

# Preoperative Left Ventricular Diastolic Dysfunction Is Associated with Pulmonary Edema after Carotid Endarterectomy

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## Abstract

This retrospective study was aimed to investigate the association between preoperative left ventricular (LV) cardiac function and the incidence of postoperative pulmonary edema (PE) in patients undergoing carotid endarterectomy (CEA). Most patients undergoing CEA for carotid artery stenosis have concomitant heart diseases, leading to hemodynamic instability that can cause postoperative cardiac complications such as cardiac heart failure. LV diastolic function has recently been recognized as an independent predictor of adverse cardiac events in patients undergoing cardiovascular surgery. We analyzed clinical data from the anesthetic and medical records of 149 consecutive patients who underwent CEA at our university hospital between March 2012 and March 2018. LV systolic and diastolic function were evaluated by ejection fraction and the ratio of LV early diastolic filling velocity to the peak velocity of mitral medial annulus ( $E/e'$ ). Postoperative PE was diagnosed based on chest X-ray and arterial gas analysis by two independent physicians. Postoperative PE was developed in four patients (2.8%). Patients with postoperative PE were not related to preoperative low ventricular ejection fraction, but had a significantly higher  $E/e'$  ratio than those without PE ( $P = 0.01$ ). Furthermore, there was an increasing trend of PE according to the  $E/e'$  category. Preoperative LV diastolic function evaluated by  $E/e'$  was associated with the development of postoperative PE in patients who underwent CEA. The results suggest that the evaluation of LV diastolic dysfunction could be possibly useful to predict PE in patients undergoing CEA.

Key words: carotid endarterectomy, pulmonary edema, preoperative cardiac function, left ventricular diastolic dysfunction

## Introduction

Most patients undergoing carotid endarterectomy (CEA) for carotid artery stenosis are accompanied by comorbidities, e.g. hypertension, diabetes, coronary artery disease, and hyperlipidemia; this leads to hemodynamic instability following CEA. Patients undergoing CEA are at high risk for cerebral and cardiac complications—for example, major stroke (0.67%), minor stroke (1.33%), wound hematoma (3.33%), myocardial infarction (1.33%) and pulmonary edema (PE) (0.6–2.1%).<sup>1,2)</sup>

Postoperative hypertension or hypotension is associated with perioperative mortality, stroke, and cardiac complications.<sup>3)</sup> Hypertension could easily induce PE and heart failure (HF), which are considered to be associated with the cardiac function, particularly the left ventricular (LV) systolic function, in such patients. However, LV diastolic function has recently been reported as an independent predictor of prognosis and adverse cardiac events, including PE, in patients undergoing cardiovascular and non-cardiac surgeries.<sup>4–8)</sup> Therefore, we aimed to investigate the relation between preoperative LV cardiac function and the incidence of postoperative PE in patients undergoing CEA.

## Materials and Methods

This retrospective study was approved by our Institutional Review Board (IRB No. 15-10-15). We analyzed

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clinical data from the anesthetic and medical records of 149 consecutive patients who underwent CEA at our university hospital between March 2012 and March 2018. Exclusion criteria of our study were emergency case and dialysis.

### Echocardiographic data

Transthoracic echocardiography with tissue Doppler measurements was performed before surgery by an experienced clinical laboratory technologist on all patients. LV systolic function was evaluated by LV ejection fraction (EF) using the biplane Simpson's technique. Early trans-mitral inflow velocity ( $E$ ), deceleration time, and late trans-mitral inflow velocity ( $A$ ) were determined using pulse-wave Doppler echography in the apical four chamber view, and the  $E/A$  as a basic parameter of LV diastolic function was acquired. Early diastolic mitral annular velocity ( $e'$ ) was determined by pulse-wave tissue Doppler imaging at the septal side of the mitral annulus, and the ratio of LV early diastolic filling velocity to the peak velocity of mitral medial annulus ( $E/e'$ ) correlated with left atrial pressure that elevated in the presence of LV diastolic dysfunction was acquired.

### Definition of left ventricular dysfunction

Left ventricular systolic dysfunction was defined as LVEF <50%. LV diastolic function was defined as normal when  $E/e' < 8$ , and LV diastolic dysfunction was defined as  $E/e' > 15$ .

### Anesthetic management

Anesthesia was induced with propofol (1.5–2.0 mg/kg) and fentanyl (10–20  $\mu$ g/kg) or remifentanyl (0.2–0.3  $\mu$ g/kg/min), and tracheal intubation was performed following the induction of muscular relaxation with rocuronium (0.6–0.9 mg/kg). Anesthesia was maintained with sevoflurane (1.5–2.0%), oxygen–air mixture (FIO<sub>2</sub> 0.4), and continuous infusion of remifentanyl (0.1–0.2  $\mu$ g/kg/min). A radial artery catheter and a peripherally inserted central catheter were placed in all patients for the measurement of arterial blood pressure and the administration of nitroglycerin or catecholamine. Patients were transferred to the surgical intensive care unit (SICU) without extubation after surgery and underwent artificial respiration with sufficient sedation by propofol. They were monitored for the bispectral index using VISTA (Aspect Medical Systems, MA, USA) and for regional cerebral oxygen saturation using near-infrared spectroscopy (INVOS; Covidien Somanetics, MI, USA) in the SICU. Patients' blood pressure was strictly controlled within 100–120 mmHg of systolic pressure for preventing cerebral

hyperperfusion syndrome (CHS). At the next day of surgery, patients were extubated when the blood flow velocity of their middle cerebral artery (MCA), measured with transcranial Doppler, did not exceed that of preoperative data. Patient's blood pressure was continuously controlled using vasodilators after extubation.

### Definition of pulmonary edema

Postoperative PE was defined as signs on the chest X-ray and low PaO<sub>2</sub>/FIO<sub>2</sub> (P/F) of <250 mmHg after surgery. Postoperative PE was confirmed by two independent physicians. We examined the incidence of PE in three groups classified according to  $E/e'$ : <8, 8–15, and >15. Information on perioperative fluid balance and minimal saturation was collected from the anesthetic and medical records.

### Statistical analysis

The Statistical Package for Social Science program version 23.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The primary outcome was the incidence of PE and its relation to preoperative LV diastolic dysfunction. Differences between groups were evaluated for statistical significance using Welch's *t*-test and the Chi-square test. Multivariate logistic regression was used to adjust for the effects of factors. A *P*-value of <0.05 was considered to be statistically significant.

## Results

We included 149 patients [119 men (80%), 30 women (20%); mean age, 73.4  $\pm$  7.3 years] in this study and no patients were excluded. Four patients (2.8%) developed PE 2–4 days after surgery. There was no upper airway obstruction such as laryngospasm or glottis edema in these patients perioperatively. There were no significant differences in demographics, comorbidities and medications between patients with and without PE (Table 1).

Preoperative data of transthoracic echocardiography with and without PE is shown in Table 2. Patients with PE had a significantly higher  $E/e'$  ( $P = 0.01$ ) than those without PE. However, there were no significant differences in LVEF, left atrial volume index, ratio of peak early and late (atrial) flow of mitral inflow ( $E/A$ ), and deceleration time (DcT) of the  $E$ -wave velocity between the groups. There were four patients with LV systolic dysfunction (EF <50%), but no patients developed with PE. Table 3 showed the result of exact logistic regression. Odds ratio (OR) of developed PE was increased in those who have higher  $E/e'$  after adjusting age and EF (OR = 3.9, 95% CI: 1.2–12.7).

**Table 1 Patients' characteristics with and without PE**

	PE (n = 4)	Non-PE (n = 145)	P-value
Demographics			
Age (years)	77.0 (73.0–81.0)	73.3 (72.1–74.5)	0.18
Height (cm)	155.8 (147.7–163.8)	161.0 (159.6–162.0)	0.31
Weight (kg)	65.0 (57.3–72.7)	58.9 (57.3–60.6)	0.23
Comorbidities			
Hypertension	3	111	0.94
Diabetes mellitus	1	57	0.56
OMI	2	27	0.12
Hyperlipidemia	4	97	0.16
Medications			
$\beta$ -blocker	0	5	0.71
Ca-blocker	3	51	0.10
ARB	2	32	0.19
Aspirin	3	70	0.29
Clopidogrel	1	78	0.26
Statin	4	97	0.16

Data are expressed as number of patients or mean (95% confidence interval). ARB: angiotensin receptor blockers, OMI: old myocardial infarction, PE: pulmonary edema.

**Table 2 Preoperative data of transthoracic echocardiography with and without PE**

	PE (n = 4)	Non-PE (n = 145)	P-value
LVEF (%)	75.0 (69.2–80.7)	69.6 (68.3–70.9)	0.17
LVEF <50% (n)	0	4	0.74
LAVI (mL/m <sup>2</sup> )	22.9 (19.6–26.3)	22.8 (20.8–24.9)	0.93
E/A	0.75 (0.61–0.88)	0.77 (0.65–0.9)	0.72
DcT (ms)	284 (203.1–364.9)	255.3 (243.5–267.1)	0.54
E/e'	15.7 (13.4–17.9)	8.9 (8.5–9.3)	0.01*

Data are expressed as means and 95% confidence interval. \*Welch's *t*-test was used for differences in mean value. PE: pulmonary edema, LVEF: left ventricular ejection fraction, LAVI: left atrial volume index, E/A: ratio of peak early and late (atrial) flow of mitral inflow, DcT: deceleration time of the E-wave velocity, E/e': ratio of LV early diastolic filling velocity to the peak velocity of mitral medial annulus.

**Table 3 Odd ratios and 95% confidence interval of PE**

Variables	Adjusted OR (95% CI)	P-value
E/e'	3.91 (1.2–12.7)	0.02*
LVEF	1.14 (0.95–1.36)	0.17
Age	1.09 (0.92–1.28)	0.32
In–out balance	1.00 (0.99–1.00)	0.21

\*Multivariate logistic regression was used to adjust for the effects of factors. PE: pulmonary edema, OR: odds ratios, CI: confidence interval, E/e': ratio of LV early diastolic filling velocity to the peak velocity of mitral medial annulus, LVEF: left ventricular ejection fraction.

**Table 4 Incidence of PE classified according to E/e'**

E/e'	PE/non-PE	Ratio (%)
<8	0/59	0
8–15	1/85	1.2
>15	3/1	75.0

*P* = 0.002. Chi-square test was used for trend analysis for proportions. PE: pulmonary edema, E/e': ratio of LV early diastolic filling velocity to the peak velocity of mitral medial annulus.

Three of four patients with LV diastolic dysfunction ( $E/e' >15$ ) developed PE. Furthermore, the proportion of  $E/e' >15$  was higher in patients with PE ( $P = 0.002$ ). Conversely, all patients with  $E/e' <8$ —defined as normal LV diastolic function—did not develop PE (Table 4).

Table 5 shows the perioperative parameters. There were no significant differences in fluid in–out balance in the perioperative period. *P/F* on the day after surgery in patients with PE was significantly lower than that in those without PE ( $P = 0.0001$ ).

One patient suspected CHS developed PE postoperatively. As there were the presence of parameter suspected CHS as follow: the increase of right regional cerebral oxygen saturation with INVOS, the blood flow velocity of right MCA with transcranial Doppler and the blood flow of right cerebral hemisphere with single-photon emission computed tomography, the patient was managed to control her blood pressure strictly by the adequate sedation under mechanical ventilation and the administration of calcium channel blocker and nitroglycerin for 3 days after CEA. Three were no cerebral hemorrhage or infarction on CT postoperatively. The patient developed PE the day after extubation, but her respiratory condition was improved without re-intubation. PE of other three patients had improved within several days after CEA, and no patients required artificial respiration management.

**Table 5** Perioperative parameters in patients with and without PE

	PE (n = 4)	Non-PE (n = 145)	P-value
Duration of operation (min)	216.8 (151.2–282.3)	169.5 (164.4–174.6)	0.25
Duration of anesthesia (min)	322.8 (261.1–384.4)	275.7 (270.2–281.2)	0.23
In–out balance (mL)			
Operative day	–132.5 (–581.9–316.9)	8.6 (–268.7 to –49.8)	0.59
POD1	648.3 (43.1–1253.4)	478.3 (373.1–583.6)	0.63
2	479.5 (–146.8–1105.8)	28.4 (–103.8–160.6)	0.24
3	309.0 (–877.6–1495.6)	–441.1 (–591.2 to –290.9)	0.31
Total of POD1–3	1304.3 (–464.2–3072.7)	84.9 (–169.7–339.5)	0.27
P/F at POD1 (mmHg)	223 (200.6–244.4)	361 (348.5–372.5)	0.0001*

Data are expressed as mean (95% confidence interval). \*Welch's *t*-test was used for differences in mean value. PE: pulmonary edema, POD: postoperative day, P/F: PaO<sub>2</sub>/FIO<sub>2</sub>.

## Discussion

Our results demonstrated that postoperative PE developed in 2.8% of patients undergoing CEA and that this was related to preoperative LV diastolic dysfunction.

In this study, PE was defined as signs of congestion on the chest X-ray and postoperative P/F of <250 mmHg, and a ratio of patients (2.8%) defined as having postoperative PE was approximately equivalent to that in previous reports. PE is mainly associated with an elevated LV diastolic pressure concomitant with pulmonary venous pressure; therefore, it is strongly related to LV function and HF. LV systolic function was traditionally thought to be associated with chronic HF. However, isolated diastolic LV dysfunction without LV systolic dysfunction is also an independent factor of postoperatively developed PE, 30-day and long-term cardiovascular outcomes in patients undergoing elective vascular surgery.<sup>7)</sup> Apart from our results, preoperative LV diastolic dysfunction has recently been reported to correlate with postoperative PE,<sup>6,7)</sup> and is an independent risk factor in patients undergoing non-cardiac surgery.<sup>8)</sup> It has recently been recognized that a half of patients with chronic HF have normal systolic function with LVEF >50%: HF preserved EF (HFpEF).<sup>9)</sup> In the presence of LV diastolic dysfunction, LV end-diastolic pressure is easily elevated, which results in PE. Therefore, the preoperative evaluation of not only LV systolic function but LV diastolic function is also important in patients of high-risk surgeries, including CEA. In a limited number of our cases, the patient with diastolic dysfunction developed PE, but patients with isolated LV systolic dysfunction did not.

The evaluation of LV diastolic function can be assessed by echocardiography using pulse Doppler

flow and tissue Doppler imaging.<sup>10)</sup> The *E/e'* measured by tissue Doppler imaging can predict LV filling pressure<sup>11,12)</sup> and is considered as a relatively load independent parameter of LV diastolic function. In this present study, the *E/e'* was significantly higher in patients with PE than that in those without it. However, *E/A*, traditional parameter of LV diastolic function was not significantly different between the groups. This parameter is strongly influenced by loading conditions, heart rate, and rhythm disturbances and is limited in several clinical situations.<sup>13–15)</sup> DcT may also be inadequate as the parameter of LV diastolic dysfunction due to because it occasionally shows pseudonormal. Therefore, the *E/e'* is a more effective parameter than *E/A* or DcT in clinical settings. *E/e'* of >15 correlates with increased LV filling pressure, whereas *E/e'* of <8 is associated with normal LV filling pressure.<sup>16)</sup> The diagnosis of LV diastolic dysfunction in patients with *E/e'* of 8–15 needs to be implemented with other information such as brain natriuretic peptide (BNP), echo Doppler flow, echo-derived parameters, or the presence of atrial fibrillation. In a case of no data of BNP and other, an *E/e'* of >15 as an appropriate cut-off value is used to define LV diastolic dysfunction.<sup>10,17)</sup> In this study, we evaluated the incidence of PE in three categories of *E/e'*: <8, 8–15, and >15. There was an increasing trend of PE according to the *E/e'* category.

The mechanism of LV diastolic function is now recognized as based on a systemic proinflammatory state induced by comorbidities—for example, age, obesity, hypertension, diabetes, chronic obstructive pulmonary disease, anemia (iron deficiency), hyperlipidemia, and end-stage liver and renal diseases.<sup>18,19)</sup> Risk factors for carotid artery stenosis are age and any comorbidities such as hypertension, diabetes, myocardial infarction, and hyperlipidemia, which overlap as risk factors for LV diastolic dysfunction.<sup>20)</sup>

Left ventricular diastolic dysfunction is highly prevalent with advancing age and the progression of diastolic dysfunction is an independent risk factor for HF in the elderly.<sup>21)</sup> In this study, most of the patients had comorbidities such as age, hypertension, diabetes, and hyperlipidemia, and all of the patients who developed PE had hyperlipidemia. Angiotensin converting enzyme inhibitor or beta-blocker is not effective on HFpEF. There are a few reports about the effects of statins on LV diastolic function.<sup>22–25)</sup> In this study, all patients with hyperlipidemia were treated with statins: 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors. However, the effects of statins related to diastolic function in patients with PE are unclear in this study.

Excess fluid balance is also concern with PE, especially in patient reduced cardiac function. In this study, there were no significant differences in fluid in–out balance in the perioperative period. Intravenous fluid infusion was controlled at 40–60 mL/h rate of administration in the postoperative period. However, oral fluid infusion after restarting the ingestion was not regulated. There is some possibility of that postoperative management of fluid balance may influence the development of PE. In this study, the fluid balance of the patient developed PE suspected CHS was over 1000 mL/day for 3 days after CEA because the quantity of sedative and hypotensive drug administered for the purpose of controlling patient's blood pressure to avoid the CHS increased. PE of this patient whose preoperative  $E/e'$  was <15 may be correlated with excessive fluid balance after CEA. Neurogenic PE or negative pressure PE are known as rare cause of PE after neurosurgery. However, these pathogenesis are contradicted in patients developed PE of this study because there were no intracranial lesion or upper airway obstruction perioperatively.

This study has several limitations. First, it was a retrospective study, and the treatment strategy was not controlled. The attending anesthesiologist or surgeon managing perioperative fluid volume referred to arterial pressure and urinary output.

Second, in our hospital patients underwent CEA are continued to mechanical ventilation under sedation until the next day of surgery to avoid CHS. Although this protocol may not be a standard, it based on a report that poor postoperative control of blood pressure was significantly associated with the development of intracranial hemorrhage in patients with CHS after CEA.<sup>26)</sup> The patients are extubated at the next day of surgery after confirming that the blood flow velocity of their MCA measured by transcranial Doppler did not exceed that of preoperative data. This protocol may be criticized not

to be able to assess patient's neurological status after surgery, but we manage these patients with emphasis avoiding CHS.

Third, the diagnosis of diastolic dysfunction using  $E/e'$  needs other parameters including BNP level, color Doppler flow parameters, and atrial fibrillation—especially in patients with  $E/e'$  of 8–15. However, in our retrospective study, we did not measure these parameters in all patients and could not evaluate this. The prospective study with more parameters is necessary to indicate an adequate diagnostic criteria.

## Conclusion

Preoperative LV diastolic dysfunction evaluated by  $E/e'$  correlated with the development of postoperative PE in patients undergoing CEA. The results suggest that the preoperative evaluation of LV diastolic function could be possibly useful to predict PE in patients undergoing CEA. Closely perioperative management may be important to avoid postoperative PE in patients with LV diastolic dysfunction.

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## Conflicts of Interest Disclosure

None of the authors have any conflict of interest associated with this study.

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