Positive end-expiratory pressure aggravates left ventricular diastolic relaxation further in patients with pre-existing relaxation abnormality


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Editor’s key points
- PEEP can adversely affect cardiac output.
- Doppler tissue imaging (DTI) measures regional myocardial velocities during systole and diastole.
- DTI showed that PEEP worsened diastolic function in patients with existing impaired LV function.

Background. Positive end-expiratory pressure (PEEP) has been known to adversely influence cardiac output. Even though left ventricular (LV) diastolic function significantly contributes to LV performance, the effects of PEEP on LV diastolic function remains controversial. We, therefore, aimed to examine the effects of PEEP on LV diastolic function by use of pulsed wave Doppler tissue imaging in patients with pre-existing LV relaxation abnormality.

Methods. Seventeen patients with peak early diastolic velocity of lateral mitral annulus ($E'$), 8.5 cm s$^{-1}$ among patients who underwent coronary artery bypass graft surgery were evaluated. Echocardiographic and haemodynamic variables were measured with 0, 5, and 10 cmH$_2$O of PEEP. $E'$ and deceleration time (DT) of peak early transmitral filling velocity ($E$) were used as echocardiographic indicators of LV diastolic function.

Results. Mean arterial blood pressure decreased during 10 cmH$_2$O PEEP, compared with that during 0 cmH$_2$O PEEP. $E'$ showed a gradual and significant decrease with an incremental increase in PEEP ($6.9 \pm 0.9$, $5.8 \pm 0.9$, and $5.2 \pm 1.2$ cm s$^{-1}$ during 0, 5, and 10 cmH$_2$O PEEP, respectively), and DT of $E$ was prolonged during 10 cmH$_2$O PEEP, compared with that during 0 cmH$_2$O PEEP.

Conclusions. Increasing PEEP led to a progressive decline in LV relaxation in patients with pre-existing LV relaxation abnormality.

Keywords: echocardiography; heart, myocardial function; ventilation, positive end-expiratory pressure

Although positive end-expiratory pressure (PEEP) ventilation is recommended to improve arterial oxygenation, PEEP usually exerts detrimental effects on cardiac output. Restricted venous return caused by the elevated intra-thoracic pressure during PEEP has been known to be the major cause of decreased cardiac output.1–3 Left ventricular (LV) diastolic filling is affected by LV diastolic function as well as venous return, and the increased pericardial pressure during PEEP has been considered to constrain LV diastolic expansion, leading to limited LV diastolic filling.1–3 Even though LV diastolic function has a significant influence on LV performance,4 few studies have investigated LV diastolic function during PEEP and these have yielded conflicting results regarding LV diastolic function during PEEP.5–6

In patients with reduced diastolic function, elevated LV filling pressure is usually observed, precipitating myocardial ischaemia by increasing the LV wall tension.7 If the lungs of patients with diastolic dysfunction are ventilated using PEEP, there is the possibility of deterioration of pre-existing myocardial perfusion abnormalities as PEEP ventilation has been known to decrease myocardial perfusion.8–9 This effect of PEEP might have an unfavourable effect on cardiac function, including cardiac diastolic function.

Previous studies regarding the effect of PEEP on diastolic function evaluated cardiac diastolic function using conventional Doppler echocardiography. However, conventional Doppler echocardiography has limitations in that echocardiographic parameters which represent LV diastolic function are preload-dependent.10 Therefore, it may be complicated to evaluate LV diastolic function using conventional Doppler echocardiography during PEEP ventilation. In contrast, DTI, a novel ultrasound tool which measures regional myocardial velocities during systole and diastole, is preload-independent in the patient with pre-existing LV relaxation impairment and
less operator-dependent than two-dimensional or conventional Doppler echocardiography.\textsuperscript{11–16} Peak early diastolic velocity of the mitral annulus on DTI has been known to represent LV relaxation more sensitively than the parameter in conventional Doppler echocardiography.\textsuperscript{11, 12}

We, therefore, aimed to investigate whether LV diastolic function is affected by increasing PEEP in the patients with pre-existing LV relaxation impairment by use of pulsed wave DTI.

Methods

The Institutional Review Board at the Asan Medical Center approved this study of patients undergoing elective coronary artery bypass graft surgery, and written informed consent was obtained from all patients. Patients were included in the study if they showed normal sinus rhythm on preoperative electrocardiogram and LV ejection fraction >50% with normal LV basal lateral segment wall motion on preoperative echocardiographic evaluation. Exclusion criteria were age <18, patients with valvular heart disease that was not surgically corrected, pulmonary disease, or peak early diastolic velocity of lateral mitral annulus (E') ≥ 8.5 cm s\textsuperscript{-1} immediately after anaesthetic induction. Seventeen patients (13 men and 4 women) with a mean age of 67.4 ± 8.4 years were evaluated for this study.

No premedication was given to any patients. A total of 500 ml of colloid (Voluven\textsuperscript{w}, Fresenius Kabi, Germany) was infused for 30 min before the first measurement in order to minimize the cardiac output reduction caused by restricted venous return when PEEP is applied. Anaesthesia was induced with a bolus i.v. injection of 0.2 mg kg\textsuperscript{-1} etomidate followed by 0.6 mg kg\textsuperscript{-1} rocuronium to facilitate orotracheal intubation. Simultaneously, continuous infusion with propofol and remifentanil using a target controlled infusion pump (TCI pump, Orchestra Base Primea\textsuperscript{w}, Fresenius Vial, France) was initiated under Bispectral Index monitoring (BIS, A-2000, Aspect Medical Systems, Newton, MA, USA). An arterial catheter was inserted in a radial artery and a pulmonary artery catheter (Swan-Ganz CCOmbo V CCL/SvO\textsubscript{2}/CEDV, Edwards Lifesciences LLC, Irvine, CA, USA) was inserted via the right internal jugular vein. The lungs were mechanically ventilated in a volume controlled mode with a tidal volume of 8 ml kg\textsuperscript{-1} of body weight at a respiratory rate of 10 min\textsuperscript{-1} using 50–100% oxygen according to patient’s clinical status. Then, the effect site concentration of remifentanil was set to 5 ng ml\textsuperscript{-1} and the effect site concentration of propofol was titrated to maintain a BIS value of 50–55.

Measurements of the echocardiographic, haemodynamic and respiratory variables were performed before surgical skin incision under fixed effect site concentration of propofol and remifentanil. All echocardiograms were obtained using an IE33 Ultrasound System (Philips Ultrasound, Bothell, WA, USA) and a S7-2 OMNI probe. One echocardiographer performed all echocardiographic examinations. Initially, E' was measured to determine whether the patient met the criteria for diastolic relaxation impairment, or E' < 8.5 cm s\textsuperscript{-1}.\textsuperscript{15, 16} If a patient showed E' < 8.5 cm s\textsuperscript{-1}, measurements of echocardiographic, haemodynamic and respiratory variables were performed at baseline with 0 cmH\textsubscript{2}O PEEP and then after increases of PEEP levels. The sequence of increasing PEEP levels was randomized after the first measurement in order to exclude the effect of the first PEEP level on the second PEEP level. The second measurements were performed at the end of 10 min of 5 cmH\textsubscript{2}O PEEP or 10 cmH\textsubscript{2}O PEEP according to the randomization table, followed by 10 min of 0 cmH\textsubscript{2}O PEEP, and then the third at the end of 10 min of the other PEEP level. Standard LV short axis and four-chamber views were obtained by standard transgastric and mid-oesophageal views. For recording of pulsed wave DTI, the sample volume was placed at the lateral side of the mitral annulus. For pulsed wave Doppler recording of mitral inflow, the sample volume was positioned between the tips of the open mitral leaflets using optimal alignment with transmitral blood flow. Comprehensive echocardiographic assessment included measurement of the following variables (Fig. 1): E', late diastolic velocity of lateral mitral annulus (A'), peak systolic velocity of lateral mitral annulus (S'), secondly placed IVRT (IVRT), peak early (E) and late (A) transmitral filling velocities, deceleration time (DT) of E, and end-diastolic and end-systolic dimension (EDD, ESD) of LV. From these data, fractional shortening (FS) was calculated as $[FS=\left(EDD-ESD\right)/EED\times 100]$. All images of echocardiography along with electrocardiogram were stored digitally for subsequent offline analysis by one of two investigators who were blinded to other participant data. All variables were measured at end-expiration over three preferably consecutive cardiac cycles and averaged. To determine intra-observer and inter-observer variability, a random sample of 25% of DTI recordings, transmitral filling velocities, EDD, and ESD was submitted twice to the first investigator and once to a second investigator. The inter-observer variabilities were then calculated as the mean absolute difference between the two readings from the first and the second investigator divided by their mean and expressed as a percentage and their 95% confidence intervals (CI). Similarly, the intra-observer variabilities were calculated as the mean absolute difference between the two readings from the first investigator divided by their mean and expressed as a percentage and their 95% CI. Haemodynamic parameters, including mean arterial blood pressure (ABP), heart rate (HR), central venous pressure (CVP) and pulmonary artery occlusive pressure (PAOP), and respiratory variables, including the airway peak and plateau pressure, were measured at the time of echocardiographic recording during different levels of PEEP.

Data were expressed as mean (so) or median (interquartile range) for parametric and non-parametric data, respectively. Echocardiographic, haemodynamic, and respiratory variables were compared using one way repeated measures analysis of variance (ANOVA) with Holm-Sidak multiple comparison procedure or repeated measures ANOVA on Rank with Tukey multiple comparison procedure, as appropriate. The sample size calculation was based on our pilot study regarding E'.
estimating that a size of 17 patients would allow an \( \alpha \) of 5% and a power of 80% using the G* power software. Data manipulation and statistical analyses were conducted using SPSS® Version 12.0 for Windows™ (SPSS, Inc., Chicago, IL, USA). A \( P \)-value of \( \leq 0.05 \) was considered to indicate a significant difference.

**Results**

Haemodynamic and respiratory variables at different levels of PEEP are given in Table 1. HR did not change significantly with PEEP. Mean ABP decreased with PEEP, while CVP and PAOP increased with PEEP. Airway peak and plateau pressure gradually increased with an incremental PEEP increases.

Pulsed wave DTI indicated that \( E' \) decreased by 15.9% during 5 cmH\(_2\)O PEEP, compared with that from baseline and by 10.3% during 10 cmH\(_2\)O PEEP, compared with that during 5 cmH\(_2\)O PEEP, and thus implying a gradual decrease in diastolic relaxation (Fig. 2). \( A' \) decreased during 5 and 10 cmH\(_2\)O PEEP, compared with that from baseline, and thus implying a decrease in the atrial contractile function (Table 2). \( S' \) also decreased with PEEP (Table 2). However, there was no significant change in IVRT with PEEP (Table 2). On pulsed wave conventional Doppler echocardiography, \( E \) decreased with PEEP, whereas \( A \) did not change with PEEP (Table 2). Consequently, a decrease in the \( E/A \) ratio was observed (Table 2). DT was prolonged by 20.7% with 10 cmH\(_2\)O PEEP, compared with that from baseline (Table 2). In addition, two-dimensional echocardiography showed that EDD and ESD gradually and significantly decreased as PEEP increased, while leaving FS unchanged (Table 2).

The intra- and inter-observer variabilities for echocardiographic parameters are given in Table 3.

**Discussion**

In the present study, we found that progressive impairment of LV relaxation was indicated by a decrease in \( E' \) on DTI with an incremental increase in PEEP in patients with pre-existing relaxation abnormality. Patients with impaired diastolic function usually show increased LV filling pressure which makes LV susceptible to myocardial ischaemia. Therefore, PEEP ventilation in patients with pre-existing reduced diastolic function might impose a further increase of LV

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**Table 1** Haemodynamic and respiratory parameters at different levels of PEEP. Values are expressed as mean (SD) or median (inter-quartile range). PEEP, positive end-expiratory pressure; HR, heart rate; MABP, mean arterial blood pressure; CVP, central venous pressure; PAOP, pulmonary artery occlusive pressure; Ppeak, airway peak pressure; Pplat, airway plateau pressure. *\( P \leq 0.05 \) vs PEEP 0; †\( P \leq 0.05 \) vs PEEP 5

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PEEP (cmH(_2)O)</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>HR (beats min(^{-1}))</td>
<td>57.0 (52.0–60.0)</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>75.7 (64.0–80.1)</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>7.0 (5.8–9.3)</td>
</tr>
<tr>
<td>PAOP (mm Hg)</td>
<td>12.0 (8.5–13.0)</td>
</tr>
<tr>
<td>Ppeak (cmH(_2)O)</td>
<td>13.0 (11.0–13.0)</td>
</tr>
<tr>
<td>Pplat (cmH(_2)O)</td>
<td>12.0 (10.5–13.0)</td>
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</tbody>
</table>

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**Fig 1** (A) Mitral inflow velocity recorded with pulsed wave Doppler. \( E \), peak early transmitral filling velocity; \( A \), peak late transmitral filling velocity; DT, deceleration time of \( E \). (a) DTI at lateral mitral annulus. \( E' \), early diastolic annulus velocity; \( A' \), late diastolic annulus velocity; \( S' \), peak systolic annulus velocity; IVRT, isovolumetric relaxation time.
filling pressure by aggravating a pre-existing LV relaxation abnormality and thus subsequently increase the potential risk of myocardial ischaemia.

LV relaxation is one of the major determinants of LV filling during diastole. Ventricular relaxation is a complex energy-dependent process during which the contractile elements are deactivated and myofibrils return to their pre-contraction length. \( E' \) wave represents LV relaxation and is a more sensitive parameter for LV relaxation than transmitral filling velocities. Moreover, it has been shown that \( E' \) is preload-independent in the patients with pre-existing LV relaxation impairment unlike transmitral filling velocities, whereas it is preload-dependent in the patients with normal LV relaxation. Thus, our results were not affected by diminished preload during PEEP because we examined patients with pre-existing LV relaxation abnormality which was diagnosed with \( E' \leq 8.5 \text{ cm s}^{-1} \). Consequently, it may be concluded that PEEP disturbed LV relaxation with a gradual decrease in \( E' \) during the increase in PEEP. In addition, prolonged DT of \( E' \) is

### Table 2: LV echocardiographic parameters at different levels of PEEP. Values are expressed as mean (SD) or median (inter-quartile range). PEEP, positive end-expiratory pressure; DTI, Doppler tissue imaging; \( E' \), peak early diastolic velocity of lateral mitral annulus; \( A' \), peak late diastolic velocity of lateral mitral annulus; \( S' \), peak systolic velocity of lateral mitral annulus; IVRT, isovolumetric relaxation time; \( E \), peak early transmitral filling velocity; \( A \), peak late transmitral filling velocity; DT, deceleration time of \( E \); EDD, end-diastolic dimension of left ventricle; ESD, end-systolic dimension of left ventricle; FS, fractional shortening. * \( P < 0.05 \) vs PEEP 0; † \( P < 0.05 \) vs PEEP 5

<table>
<thead>
<tr>
<th>PEEP (cmH₂O)</th>
<th>0</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>( E' ) (cm s(^{-1} ))</td>
<td>6.9 ± 0.9</td>
<td>5.8 ± 0.9*</td>
<td>5.2 ± 1.2†</td>
</tr>
<tr>
<td>( A' ) (cm s(^{-1} ))</td>
<td>6.7 (5.4–8.3)</td>
<td>6.0 (4.4–7.7)*</td>
<td>5.2 (4.5–7.1)*</td>
</tr>
<tr>
<td>( S' ) (cm s(^{-1} ))</td>
<td>7.1 ± 2.2</td>
<td>5.8 ± 2.1*</td>
<td>5.3 ± 1.9*</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>100.0 (90.0–109.8)</td>
<td>100.0 (86.8–113.3)</td>
<td>111.0 (95.0–124.8)</td>
</tr>
<tr>
<td>Conventional Doppler</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>( E ) (cm s(^{-1} ))</td>
<td>67.5 ± 14.8</td>
<td>60.3 ± 14.0*</td>
<td>53.6 ± 11.2†</td>
</tr>
<tr>
<td>( A ) (cm s(^{-1} ))</td>
<td>61.3 ± 12.0</td>
<td>58.8 ± 15.8</td>
<td>56.0 ± 13.3</td>
</tr>
<tr>
<td>( E/A ) ratio</td>
<td>1.1 ± 0.3</td>
<td>1.1 ± 0.4</td>
<td>1.0 ± 0.3*</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>251.6 ± 65.5</td>
<td>276.5 ± 49.9</td>
<td>303.7 ± 52.1*</td>
</tr>
<tr>
<td>Two-dimensional</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDD (mm)</td>
<td>41.9 ± 4.3</td>
<td>38.0 ± 4.7*</td>
<td>33.9 ± 5.6†</td>
</tr>
<tr>
<td>ESD (mm)</td>
<td>26.2 ± 4.7</td>
<td>23.2 ± 4.2*</td>
<td>20.0 ± 4.6†</td>
</tr>
<tr>
<td>FS (%)</td>
<td>60.5 ± 9.4</td>
<td>59.3 ± 9.5</td>
<td>61.9 ± 10.8</td>
</tr>
</tbody>
</table>

### Table 3: Intra- and inter-observer variabilities for echocardiographic parameters. Values are expressed as percentages (95% CI). \( E' \), peak early diastolic velocity of lateral mitral annulus; \( A' \), peak late diastolic velocity of lateral mitral annulus; \( S' \), peak systolic velocity of lateral mitral annulus; IVRT, isovolumetric relaxation time; \( E \), peak early transmitral filling velocity; \( A \), peak late transmitral filling velocity; DT, deceleration time of \( E \); EDD, end-diastolic dimension of left ventricle; ESD, end-systolic dimension of left ventricle

<table>
<thead>
<tr>
<th>E'</th>
<th>3.6 (2.2–5.0)</th>
<th>4.2 (1.2–7.3)</th>
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<tbody>
<tr>
<td>A'</td>
<td>3.8 (1.7–5.8)</td>
<td>4.8 (1.9–7.8)</td>
</tr>
<tr>
<td>S'</td>
<td>2.8 (2.2–3.4)</td>
<td>6.0 (3.6–8.4)</td>
</tr>
<tr>
<td>IVRT</td>
<td>5.9 (2.5–9.3)</td>
<td>7.0 (1.7–12.4)</td>
</tr>
<tr>
<td>E</td>
<td>2.9 (0.5–5.4)</td>
<td>2.8 (1.3–4.4)</td>
</tr>
<tr>
<td>A</td>
<td>3.6 (3.0–4.3)</td>
<td>5.0 (2.3–7.6)</td>
</tr>
<tr>
<td>DT</td>
<td>6.7 (4.2–9.1)</td>
<td>8.9 (6.3–11.5)</td>
</tr>
<tr>
<td>EDD</td>
<td>3.3 (2.1–4.6)</td>
<td>3.4 (0.8–6.0)</td>
</tr>
<tr>
<td>ESD</td>
<td>2.7 (0.2–5.2)</td>
<td>3.7 (1.6–5.8)</td>
</tr>
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</table>

Fig 2: The gradual decrease of peak early diastolic velocity of lateral mitral annulus (\( E' \)) with an incremental increase of PEEP. Each data point represents the mean (SD). * \( P < 0.05 \) vs PEEP 0; † \( P < 0.05 \) vs PEEP 5.
associated with the diastolic relaxation impairment when dia-
stolic dysfunction is not severe. Therefore, our results regard-
ing DT of E′ might provide additional information related to
decreased diastolic relaxation.

IVRT is also useful for assessment of LV relaxation. How-
however, IVRT has limited accuracy, when left atrial pressure
increases. Left atrial pressure is one of the determinants of
IVRT, since IVRT is measured as the time interval between
aortic valve closure and mitral valve opening. Thus, a pro-
gressive rise in left atrial pressure would tend to cause an
earlier opening of the mitral valve, which results in shorter
IVRT. The present study showed that LA pressure, mani-

fested as PAOP, increased with PEEP even though actual LV preload decreased, probably owing to increased
pericardial restraint. Therefore, we speculated that earlier
opening of the mitral valve would leave IVRT unchanged
despite an exacerbation of LV relaxation during PEEP.

Few studies have examined the effects of PEEP on LV diastol-
ic function, and the results have been discordant. In contrast to
our results, previous research has reported that PEEP had no
effect on LV relaxation, based on an unchanged IVRT during
PEEP. However, IVRT was not considered to provide the infor-
mation regarding LV relaxation during PEEP, because of the
limitation of IVRT mentioned above. In regard to LV compli-
ance, PEEP has been shown to reduce LV compliance in some
previous studies, whereas another study has failed to find
decreased LV compliance during PEEP. Unfortunately,
the present study did not confirm an effect of PEEP on diastolic
compliance and the direct estimation method of LV compli-
ance is diastolic pressure-volume curves as a gold standard
method. Further studies may be needed to investigate
the effect of PEEP on diastolic compliance.

In addition, A′ has been proven to be a highly sensitive
tool for quantifying left atrial contractile function and it is a
better indicator of atrial contractile function than transmitral
atrial filling velocity, even in patients with diastolic dysfunc-
tion. Therefore, our results indicated that PEEP might exert an adverse effect on left atrial contractile function
during diastole.

The DTI parameters next to the mitral annulus, as mea-
sured in our study, quantify myocardial longitudinal motion. Myocardial longitudinal motion provides informa-
tion regarding subendocardial function which is most vulner-
able to ischaemia, and decreased longitudinal motion is
compensated for by increased radial motion. It has been
reported that radial contractility seems to compensate for
decreased longitudinal contractility in patients with a
normal LV ejection fraction, no LV hypertrophy, and no is-
chaemia. FS, as measured in our study, primarily reflects
radial motion, and is thus speculated to be unchanged
even though aggravated relaxation impairment might
result in subclinical ischaemia during PEEP ventilation.

In our study, there was no measurement of cardiac
output. Although there is no direct data regarding the
change in cardiac output, a reduction in cardiac output
may be speculated from a decreased MBP measured
because haemodynamic measurements were performed
during fixed anaesthetic concentration without any stimula-
tion to patient. Worsening of diastolic relaxation impairment,
as shown in our study, might aggravate LV filling, thus
leading to decreased cardiac output which consequently
decreases the mean ABP.

Our study has the following limitations. First, we did not
examine patients with normal LV relaxation. Because E′ has
been known to be preload-dependent in patients with normal
LV relaxation, it is difficult to differentiate the effect of PEEP
and preload change for explaining the change in E′ on TDI
during PEEP ventilation in patients with normal diastolic func-
tion. Secondly, invasively derived information on the decrease
in LV isovolumetric pressure or its time constant τ was not avail-
able. However, E′ is a well-validated echocardiographic param-
eter of diastolic function and is closely correlated with τ.

In conclusion, PEEP resulted in further aggravation of LV dia-
static relaxation abnormality in patients with pre-existing LV
relaxation impairments. Therefore, we proposed that
restricted LV diastolic function as well as decreased venous
return would contribute to the LV preload reduction during
PEEP. Ventilation with PEEP in patients with pre-existing dia-
static dysfunction may increase further LV filling pressure
which is already at a higher than normal level. Consequently,
the risk of perturbation of myocardial blood flow may increase,
and thus close observation of haemodynamic parameters
should be emphasized when PEEP is given to patients with ab-
normal diastolic function during the peri-operative period.

Declaration of interest
None declared.

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