.3–61.8)	66.2 (60.0-67.8)	< 0.001
MDRD-GFR, mL/min/1.73 m2	83.1 (66.5–95.9)	88.2(76.5–97.9)	80.2 (48.7-102.6)	76.6 (52.1–92.5)	67.6 (47.5–81.9)	0.002
CKD stage ≥ 4, n(%)	20 (12.2)	5 (5.6)	4 (14.3)	7 (24.1)	4 (22.2)	0.015
Mean baPWV, m/s	16.3 (14.2–19.3)	15.0 (13.3–16.7)	20.6 (19.8–21.6)	15.2 (13.5–16.9)	22.8 (20.2–23.8)	< 0.001
right baPWV, m/s	16.5 (14.2–19.5)	15.1 (13.6–17.0)	20.9 (19.7–22.1)	15.4 (13.8–17.1)	22.0 (20.7–24.2)	< 0.001
left baPWV, m/s	16.3 (14.2–19.5)	15.2 (13.1–16.7)	20.6 (19.6–22.2)	14.9 (13.4–16.7)	23.6 (21.6–24.5)	< 0.001
E, cm/s	59.0 (50.0–71.0)	56.0 (49.0–64.0)	58.0 (47.0–65.0)	79.0 (65.0-98.8)	70.5 (52.8–93.8)	< 0.001
A, cm/s	82.0 (67.7–97.0)	72.0 (64.0–86.0)	91.0 (74.0–97.0)	94.5 (61.8–115.0)	108.0 (84.0-122.0)	< 0.001
E/A	0.7 (0.6–0.9)	0.8 (0.6–0.9)	0.6 (0.6–0.7)	0.8 (0.6–1.6)	0.7 (0.7–0.9)	0.004
e', cm/s	5.0 (4.0–6.0)	5.0 (4.0–7.0)	5.0 (4.0–6.0)	4.0 (3.0–5.0)	4.0 (3.0–5.0)	< 0.001
E/e'	12.2 (9.6–16.5)	10.8 (8.7–12.5)	10.8 (9.6–14.0)	18.8 (16.9–23.9)	19.9 (17.5–23.5)	< 0.001
EuroSCORE II	1.6 (0.9–2.9)	1.0 (0.8–1.7)	1.9 (1.4–3.2)	2.8 (1.5–4.4)	1.9 (1.6–3.2)	< 0.001

A:late diastolic mitral inflow velocity; AMI: acute myocardial infarction; baPWV: brachial-ankle pulse wave velocity; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; E: early diastolic mitral inflow velocity; e': early diastolic mitral annular tissue velocity; GFR: glomerular filtration rate.

*Reference: neither high PWV nor high E/e'.

†One-way ANOVA, the Kruskal-Wallis test, and the $\chi 2$ test were used to test differences across groups for normally distributed, non-normally distributed, and categorical variables, respectively.

	Total	*Reference	High-PWV-only	High-E/e'-only	High-PWV-and-E/e'	†p value
EuroSCORE II > 4, n(%)	24 (14.6)	7 (7.9)	5 (17.9)	9 (31.0)	3 (16.7)	0.018
CHA2DS2-VASc SCORE	4 (2–5)	3 (2–4)	5 (4–5)	4 (3–6)	6 (5–7)	< 0.001

A:late diastolic mitral inflow velocity; AMI: acute myocardial infarction; baPWV: brachial-ankle pulse wave velocity; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; E: early diastolic mitral inflow velocity; e': early diastolic mitral annular tissue velocity; GFR: glomerular filtration rate.

*Reference: neither high PWV nor high E/e'.

†One-way ANOVA, the Kruskal-Wallis test, and the $\chi 2$ test were used to test differences across groups for normally distributed, non-normally distributed, and categorical variables, respectively.

Postoperative outcome

Table 2 presents the statistics of postoperative outcome. There was no operative mortality. The complication variables demonstrating significant differences across the groups were POAKI ($p < 0.001$), postoperative atrial fibrillation (POAF) ($p < 0.001$), intra-aortic balloon pump support ($p = 0.025$), ventilator support duration (VSD) ($p = 0.004$), and hospital stay (HS) ($p = 0.029$). Especially, increasing trends in VSD and HS were observed in the order of the following groups: reference, high-PWV-only, high-E/e'-only, and high-PWV-and-E/e' ($p < 0.001$) (Fig. 1). In pairwise comparison, significant differences in duration were observed only between high-PWV-and-E/e' and reference groups ($p = 0.003$ for VSD; $p = 0.026$ for HS). Table 3 presents the impact of combined elevation of PWV and E/e' on major postoperative complications after adjustment for various pre-existing comorbidities. Although the risk of POAKI was significantly higher in both high-PWV-only and high-PWV-and-E/e' groups compared with the reference group, the adjusted odds ratio (OR) was substantially higher in the high-PWV-and-E/e' group (OR = 4.8; 95% confidence interval (CI), 1.3–17.1; $p = 0.016$ vs. OR = 22.6; CI, 5.9–86.1; $p < 0.001$). Adjusted OR of POAF was significantly higher only in the high-PWV-and-E/e' group (OR = 5.7; CI, 1.9–16.9; $p = 0.002$), while the high-PWV-only and high-E/e'-only group did not show any statistical significance. The risk of POSD was also significantly higher only in the high-PWV-and-E/e' group compared with the reference group (OR = 4.1; CI, 1.1–15.7; $p = 0.039$).

Table 2
Postoperative complications

	Total	Reference	High-PWV-only	High-E/e'-only	High-PWV-and-E/e'	*p value
N	164	89	28	29	18	
Acute kidney injury, n(%)	26 (15.9)	5 (5.6)	7 (25.0)	3 (10.3)	11 (61.1)	**< 0.001**
Stroke/delirium, n(%)	19 (11.6)	8 (9.0)	4 (14.3)	2 (6.9)	5 (27.8)	0.133
Atrial fibrillation, n(%)	45 (27.4)	21 (23.6)	2 (7.1)	11 (37.9)	11 (61.1)	**< 0.001**
Perioperative MI, n(%)	16 (9.8)	10 (11.2)	4 (14.3)	2 (6.9)	0 (0.0)	0.393
IABP support, n(%)	5 (3.0)	1 (1.1)	0 (0)	4 (13.8)	0 (0.0)	**0.025**
ECMO support, n(%)	0	0	0	0	0	-
Pneumonia, n(%)	13 (7.9)	5 (5.6)	2 (7.1)	4 (13.8)	2 (11.1)	0.416
Peak troponin-I, ng/mL	2.3 (1.0-5.2)	2.5 (1.1–5.2)	2.2 (1.3–5.2)	1.3 (0.6–3.6)	2.8 (1.3–5.5)	0.294
Ventilator support, hrs	18.0 (14.4–22.1)	16.7 (13.0-20.9)	18.5 (15.0–22.0)	19.0 (15.5–24.1)	23.1 (19.3–26.1)	**0.004**
ICU stay, hrs	46.0 (28.8–65.1)	46.0 (26.0–68.0)	44.0 (29.0-59.5)	46.0 (26.0–71.0)	49.5 (38.0-85.5)	0.545
Hospital stay, days	9.0 (8.0–13.0)	8.0 (8.0–12.0)	9.0 (8.0-12.2)	10.0 (8.0–13.0)	10.5 (9.0–19.0)	**0.029**
30-day mortality	0	0	0	0	0	-

E: early diastolic mitral inflow velocity; e': early diastolic mitral annular tissue velocity; ECMO: extracorporeal membrane oxygenator; IABP: intraaortic balloon pump; ICU: intensive care unit; MI: myocardial infarction; PWV: pulse wave velocity.

*The Kruskal-Wallis test, and the $\chi 2$ test were used to test differences across groups for non-normally distributed and categorical variables, respectively.

Table 3
Comparison of major postoperative complications across the groups

	n(%)	OR(95% CI)	p value
POAKI	26 (15.9)		**< 0.001**
Reference*	5 (5.6)	1	
High-PWV-only	7 (25.0)	4.782 (1.335, 17.131)	**0.016**
High-E/e'-only	3 (10.3)	1.243 (0.251, 6.148)	0.789
High-PWV-and-E/e'	11 (61.1)	22.573 (5.918, 86.105)	**< 0.001**
		Hosmer-Lemehos test	0.850
POAF	45 (27.4)		**0.001**
Reference*	21 (23.6)	1	
High-PWV-only	2 (7.1)	0.219 (0.046, 1.033)	0.055
High-E/e'-only	11 (37.9)	2.259 (0.896, 5.693)	0.084
High-PWV-and-E/e'	11 (61.1)	5.668 (1.896, 16.947)	**0.002**
		Hosmer-Lemehos test	0.779
POSD	19 (11.6)		0.102
Reference	8 (9.0)	1	
High-PWV-only	4 (14.3)	2.066 (0.497, 7.851)	0.296
High-E/e'-only	2 (6.9)	0.550 (0.087, 2.395)	0.469
High-PWV-and-E/e'	5 (27.8)	4.115 (1.060, 15.680)	**0.039**
		Hosmer-Lemehos test	0.964

E: early diastolic mitral inflow velocity; e': early diastolic mitral annular tissue velocity; POAF: postoperative atrial fibrillation; POAKI: postoperative acute kidney injury; POSD: postoperative stroke and/or delirium; PWV: pulse wave velocity.

*Reference: neither high PWV nor high E/e'.

All logistic regression models were adjusted for old age (> 75), sex, preexisting comorbidities (diabetes, hypertension, dislipidemia, stroke history (this was excluded only for the regression model for POSD), acute myocardial infarction history, peripheral arteriopathy, chronic obstructive pulmonary disease, chronic kidney disease > 4, previous coronary intervention, preoperative IABP insertion, triple vessel disease, left main disease, urgent operation), left ventricular ejection fraction, estimated pulmonary hypertension, Euroscore II, and CHA2DS2-VASc score.

Independent variables were entered into this model by backward elimination (Likelyhood Ratio). The model fits were all turned out to be good by Hosmer and Lemeshow Goodness-of-fit tests.

Late mortality and long-term survival

Late all-cause mortality of the patient cohort was 12.8% (21 of 164 patients). Late mortalities of each group were 5.6%, 7.1%, 20.7%, and 44.4% in reference, high-PWV-only, high-E/e'-only, and high-PWV-and-E/e' group, respectively. The unadjusted estimated overall survivals of respective groups are presented as Kaplan-Meier curves in Fig. 2. The 7-year overall survival rates differed significantly across the groups ($p < 0.001$) and were 93.9% (CI, 88.9–99.3%), 92.9% (CI, 83.8–99.9%), 75.6% (CI, 59.9–95.4%), and 53.5% (CI, 34.0–84.03%) in reference, high-PWV-only, high-E/e'-only, and high-PWV-and-E/e' group, respectively. Compared with the reference group, a significant survival difference was observed in the high-E/e'-only and high-PWV-and-E/e' group ($p = 0.029$ and $p < 0.001$, respectively). However, after adjustment for clinical confounders, significantly increased hazard ratio of mortality was observed only in the high-PWV-and-E/e' group (HR = 6.3; CI, 1.9–20.3; $p = 0.002$) (Table 4). From additional pairwise group comparison (Table 5), there was a trend that concurrent elevation of PWV and E/e' was associated with more increased hazard of mortality than single isolated elevation of PWV or E/e'. We also found that the following covariates were independent risk factors for all-cause mortality: CKD grade ≥ 4 (HR = 3.5; CI, 1.4–9.0; $p = 0.008$) and chronic obstructive pulmonary disease (COPD) (HR = 7.0; CI, 2.2–22.2; $p = 0.001$).

Table 4
Cox regression analysis for all-cause mortality

	Univariable analysis		Multivariable analysis	
Risk factors	HR (95% CI)	p value	HR (95% CI)	p value
Group		0.001		**0.018**
Reference*	1		1	
High-PWV-only	1.299 (0.252, 6.698)	0.754	1.337 (0.256, 6.994)	0.731
High-E/e'-only	3.748 (1.144, 12.286)	0.029	2.457 (0.719, 8.398)	0.152
High-PWV-and-E/e'	9.190 (3.004, 28.118)	< 0.001	6.265 (1.931, 20.327)	**0.002**
Sex, Female	0.894 (0.360, 2.216)	0.808		
Age	1.047 (0.997, 1.100)	0.068		
Age75	2.156 (0.835, 5563)	0.112		
Body mas index	0.853 (0.749, 0.971)	0.016		
Obesity	0.284 (0.096, 0.845)	0.024		
NYHA functional class	0.999 (0.552, 1.812)	0.999		
Hypertenstion	8.680 (1.165, 64.685)	0.035	5.574 (0.710, 43.793)	0.102
Diabetes	1.852 (0.747, 4.590)	0.183		
Insulin	1.944 (0.712, 5.309)	0.194		
Dyslipidemia	1.982 (0.842, 4.669)	0.117		
Cerebrovascular accident	2.917 (1.177, 7.230)	0.021	2.469 (0.923, 6.606)	0.072
Peripheral arteriopathy				
CKD grade ≥ 4	5.237 (2.165, 12.672)	< 0.001	3.545 (1.392, 9.025)	**0.008**
COPD	4.693 (1.574, 13.995)	0.006	6.968 (2.184, 22.232)	**0.001**
Acute myocardial infarction	1.300 (0.437, 3.867)	0.637		
Atrial fibrillation	1.848 (0.015, 13.402)	0.696		

CKD: chronic kidney disease; E: early diastolic mitral inflow velocity; e': early diastolic mitral annular tissue velocity; IABP: intraaortic balloon pump; PCI: percutaneous coronary intervention; PWV: pulse wave velocity.

*Reference: neither high PWV nor high E/e'.

The covariates included in the multivariable models were selected based on statistical significance in univariable analysis.

	Univariable analysis		Multivariable analysis
PCI	1.242 (0.365, 4.223)	0.729	
Euroscore II	1.111 (1.010, 1.223)	0.031	
Euroscore II ≥ 4	2.263 (0.878, 5.834)	0.091	
Euroscore II > 7	3.407 (0.793, 14.633)	0.099	
CHA2DS2-VASc SCORE	1.100 (1.032, 1.173)	0.004	
Ejection fraction	0.996 (0.965, 1.028)	0.825	
Pulmonary hypertension	1.075 (0.979, 1.181)	0.127	
PreOP IABP insertion	0.486 (0.004, 3.507)	0.569	
Three vessel disease	0.571 (0.221, 1.473)	0.246	
Left main disease	0.921 (0.372, 2.283)	0.860	
Urgency	1.254 (0.168, 9.349)	0.825	
CKD: chronic kidney disease; E: early diastolic mitral inflow velocity; e': early diastolic mitral annular tissue velocity; IABP: intraaortic balloon pump; PCI: percutaneous coronary intervention; PWV: pulse wave velocity.			
*Reference: neither high PWV nor high E/e'.			
The covariates included in the multivariable models were selected based on statistical significance in univariable analysis.			

Table 5
Group comparison with Cox regression analysis for all-cause mortality

Group comparison	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
High-E/e'-only vs. High-PWV-only	2.885 (0.582, 14.298)	0.195	1.838 (0.347, 9.743)	0.474
High -PWV-and-E/e' vs. High-PWV-only	7.073 (1.501, 33.324)	0.013	4.687 (0.951, 23.101)	**0.058**
High-PWV-and-E/e' vs. High-E/e'-only	2.452 (0.850, 7.075)	0.097	2.550 (0.841, 7.730)	**0.098**
E: early diastolic mitral inflow velocity; e': early diastolic mitral annular tissue velocity; PWV: pulse wave velocity.				

Discussion

We demonstrated that patients with concurrent elevation of PWV and E/e' carried a higher risk of POAKI, POAF, and POSD in addition to the need for longer ventilator support and hospital stay compared with patients without high PWV and E/e'. Furthermore, the significant long-term survival difference was observed even after adjustment for potential risk factors between the patient groups with and without concurrent elevation.

Due to the absence of early mortality in this study, how arterial stiffness and diastolic filling pressure affect early mortality could not be analyzed. However, POAKI, POAF, and POSD were all significantly affected by the concurrent elevation in PWV and E/e'. Whether these complications are related to early cardiovascular mortality in this kind of population needs to be further investigated [11.12]. Consistent with earlier studies [13] and our report [5], isolated high PWV was an independent risk factor associated with POAKI (OR, 4.8; $p = 0.016$). However, the combination of elevated E/e' and high PWV led to a substantial increase in the odds ratio of POAKI (OR, 22.6; $p < 0.001$) even though the isolated high E/e' was not associated with POAKI. Recently, a retrospective observational study revealed that an E/e' > 15 was an independent predictor of POAKI occurring after OPCAB [9]. There has been some explanations of the association between high E/e' and POAKI. First, the high E/e' indicates elevated LV filling pressure and may contribute to increased intra-abdominal venous pressure and subsequent reduction in renal blood flow and GFR [14]. Second, increased LV filling pressure aggravates hemodynamic instability, which is frequently triggered by lifting the heart during OPCAB, which in turn causes renal ischemia. Third, fluid overload during and after operation can induce capillary dysfunction at the glomerulus and may also trigger POAKI. In fact, high PWV is linked to elevated E/e', which affects postoperative renal function. Increased arterial stiffness triggers premature return of reflected pulse waves, which facilitates diastolic coronary artery filing during late systole [15]. This premature return decreases diastolic pressure and compromises coronary blood flow, which can aggravate the ventricular relaxation disturbance and elevate LV filling pressure [16].

Our data also emphasized the combined impact of elevated arterial stiffness and LV filling pressure on POAF. The isolated high-PWV-only and high-E/e'-only group failed to show statistical significance in predicting POAF, whereas high PWV-and-E/e' group did demonstrate significance. In fact, some reports showed the association only between AF and PWV or between AF and E/e'. PWV has been significantly correlated with left atrial dimension independent of usual determinants such as age, gender, body mass index, ventricular remodeling and filling pressure, and thus associated with the risk of AF [17]. The broad association of diastolic dysfunction and AF has been investigated [18]. Current reviews suggest that left atrial and pulmonary vein pressure overload caused by non-compliant LV lead to atrial myocardial remodeling electrically and structurally, which increases the risk of AF [19]. However, these reports did not investigate either combined effect or isolated effect of PWV and E/e' on AF.

High PWV can elicit elevated pulse pressures, which are correlated with stroke [20]. The carotid-femoral PWV exhibited poor neurocognitive dysfunction after aortic valve replacement [21]. However, this study showed that the risk of POSD was not significantly higher in the high-PWV-only group although it was significantly elevated in the high-PWV-and-E/e' group. In fact, POSD was associated with high baPWV

even in our previous study [5]. However, patients with high baPWV in the previous study involved both the high-PWV-only and high-PWV-and-E/e' groups, suggesting the role of both elevated PWV and E/e' and not from a single elevation. Thus, the combination of high PWV and E/e' has a synergistic effect on POSD.

Elevated E/e' in the two groups with high-E/e'-only and high-PWV-and-E/e' had an impact on long-term overall survival in our study, while isolated elevation of PWV did not. This negative impact is in line with a recent study of 222 patients undergoing transcatheter aortic valve replacement. Advanced and indeterminate diastolic dysfunction was associated with increased mortality during follow-up (median 385 days) [22]. In a cohort of 577 patients undergoing CABG, aortic valve replacement (AVR), or CABG with AVR, the higher LV filling pressure was associated with higher risk of mortality [4]. The prognostic implications of E/e' have been investigated mainly in non-surgical patients with various heart diseases. A retrospective review of 2018 hospitalized patients with heart failure, the all-cause mortality over more than 6 years increased in proportion to the severity of diastolic dysfunction, and in patients with EF < 40%, severe diastolic dysfunction was independently associated with increased all-cause mortality [23]. In a study enrolling 230 patients with non-valvular AF, the cumulative survival during follow-up (average 245 days) was significantly lower in subjects with E/e' > 15 than in those with E/e' ≤ 15, and the high E/e' was an independent predictor of mortality [24].

Results of multiple Cox regression analysis revealed that the elevation in both PWV and E/e', compared with the elevation in neither parameters, were independent prognostic predictors after adjustment of multiple clinical covariates (Table 4), which suggests that long-term survival is affected by the combination of E/e' and PWV but not by either parameter alone. These findings are supported by the results of our pairwise group comparison (Table 5) suggesting a statistical trend of higher hazard ratios in the high-PWV-and-E/e' group compared with the high-E/e'-only and high-PWV-only groups.

This study has some limitations that must be addressed. First, the study did not evaluate PWV as well as E/e' consecutively. A number of parameters were not measured in patients undergoing urgent operation, which contributed to selection bias. Second, the study did not consider the potential effect of antihypertensive drugs or hemodynamic alteration on E/e' and PWV. Third, no perioperative hemodynamic status or transfusion volume affecting postoperative renal function was analyzed. Fourth, we could not determine the overall cause of late mortality and thus a comprehensive survival analysis related to cardiovascular outcome is needed. Lastly, because PWV was not a routinely measured parameter, the data was relatively small and the study was retrospective, suggesting the need for a larger, prospective study to corroborate or further investigate the findings reported here.

Conclusions

Concurrent elevation in arterial stiffness and LV filling pressure may independently affect not only the rates of major postoperative complications including POAKI, POAF, and POSD but also the long-term survival after OPCAB. Large-scale studies are needed to further investigate these preliminary findings.

Abbreviations

baPWV
brachial-ankle pulse wave velocity
E/e’
early diastolic transmitral flow velocity to mitral annular tissue velocity
LV
left ventricular
OPCAB
off-pump coronary artery bypass grafting
POAKI
postoperative acute kidney injury
POAF
postoperative atrial fibrillation
POSD
postoperative stroke/delirium
LITA
left internal thoracic artery
SV
saphenous vein
eGFR
estimated glomerular filtration rate
PODs
postoperative days
LVEF
left ventricular ejection fraction
CKD
chronic kidney disease
VSD
ventilator support duration
HS
hospital stay
COPD
chronic obstructive pulmonary disease.

Declarations

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Authors’ contributions

Conceptualization and methodology: JSC SJO

Project administration: JSC

Data analysis, curation, and validation: JSC SO.

Writing – Original Draft Preparation: JSC

Writing – Review & Editing: JSC, SO

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Availability of data and materials

Statistical data are available from all authors but not available in public.

Ethics approval and consent to participate

All methods were performed in accordance with the 1964 Helsinki Declaration. The study protocol was approved by the Seoul Metropolitan Government - Seoul National University Hospital's institutional review board (IRB No. 10-2021-140), and informed consents were waived by individual participants included in the study.

Consent for publication

Publication has been approved by all authors in this article.

Competing interests

The authors declare that they have no competing interest.

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Figures

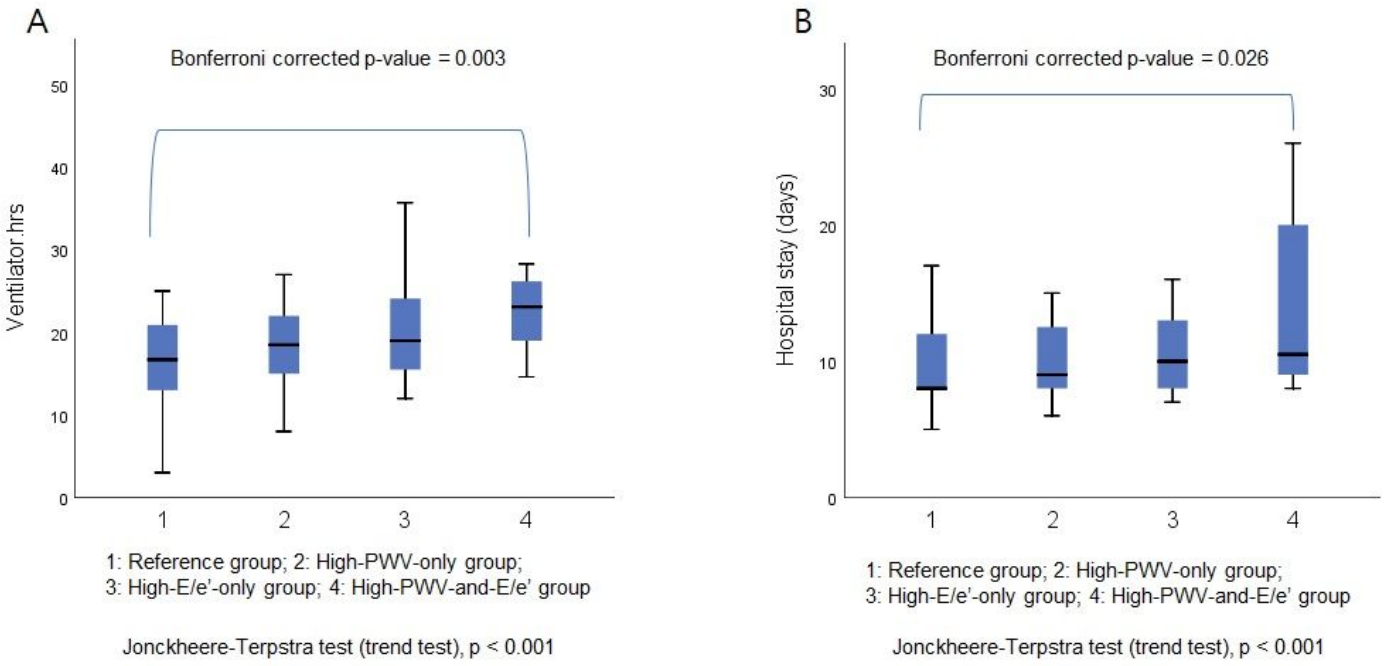

Figure 1

Comparison of ventilator support duration (A) and hospital stay (B).

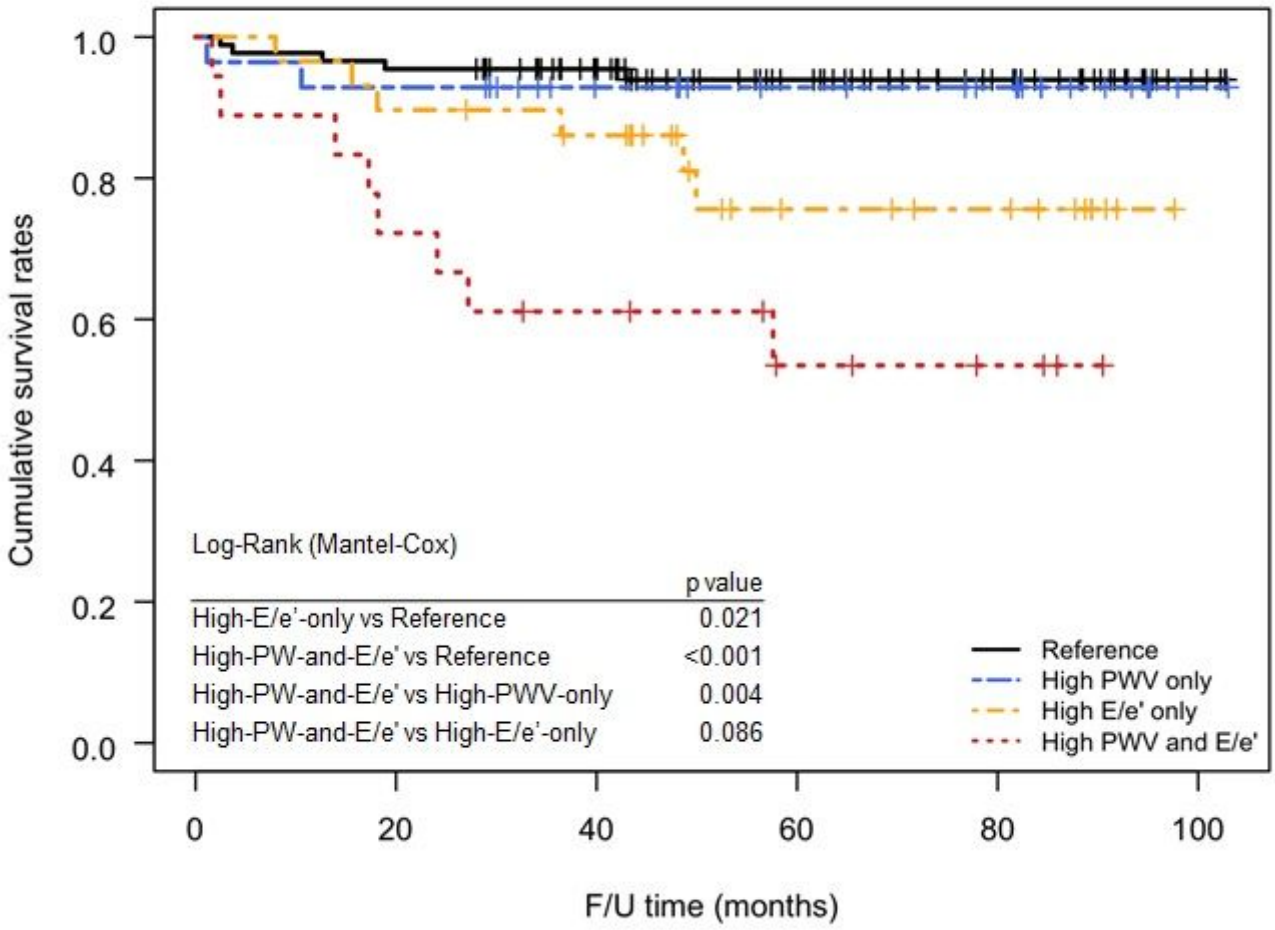

Figure 2

Comparison of Kaplan–Meier overall survival curves.