**Combined Impact of Elevated Arterial Stiffness and Left Ventricular Filling Pressure on outcomes After Off-Pump Coronary Artery Bypass Grafting**

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**Short title: PWV and E/e’ impact**

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Prospective cohort study of OPCAB patients.

Patients with high baPWV but without high E/e’, those with high E/e’ but without high PWV, those with neither high baPWV nor HF, and those with high baPWV and E/e’.

Long-term mortality was associated with AF (hazard ratio, 1.45 [95% CI, 1.33–1.59]), HF (2.07 [1.83–2.36]), and their combination (2.20 [1.96–2.46]). Recurrent stroke was associated with AF 1.50 (1.26–1.78), HF (1.33 [1.01–1.75]), and AF with HF (1.62 [1.28–2.07]).

**Abstract (250) < 4500**

**Background:** Brachial-ankle pulse wave velocity (baPWV) is the simple, non-invasive, gold-standard method for assessing arterial stiffness. However, baPWV has been shown to be associated with renal dysfunction, with a few reports demonstrating an association between baPWV and postoperative acute kidney injury (AKI) among surgical patients.

**Methods:** We retrospectively analyzed preoperative baPWV data that were prospectively collected from 164 patients who underwent off-pump coronary artery bypass grafting (CABG) between April 2013 and July 2019 (mean age: 66.2 ± 10.3 years, 29.3% females). Primarily, baPWV was investigated as an independent predictor of postoperative AKI development; secondarily, the patients were divided into high and low PWV groups according to the optimal baPWV cut-off value. Postoperative complications, mortality, and mid-term survival were compared between the two groups.

**Results:** AKI developed in 30 patients (18.3%). Univariate analysis showed that AKI was significantly associated with baPWV (20.2±7.3 vs. 16.2±2.8 m/s, *p* < 0.001), age, preoperative serum creatinine, and EuroSCORE. Multivariable logistic regression analysis revealed baPWV as independently associated with postoperative AKI even after adjustment for preoperative creatinine, old age (> 75 years), hypertension, diabetes under insulin therapy, and EuroSCORE. Moreover, area under the curve (AUC) analysis indicated that PWV can predict AKI better than preoperative creatinine levels (AUC, 0.781 [95% confidence interval, 0.688 - 0.874] vs. 0.680 [0.568 - 0.792]). The group-dividing baPWV cut-off value for AKI was 19 m/s. There were no 30-day mortality. The in-hospital mortality rates in the high and the low PWV groups were 2.2% (n = 1) and 0.8% (n = 1), respectively (*p* = 0.484). Midterm survival rates were not different between the two groups, but the rate of composite neurologic complication composed of stroke and delirium, was higher, and rate of mechanical ventilatory support was longer, in the high PWV group.

**Conclusions:** Brachial-ankle pulse wave velocity was an independent predictor of postoperative AKI following off-pump CABG, and high baPWVs may affect the composite neurologic outcome and the duration of mechanical ventilatory support.

KEYWORDS

Coronary artery bypass grafting, pulse wave velocity, diastolic dysfunction

Recently, our center revealed through a tissue Doppler

echocardiographic (TDE) analysis that baPWV was significantly

associated with E/e′, an important parameter of left ventricular (LV)

diastolic function [5]. This result was in accordance with several studies

suggesting that AS may contribute to the development of LV diastolic

dysfunction through increased afterload and pulse pressure [6,7].

Although LV diastolic dysfunction has been less frequently dealt with

as a parameter of postoperative outcome, it is an important predictor of

the difficult weaning from cardiopulmonary bypass and the mortality in

cardiac surgery [8,9].

Kim HL, Im MS, Seo JB, Chung WY, Kim SH, et al. (2013) The association

between arterial stiffness and filling pressure in an apparently healthy Korean

population. Cardiovasc Ultrasound. 11: 2.

**Introduction**

Pulse wave velocity (PWV) is now widely accepted as an index representing arterial stiffness [1,2]. 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 filling pressure and has been used to estimate the diastolic function of the heart [3,4]. E/e’ is nowadays being almost routinely checked at echocardiographic evaluation before cardiac surgery and the measurement of PWV is a simple and noninvasive procedure so that it can be easily performed before surgery. In addition, there has been many studies showing that both of elevated PWV and E/e’ are associated with higher risk of cardiovascular events and deaths in various kinds of patient populations [5-7]. But there has been rare study dealing with PWV or E/e’ associated with cardiac surgery outcome. In fact, we elucidated earlier that high brachial-ankle PWV (baPWV) was an independent predictor of postoperative acue kidney injury (AKI) and associated with the composite rate of stroke and/or delirium as well as ventilatory support duration [8]. And also our colleagues demonstrated that high PWV value was significantly linked with elevated left ventricular filling pressure index, E/e’ [9][ Kim HL, Lim WH, Seo JB, Chung WY, Kim SH, Kim MA, Zo JH. Association between arterial stiffness and left ventricular diastolic function in relation to gender and age. Medicine (Baltimore). 2017 Jan;96(1):e5783. doi: 10.1097]. Considering the reported negative impacts of diastolic dysfunction on post-cardiovascular surgery outcomes [10] [Kaw R, Hernandez AV, Pasupuleti V, Deshpande A, Nagarajan V, Bueno H, Coleman CI, Ioannidis JP, Bhatt DL, Blackstone EH ; Cardiovascular Meta-analyses Research Group. Effect of diastolic dysfunction on postoperative outcomes after cardiovascular surgery: A systematic review and meta-analysis. J Thorac Cardiovasc Surg. 2016 Oct;152(4):1142-53. doi: 10.1016/j.jtcvs.2016.05.057.], we therefore hypothesized that the combined impact of elevated PWV and E/e’ would be greater than the impact of single either elevation of the two. came to know about And also we demonstrated that high PWV value was significantly linked with elevated left ventricular filling pressure index, E/e’. After then, we have collected the echocardiographic measurement data including E/e’ and longer-term follow-up data for survival rate.

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

**Methods**

***Patient selection***

The selection of the study sample is shown in Fig 1. To avoid major bias from the influence of cardiopulmonary bypass on postoperative AKI, on-pump CABG cases were excluded. We retrospectively reviewed the electronic medical records of 243 patients who underwent isolated off-pump CABG between April 2013 and July 2019. Our exclusion criteria were as follows: 1) when PWV measurements were not taken, 2) insertion of aorto-iliac or renal stents (grafts), 3) when patients had oliguria or already started dialysis, 4) combination with any other cardiac procedure, and 5) when patients had uncontrolled, severe hypertension (blood pressure >160/100 mmHg). Based on these predetermined criteria, 79 patients were excluded, and the remaining 164 patients were included in this study. The median follow-up duration was 39.2 months (range, 1.6 - 78.0 months). There was no loss to follow-up among the included patients.

**Fig 1. Patient selection.**

CABG, coronary artery bypass grafting; EVAR, endovascular abdominal aortic repair; PWV, pulse wave velocity.

The study protocol was approved by the Seoul Metropolitan Government - Seoul National University Hospital’s institutional review board, and the requirement for informed consent was waived because this retrospective review of medical records could 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 cardiology department, took PWV measurements prospectively before surgery because several prospective studies related with PWV were being performed for the patients with coronary artery disease. The measurement was simple and noninvasive. By just wrapping cuffs around both brachialis and ankles, recordings of pulse volume waveform, blood pressure, phonogram, and heart rate were obtained simultaneously using a volume-plethysmographic apparatus (VP-1000, Colin Co. Ltd.; Komaki, Japan). Higher PWV value means stiffer arterial system. We have already described the calculation of baPWV in the previous report [Choi JS, Oh SJ, Sung YW, Moon HJ, Lee JS. Pulse wave velocity is a new predictor of acute kidney injury development after off-pump coronary artery bypass grafting. PLoS One. 2020;15(4):e0232377. doi:10.1371/journal.pone.0232377]. The mean values between the left and right baPWVs were used for analysis.

A 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 a pulsed-wave Doppler examination of the mitral inflow, as well as tissue Doppler imaging of the mitral annulus. Although we planned to exclude the cases where e′ and E/e′ may not provide a reliable estimate of LV filling pressure due to the severely diseased valves including significant mitral annular calcification and moderate to severe mitral regurgitation, there were no case excluded.

***Surgical techniques***

Details of our off-pump CABG strategy had already been described in the previous study dealing with the association between baPWV and postoperative acute kidney injury (AKI) [Jae-Sung]. In short, we first made 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. And then, 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 a flow competition, the proximal end of the SV graft was attached to the proximal ascending aorta using a partial clamping or a Heatstring III proximal seal system (Maquet holding B.V. & Co., Rastatt, Germany). Sometimes totally arterial bypass was performed using the right internal thoracic artery or radial artery for the patients less than 60 years of age.

***Definitions of postoperative complications***

Perioperative myocardial infarction was defined based upon an elevation of biomarkers (either creatine kinase (CK-MB) concentration >40 ng/mL or peak troponin I levels >15 ng/mL at 12 hours after operation) and the presence of new pathological Q waves or left bundle branch block. Renal function was assessed by serum creatinine and 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 Globall Outcomes (KDIGO) Foundation consensus statement [Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL et al. Kidney Disease: Improving Golbal Outcomes (KDIGO) – clinical practice guideline for acute kidney injury. Kidney Inter. 2012;2(1):1-138.], Postoperative AKI (POAKI) was defined at a stage of 1 or higher, by any of the following benchmarks: urine output <0.5 mL/kg/hr for 6 hours or longer; elevation of serum creatinine within 2 PODs >0.3 mg/dL; and a serum creatinine increase >1.5 times relative to the baseline value within 7 PODs. Postoperative stroke/delirium (POSD) was a composite variable which combined isolated stroke, isolated delirium, and both. Stroke was defined as a cerebral infarction of ischemic or hemorrhagic etiology, or transient ischemic attack based on brain imaging studies and consulting neurologists. To characterize delirium, the practical framework formed by the criteria of the fifth edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-5) was used and the diagnosis was confirmed by consultation to neuropsychiatrists. Postoperative pneumonia was defined as a lower respiratory tract infection with accompanying consolidation detected on chest x-ray. ~~Late mortality was defined as any-cause mortality after POD 30.~~

***Statistical analysis***

For descriptive statistics, categorical variables are expressed as counts and percentages. 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 according to the normally assumption, which was examined by the Kolmogorov–Smirnov test. Post-hoc analysis was also performed using Bonferroni’s t-test or Dunn test. For categorical variables, the Pearson χ2 test or the Fisher’s exact test was used. When some trends of continuous postoperative complication variables, like ventilator support duration, were observed across the groups, it was confirmed by the Jonckheere-Terpstra test.

For the several important postoperative complication parameters, odds ratios of each group compared to the reference group were obtained using multivariable logistic regression models that were adjusted for baseline characteristics including preexisting comorbidities. Survival rate was estimated using Kaplan–Meier methods and between-group comparisons were performed using the log-rank test. In order to evaluate impacts of the risk factors on overall survival, univariable and multivariable Cox proportional hazards model were used. 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).

STATISTICAL ANALYSIS. Categorical variables are expressed as counts and percentages and compared with Pearson c2 test or Fisher exact test. Continuous variables are reported as mean SD or median (interquartile range [IQR]) for nonnormally distributed data and were compared with a 2-sided unpaired Student t test or Wilcoxon rank sum test, as appropriate. The Wilcoxon signed rank test was used to compare pre- and postoperative (pre-dismissal) measurements in patients for whom paired data were available. Kaplan-Meier analysis and the log-rank test were used to create survival curves and estimate survival. Cox proportional hazards analysis was performed to study the association of the clinical and echocardiographic parameters with mortality. The covariates included in the multivariable models were selected based on statistical evidence of a univariate association or known association with outcomes. The associated risk for each outcome was expressed as hazard ratio (HR) with corresponding 95% confidence interval (CI). For survival analysis after identifying RV reverse remodeling, survival was estimated starting from the date of follow-up echocardiogram that identified reverse remodeling. All P values were based on 2-sided tests and were considered statistically significant at P < .05. Analyses were performed using BlueSky Statistics v6.30 (BlueSky Statistics LLC, Chicago, IL) and SPSS v25.0 (IBM Corp., Armonk NY).

**Results**

***Baseline characteristics***

The median age of this study population was 66.2 years old and 79.9% of the patients had triple-vessel disease, median left ventricular ejection fraction (LVEF) was 57.3%, and median EuroSCORE II value was 1.6. In order to assess the effect of each group on the outcomes, the patients were divied into four groups; only baPWV was elevated (High PWV only group), only E/e’ was elevated (High E/e’ only group), both baPWV and E/e’ were elevated (High PWV and E/e’ group), and neither baPWV nor E/e’ was elevated (Reference group). Age, sex, Diabetes, LVEF, eGFR, advanced chronic kidney disease (CKD stage ≥ 4), EuroSCORE II values, and CHA2DS2-VAScSCORE values were different across the four groups (Table 1). Compared to Reference group, CHA2DS2-VAScSCORE value and the rates of old age (>75 yrs), male patients, and diabetes are highest in High PWV and E/e’ group. LVEF was the lowest and EuroSCORE II value was the highest in High E/e’ only group. Estimated GFR was the lowest in High PWV and E/e’ group. However, there were no differences across the groups in the frequencies of cerebrovascular accidents, peripheral arteriopathy, acute myocardial infarction, extent of coronary vessel involvement including left main disease, and previous coronary intervention.

***Postoperative complications***

Table 2 shows the statistics of postoperative complications. The complication variables demonstrating significant difference 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 (p = 0.004), and hospital stay (p = 0.029). In the High PWV and E/e’ group, highest were the rates of POAKI (61.1 %) and POAF (61.1 %) as well as the duration of ventilator support (23.1 hours) and hospital stay (10.5 days). For the ventilator support duration and the hospital stay, box plot was used for group comparison (Fig 1). A respective significant differences of the two time durations were observed only between High-PWV-and-E/e’ and Reference group. Moreover, there were increasing trends of the two in order of Reference, High-PWV-Only, High-E/e’-Only, and High-PWV-and-E/e’ group. Table 3 demonstrates impact of combined elevation of PWV and E/e’ on major postoperative complications under adjustment of various preexisting comorbidities. Although POAKI risk was significantly higher in both High-PWV-only group and High-PWV-and-E/e’ group compared to Reference group, the odds ratio (OR) was much higher in High-PWV-and-E/e’ group (OR (95% confidence interval [CI]=4.8 [1.3-17.1], p=0.016 vs 22.6 [5.9-86.1], p<0.001). With regard to POAF, adjusted OR of POAF was significantly higher only in the High-PWV-and-E/e’ group (OR [CI] = 5.7 [1.9-16.9], p=0.002), while the High-PWV-only and High-E/e’-only group did not have a statistical significance. The risk of POSD was also significantly higher only in the High-PWV-and-E/e’ group as compared to Reference group (OR [CI] = 4.1 [1.1-15.7], p=0.039).

***Overall survivals***

The unadjusted estimated overall survivals of respective groups are depicted as Kaplan-Meier curves in Fig 2. The 7-year survival rates were significantly different across the groups (p<0.001) and were 93.9% (95% CI, 88.9-99.3%), 92.9% (95% CI, 83.8-99.9%), 75.6% (95% CI, 59.9-95.4%), and 53.5% (95% 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=0.021 and p<0.001, respectively). However, when potential risk factors for all-cause mortality were adjusted by multiple Cox regression analysis, the survival difference between the Reference and High-E/e’-group disappeared (Table 4). Looking at inter-group comparison, there were a trend rather than a definite statistical significance when the High-PWV-and-E/e’ group was compared to the High-PWV-only and High-E/e’-only group (HR, 4.7; CI, 1.0-23.1; p=0.058 and HR, 2.6; CI, 0.8-7.7; p=0.098, respectively) (Table 5). We also discovered that the following covariates were independent risk factors for all-cause mortality: CKD grade ≥4 (hazard ratio (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).

**Discussion**

We demonstrated that the patients with concurrent elevation of PWV and E/e’ had higher risk of POAKI, POAF, and POSD as well as longer ventilator support and hospital stay compared to the patients without high PWV and E/e’. More importantly, the significant mid-to-long term survival difference was observed even after adjustment of the potential risk factors between the patient groups with the concurrent elevation and without any elevation.

PWV 와 E/e’ 의미 설명

Because the early mortality was zero in this small patient cohort undergoing OPCAB, effects of arterial stiffness and diastolic filling pressure on early mortality could not be analyzed though but AKI, AF, and stroke which were all affected in this study have been reported to badly influence cardiovascular mortality [7, Tanaka Y, Shah NS, Passman R, Greenland P, Lloyd-Jones DM, Khan SS. Trends in Cardiovascular Mortality Related to Atrial Fibrillation in the United States, 2011 to 2018. J Am Heart Assoc. 2021 Aug 3;10(15):e020163. doi: 10.1161/JAHA.120.020163. Predictors of early cardiac morbidity and mortality after ischemic stroke. Prosser J, MacGregor L, Lees KR, Diener HC, Hacke W, Davis S; VISTA Investigators.

Stroke. 2007 Aug;38(8):2295-302. doi: 10.1161/STROKEAHA.106.471813.] With regard to POAKI, as had been reported earlier by some researchers [ Greenwood SA, Mangahis E, Castle EM, Wang J, Campbell J, Deshpande R, Jayawardene S. Arterial stiffness is a predictor for acute kidney injury following coronary artery bypass graft surgery. J Cardiothorac Surg. 2019;14(1):51. PMID: 30845970 ] and our group [ Choi JS, Oh SJ, Kim H,Sung YW, Moon HJ. The Association between Arterial Stiffness and Post-cardiac Surgery Renal and Diastolic Heart Functions. J Cardiovasc Res. 2016;5:5], [Pulse wave velocity is a new predictor of acute kidney injury development after off-pump coronary artery bypass grafting. Choi JS, Oh SJ, Sung YW, Moon HJ, Lee JS. PLoS One. 2020 Apr 30;15(4):e0232377. doi: 10.1371/journal.pone.0232377], isolated high PWV was found to be an independent risk factor associated with POAKI (OR, 4.8; p=0.016)., However, when high E/e’ was added to the high PWV, odds ratio of POAKI was observed to be more increased (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 E/e’ > 15 was an independent predictor of POAKI developing after OPCAB [Hur M, Nam K, Jo WY, Kim G, Kim WH, Bahk JH. Association Between Elevated Echocardiographic Index of Left Ventricular Filling Pressure and Acute Kidney Injury After Off-Pump Coronary Artery Surgery. Circ J. 2018 Feb 23;82(3):857-865. doi: 10.1253/circj.CJ-17-0660. ] . There has been some explanations to associate high E/e’ with POAKI. First, high E/e’ indicates elevated LV filling pressure and it may contribute to elevations in intra-abdominal venous pressure and a subsequent reduction of renal blood flow and GFR [Lazzeri C,Valente S, Tarquini R, Gensini GF. Cardiorenal syndrome caused by heart failure with preserved ejection fraction. Int J Nephrol. 2011;2011,634903.]. Second, inceased LV filling pressure can aggravate hemodynamic instability which is frequently provoked by lifting a heart during OPCAB, which in turn causes renal ischemia. Third, fluid overload developed during and after operation can be a component of capillary dysfunction at the glomerulus and may also proceed POAKI. In fact, high PWV is linked with elevated E/e’ to affect postoperative renal function. Increased arterial stiffness triggers premature return of reflected pulse waves, which assist with diastolic coronary artery filing, to the coronary artery os during late systole [12]. This premature return decreases diastolic pressure and compromises coronary blood flow, which can aggravate the ventricular relaxation disturbance and elevate LV filling pressure [13,14].

The combined impact of elevated arterial stiffness and LV filling pressure on POAF was also prominent in our data. The isolated High-PWV-only and High-E/e’-only group failed to show statistical significance in predicting POAF but high PWV-and-E/e’ group did demonstrate the significance. Although we did not find a study that investigated an isolated effect of PWV or E/e’ excluding the other like this study, there has been some reports showing the association just between AF and PWV or between AF and E/e’. PWV has been demonstrated to be significantly correlated with left atrial dimension independently of classical determinants like age, gender, body mass index, ventricular remodeling (i.e. dimensions and geometry) and filling pressure, and thus with the risk of AF development. Increased aortic stiffness marked by carotid-femoral PWV has been reported to be associated with lone AF [ **Chen LY, Foo DC, Wong RC, Seow SC, Gong L, Benditt DG, Ling LH. Increased carotid intima-media thickness and arterial stiffness are associated with lone atrial fibrillation. Int J Cardiol. 2013;*168*:3132–3134. doi: 10.1016/j.ijcard.2013.04.034.**]. The broad association of diastolic dysfunction and AF has been examined [Rosenberg MA, Manning WJ. Diastolic dysfunction and risk of atrial fibrillation: a mechanistic appraisal. Circulation. 2012 Nov 6;126(19):2353-62. doi: 10.1161/CIRCULATIONAHA.112.113233. ] [ Nagarakanti R, Ezekowitz M. Diastolic dysfunction and atrial fibrillation. J Interv Card Electrophysiol. 2008; 22:111–118]. Current reviews suggest that left atrial and pulmonary vein pressure overload caused by non-compliant LV lead to atrial myocardial remodeling electrically and structurally, and this creates vulnerable substrate of AF [Melduni RM, Cullen MW. Role of Left Ventricular Diastolic Dysfunction in Predicting Atrial Fibrillation Recurrence after Successful Electrical Cardioversion. J Atr Fibrillation. 2012;5(4):654. Published 2012 Dec 16. doi:10.4022/jafib.654].

High PWV can elicit elevated pulse pressures which has been shown to be correlated with stroke [17,18], and carotid-femoral PWV exhibited poor neurocognitive dysfunction after aortic valve replacement [16]. However, this study showed that the risk of POSD was not significantly higher in the High-PWV-only group though the High-PWV-and-E/e’ group showed the significance. In fact, even our previous report [CHOI JAE SUNG] demonstrated that POSD was associated with high baPWV. However, if we look at more closely, those patients with high baPWV in the previous study included both the High-PWV-only and High-PWV-and-E/e’ group. It could be told that the significance was derived from the both elevation not from the sinlge elevation. Thus, now we think that high PWV and E/e’ can influence on POSD by some synergistic mechanism when they are combined.

Isolated elevation of E/e’ affected mid-to-long term overall survival in our study while isolated elevation of PWV did not. This negative impact is in line with a recent study enrolling 222 patients undergoing transcatheter aortic valve replacement. Advanced and indeterminate diastolic dysfunction were associated with increased mortality during follow-up (median 385 days) [Megaly M, Florea V, Sharma A, Cavalcante JL, Garcia S. Impact of diastolic dysfunction on long-term mortality and quality of life after transcatheter aortic valve replacement. Catheter Cardiovasc Interv. 2020 Apr 1;95(5):1034-1041. doi: 10.1002/ccd.28444.] Septal E/e' ratio is an independent determinant of all-cause mortality in patients with HFrEF.The prognostic implication of E/e' has been addressed in patients with various heart diseases. In a study enrolling 230 patients with non-valvular AF, cumulative survival during follow-up (average 245 days) was significantly lower in a group with E/e’ > 15 than in a group with E/e’ ≤ 15, and the high E/e’ was an independent predictor of mortality from multivariable logistic regression analysis [Okura H, Takada Y, Kubo T, Iwata K, Mizoguchi S, Taguchi H, Toda I, Yoshikawa J, Yoshida K. Tissue Doppler-derived index of left ventricular filling pressure, E/E', predicts survival of patients with non-valvular atrial fibrillation. Heart. 2006 Sep;92(9):1248-52. doi: 10.1136/hrt.2005.082594.]. As a matter of fact, there has been lack of studies investigating long term effect of elevated LV filling pressure on survival but most studies of reference are dealing with the effects on short-term mortality. Hillis et al [Hillis G S, Moller J E, Pellikka P A.et al Noninvasive estimation of left ventricular filling pressure by E/e′ is a powerful predictor of survival after acute myocardial infarction. *J Am Coll Cardiol* 200443360–367. ] reported that E/e′ is a strong predictor of mortality in patients after acute myocardial infarction. In a cohort of 577 patients undergoing CABG, AVR, or CABG with AVR, higher LV filling pressure was associated with higher risk of mortality [Metkus TS, Suarez-Pierre A, Crawford TC, et al. Diastolic dysfunction is common and predicts outcome after cardiac surgery. J Cardiothorac Surg. 2018;13(1):67. Published 2018 Jun 15. doi:10.1186/s13019-018-0744-3.]. 수술후 survival 논문비교, 여기에 PWV 를 합한 것은 더욱 SURVIVAL 이 나쁜 것에 대한 비교, pwv 가 long term survival 에 영향을 줄 수 있음.

??We think it is possible that adjustment of the contributing risk factors, like old age, hypertension, low ejection fraction, and CHA2DS2-VASc score, POAF 는 The exponential rise in AF incidence with advancing age parallels a rapid age-related increase in aortic stiffness.[12](https://www.ahajournals.org/reader/content/1652350be02/10.1161/HYPERTENSIONAHA.116.07650/format/epub/EPUB/xhtml/index.xhtml#R12) [Mitchell GF, Vasan RS, Keyes MJ, Parise H, Wang TJ, Larson MG, D’Agostino RB, Kannel WB, Levy D, Benjamin EJ. Pulse pressure and risk of new-onset atrial fibrillation. JAMA. 2007;297:709–715. doi: 10.1001/jama.297.7.709.]. ? 그밖의 다른 중요 factors like DM, HT, low EF, COPD, ? 우리 데이터에서도 고령의 환자에서 발생률이 높았다. (A% vs B% p= 0.05) 이를 감안, age factor 기여도가 높은데, 이를 adjusted for age factor 하고 나니, PWV, E/e’ 공히 discriminatory value in prediction of POAF 가 떨어진 것으로 생각된다.

but isolated high E/e’ was not. However, we found that risk. infthe already known With regard to POAKI, major postoperacomplications after OPCAB, The importance of renal insufficiency in association with cardiovascular mortality risk cannot be over-emphasized, both in surgical and non-surgical patients. Even minor reductions in GFR may lead to higher cardiovascular mortality rates [7] and even small increases in creatinine levels after CABG have been reported to raise the long-term risk of end-stage renal disease almost 3-fold [8]. Arterial stiffness is one of the possible mechanisms connecting renal insufficiency to cardiovascular events [9,10]. In this study, when the analysis was limited only to those patients with normal or mildly impaired preoperative renal function (eGFR ≥ 50 mLmin1.73m2), there was a negative correlation between baPWV and postoperative eGFR, as depicted in Fig 2. From this association, it can be speculated that postoperative AKI associated with elevated PWV may affect long-term cardiovascular mortality. Therefore, patients with high PWV-associated AKI should have more thorough follow up.

To the best of our knowledge, our study is one of only two that directly investigated the association between post-CABG AKI and PWV [3,5]. The other study was a prospective observational study with a similar design, and their findings were concordant with ours. The other group included 137 patients who underwent isolated CABG and carotid-femoral PWV assessment. Likewise, AKI was defined according to KDIGO practice guidelines. Their entry explanatory variables for multivariable analysis were eGFR, PWV, age, and sex; PWV and age were the final independent predictors. The odds ratio (OR) of developing AKI was 1.54, with every unit (m/s) increase in PWV aligning with our results (OR = 1.34; 95% CI, 1.17 - 1.58; *p* < 0.001). Further analysis regarding the association of PWV with postoperative outcomes was not described [3]. Limitations of that study included the fact that the authors did not elucidate whether the CABG procedures were off-pump, on-pump, or both, which adds the possibility of significant bias caused by the use of cardiopulmonary bypass.

Our observation that baPWV is associated with AKI independently of preoperative serum creatinine concentration or eGFR implies that arterial stiffness indicated by baPWV may affect postoperative renal function via its own mechanism, irrespective of baseline renal function. Although the mechanism is unknown, some inferences may be drawn. Patients with more severe arterial stiffness theoretically have higher pulse pressures. Because elevated pulse pressure can induce increases in afferent arteriolar tone and decreases in effective renal plasma flow [11], those patients are more likely to be afflicted with AKI following CABG, as fluctuating blood pressure can frequently aggravate renal perfusion. Another theory is related to development of type 2 and 4 cardiorenal syndrome.

The resultant elevated LV filling pressure may subsequently contribute to elevations in intra-abdominal venous pressure and a substantial reduction of renal blood flow and GFR [15].

The composite neurologic outcome composed of stroke and delirium was found to be associated with high baPWV, but there was no significant association observed between stroke and delirium separately. There are a lack of data testing the hypothesis that PWV is associated with the post-cardiac-surgery development of stroke or delirium. Additional studies with larger numbers of surgical patients are needed to clarify the strength and causality pattern of this relationship.

***Study limitations***

Lastly, the effect of drugs or haemodynamic alteration on E/E′ and, as a result, prognosis has not been investigated. this was a relatively small, single‐centre, retrospective study. These results therefore need to be confirmed by a larger, prospective, multicentre study

***사망원인을 모두 정확히 알지 못한다.***

There are some limitations that must be taken into consideration. Firstly, preoperative assessment of PWV was not routinely performed, especially in early period of the interval under study and in many urgent CABG cases. Thus, some study subjects who may have met the inclusion criteria were missed, contributing to selection bias. Secondly, most patients (84.8%) had near normal baseline kidney function (CKD stage 1 and 2); therefore, the predictive value of baPWV demonstrated by ROC curve analysis cannot be generalized to patients with more severe renal impairment. Thirdly, antihypertensive medications, such as vasodilators that the patients were taking before surgery, might have influenced the baPWV measurements, but they were not controlled. Fourthly, we did not collect the complete data regarding perioperative hemodynamics and transfusion volume, which must have affected postoperative renal function. Lastly, we expect there would be a long-term correlation between renal function and baPWV in this cohort, but we could not investigate that because the related data were not available.

**Conclusions**

Concurrent elevation of arterial stiffness and left ventricular filling pressure may independently affect not only the rates of major postoperative complications including POAKI, POAF, and POSD but also mid-to-long term survival after OPCAB. These results need to be further investigated in large-scale studies.

**Supporting Information**

**S1 Table. Baseline clinical characteristics of low baPWV and high baPWV groups.**

**Competing interests**

The authors declare that they have no competing interests.

**Author contributions**

Conceptualization and methodology: JSC JSL.

Project administration: JSC JSL

Data curation and validation: JSC JSL SJO YWS HJM.

Supervision: JSL

Visualization: JSC

Writing – Original Draft Preparation: JSC

Writing – Review & Editing: JSC, JSL

**References**

1. King VM, Armstrong DM, Apps R, Trott JR. Numerical aspects of pontine, lateral reticular, and inferior olivary projections to two paravermal cortical zones of the cat cerebellum. J Comp Neurol 1998;390:537-551.

1. Lagny MG, Jouret F, Koch JN, Blaffart F, Donneau AF, Albert A, et al. Incidence and outcomes of acute kidney injury after cardiac surgery using either criteria of the RIFLE classification. BMC Nephrol. 2015;16:76. pmid:26025079
2. Loef BG1, Epema AH, Smilde TD, Henning RH, Ebels T, Navis G, Stegeman CA. Immediate postoperative renal function deterioration in cardiac surgical patients predicts in-hospital mortality and long-term survival. J Am Soc Nephrol. 2005;16(1):195-200. PMID: 15563558
3. Greenwood SA, Mangahis E, Castle EM, Wang J, Campbell J, Deshpande R, Jayawardene S. Arterial stiffness is a predictor for acute kidney injury following coronary artery bypass graft surgery. J Cardiothorac Surg. 2019;14(1):51. PMID: 30845970
4. Nakagawa N, Takahashi F, Chinda J, Kobayashi M, Hayashi Y, Abe M, et al. A newly estimated glomerular filtration rate is independently associated with arterial stiffness in Japanese patients. Hypertens Res. 2008;31:193-201. PMID: 18360037
5. Choi JS, Oh SJ, Kim H,Sung YW, Moon HJ. The Association between Arterial Stiffness and Post-cardiac Surgery Renal and Diastolic Heart Functions. J Cardiovasc Res. 2016;5:5.
6. Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL et al. Kidney Disease: Improving Golbal Outcomes (KDIGO) – clinical practice guideline for acute kidney injury. Kidney Inter. 2012;2(1):1-138.
7. Henry RM, Kostense PJ, Bos G, Dekker JM, Nijpels G, Heine RJ, et al. Mild renal insufficiency is associated with increased cardiovascular mortality: The Hoorn Study. Kidney Int. 2002;62:1402–7. PMID: 12234312
8. Rydén L, Sartipy U, Evans M, Holzmann MJ. Acute Kidney Injury After Coronary Artery Bypass Grafting and Long-Term Risk of End-Stage Renal Disease. Circulation. 2014;130(23):2005-11. PMID: 25239439
9. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Kupelian V, Simonsick EM, Havlik R, et al. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. Circulation. 2005;111: 3384–90. PMID: 15967850
10. Schillaci G, Pirro M, Mannarino MR, Pucci G, Savarese G, Franklin SS, et al. Relation between renal function within the normal range and central and peripheral arterial stiffness in hypertension. Hypertension. 2006;48:616–21. PMID: 16952976
11. Verhave JC, Fesler P, du Cailar G, Ribstein J, Safar ME, Mimran A. Elevated pulse pressure is associated with low renal function in elderly patients with isolated systolic hypertension. Hypertension. 2005;45(4):586-91. Epub 2005 Feb 28. PMID: 15738348
12. Williams B, Lacy PS. Central haemodynamics and clinical outcomes: going beyond brachial blood pressure? Eur Heart J. 2010;31:1819-22. PMID: 20472919
13. Mottram P, Haluska B, Leano R, Carlier S, Case C, Marwick TH. Relation of arterial stiffness to diastolic dysfunction in hypertensive heart disease. Heart. 2005;91(12):1551-6. PMID: 16287739
14. Leite-Moreira AF, Correia-Pinto J, Gillebert TC. Afterload induced changes in myocardial relaxation a mechanism for diastolic dysfunction.Cardiovasc Res. 1999;43:344-53. PMID: 10536664
15. Lazzeri C,Valente S, Tarquini R, Gensini GF. Cardiorenal syndrome caused by heart failure with preserved ejection fraction. Int J Nephrol. 2011;2011,634903. PMID: 21331316
16. Kidher E, Harling L, Sugden C, Ashrafian H, Casula R, Evans P, et al. Aortic stiffness is an indicator of cognitive dysfunction before and after aortic valve replacement for aortic stenosis. Interact Cardiovasc Thorac Surg. 2014;19: 595-604. PMID: 24928212
17. Benjo A, Thompson RE, Fine D, Hogue CW, Alejo D, Kaw A, et al. Pulse pressure is an age-independent predictor of stroke development after cardiac surgery. Hypertension. 2007;50:630–5. PMID: 17785628
18. Fontes M, Aronson S, Mathew JP, Miao Y, Drenger B, Barash PG, et al. Pulse pressure and risk of adverse outcome in coronary bypass surgery. Anesth Analg. 2008;107:1122–9. PMID: 18806013
19. Domanski MJ, Davis BR, Pfeffer MA, Kastantin M, Mitchell GF. Isolated systolic hypertension: prognostic information provided by pulse pressure. Hypertension. 1999;34:375–80. PMID: 10489379