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Myocardial Function during Low *versus* Intermediate Tidal Volume Ventilation in Patients without Acute Respiratory Distress Syndrome

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Lower tidal volume mechanical ventilation is associated with reduced ventilation induced lung injury

What This Article Tells Us That Is New

- What is not known is if lower *versus* intermediate tidal volume mechanical ventilation is also associated with improved systolic and diastolic left ventricular and right ventricular myocardial function
- This study of 42 mechanically ventilated patients who did not have acute respiratory distress syndrome found that lower tidal volume mechanical ventilation was associated with increased right and left ventricular systolic function but not improved diastolic function

ABSTRACT

Background: Mechanical ventilation with low tidal volumes has the potential to mitigate ventilation-induced lung injury, yet the clinical effect of tidal volume size on myocardial function has not been clarified. This cross-sectional study investigated whether low tidal volume ventilation has beneficial effects on myocardial systolic and diastolic function compared to intermediate tidal volume ventilation.

Methods: Forty-two mechanically ventilated patients without acute respiratory distress syndrome (ARDS) underwent transthoracic echocardiography after more than 24 h of mechanical ventilation according to the Protective Ventilation in Patients without ARDS (PReVENT) trial comparing a low *versus* intermediate tidal volume strategy. The primary outcome was left ventricular and right ventricular myocardial performance index as measure for combined systolic and diastolic function, with lower values indicating better myocardial function and a right ventricular myocardial performance index greater than 0.54 regarded as the abnormality threshold. Secondary outcomes included specific systolic and diastolic parameters.

Results: One patient was excluded due to insufficient acoustic windows, leaving 21 patients receiving low tidal volumes with a tidal volume size (mean ± SD) of 6.5 ± 1.8 ml/kg predicted body weight, while 20 patients were subjected to intermediate tidal volumes receiving a tidal volume size of 9.5 ± 1.6 ml/kg predicted body weight (mean difference, −3.0 ml/kg; 95% CI, −4.1 to −2.0; $P < 0.001$). Right ventricular dysfunction was reduced in the low tidal volume group compared to the intermediate tidal volume group (myocardial performance index, 0.41 ± 0.13 *vs.* 0.64 ± 0.15; mean difference, −0.23; 95% CI, −0.32 to −0.14; $P < 0.001$) as was left ventricular dysfunction (myocardial performance index, 0.50 ± 0.17 *vs.* 0.63 ± 0.19; mean difference, −0.13; 95% CI, −0.24 to −0.01; $P = 0.030$). Similarly, most systolic parameters were superior in the low tidal volume group compared to the intermediate tidal volume group, yet diastolic parameters did not differ between both groups.

Conclusions: In patients without ARDS, intermediate tidal volume ventilation decreased left ventricular and right ventricular systolic function compared to low tidal volume ventilation, although without an effect on diastolic function.

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Critically ill patients admitted to the intensive care unit (ICU) frequently require mechanical ventilation to ensure adequate gas exchange. Although mechanical ventilation can be a lifesaving intervention, it is also known to induce lung injury.[1,2] Ventilation with high tidal volumes in particular contributes to ventilation-induced lung injury, with multiple studies showing that the use of low tidal volumes can improve survival in patients with acute

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respiratory distress syndrome (ARDS),[3–6] which is now considered standard care in this patient group.[7,8] In non-ARDS patients, the effect of tidal volume size on mortality is less clear. Therefore, the Protective Ventilation in Patients without ARDS (PReVENT) trial was started in 2014 in The Netherlands comparing low tidal volume ventilation with intermediate tidal volume ventilation in non-ARDS patients primarily investigating survival and ventilator-free days.[9]

Experimental studies have shown that ventilation with high tidal volumes can induce the release of various inflammatory mediators into the circulation causing injury to distant organs.[10,11] During acute lung injury, these chain of events can be magnified,[12,13] with a striking effect within several hours on myocardial function dubbed ventilation-induced myocardial dysfunction.[14,15] The effect of tidal volume on myocardial function has not yet been investigated in patients, in part because of the difficulty measuring myocardial performance. Standard echographic parameters such as stroke volume and ejection fraction are dependent of preload and afterload, and therefore do not provide load-independent information about myocardial function. The myocardial performance index is a tissue Doppler–derived index incorporating contractile and relaxation parameters in a relatively load-independent manner, and thus looking at systolic and diastolic myocardial function itself. Myocardial dysfunction induced by tidal volume ventilation assessed by myocardial performance index may potentially have clinical implications for the use of inotropes or lusitropes besides a reduction in tidal volume size.

We hypothesized that a low tidal volume strategy may ameliorate left ventricular and right ventricular systolic and diastolic dysfunction compared to intermediate tidal volume ventilation, assessed by echocardiography in both groups of the PReVENT trial after more than 24 h of mechanical ventilation.

Materials and Methods

The PReVENT trial (www.clinicaltrials.gov: NCT02153294) was a national, multicenter randomized controlled trial in mechanically ventilated ICU patients not suffering from ARDS.[9] Consecutive patients were randomized to a low tidal volume strategy targeting tidal volumes of 4 to 6 ml/kg predicted body weight or to an intermediate tidal volume strategy targeting tidal volumes of 8 to 10 ml/kg predicted body weight with exclusion of patients with ARDS at start of ventilation. The primary endpoints of the recently published PReVENT trial were the number of ventilator-free days and survival at 28 days.[16]

We performed a single center cross-sectional transthoracic echocardiography substudy of PReVENT patients mechanically ventilated more than 24 h in the Amsterdam University Medical Center to assess the effect of tidal volume size on left ventricular and right ventricular systolic and diastolic function. This noninterventional study was judged as part of standard patient care and therefore not subject to the Medical Research Involving Human Subjects act by the Institutional Review Board of the Amsterdam University Medical Center (November 4, 2014, Amsterdam, The Netherlands; reference No.: W14_299) since mechanical ventilation and transthoracic echocardiography are routinely performed following local guidelines. For this analysis no additional consent was required besides the written informed consent for the PReVENT trial. The study is listed in the Netherlands Trial Register (NTR5283) with myocardial performance index as primary outcome measure and specific systolic and diastolic parameters as secondary outcome measures. Exclusion criteria were known cardiomyopathy, cardiogenic shock, skin or thorax disorders rendering transthoracic echocardiography infeasible, or severe shock requiring norepinephrine greater than or equal to 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Transthoracic echocardiography images were recorded using a M4S transducer of a commercially available ultrasound system (Vivid 7 Dimension; GE Vingmed Ultrasound AS, Norway). Images were continuously digitally stored according to local standard protocol.

Study Protocol

Patients were randomized within 1 h of ventilation initiation in the ICU in a 1:1 ratio to a low tidal volume group or an intermediate tidal volume group. Local investigators performed the randomization using a central, dedicated, password-protected, encrypted, Web-based automated randomization system.[9] The randomization was conducted with random block sizes and was stratified for center as well as for intubation location. Blinding was not possible. The attending nurses and physicians were not blinded to the intervention or outcomes. Statistical analysis was based on the intention-to-treat principle.

Patient randomized to the low tidal volume strategy started with volume-controlled ventilation and a tidal volume of 6 ml/kg which was decreased by 1 ml/kg to a minimum of 4 ml/kg. The patients randomized to the intermediate tidal volume strategy started with volume-controlled ventilation at a tidal volume of 10 ml/kg which was decreased by 1 ml/kg to a minimum of 8 ml/kg only in case the plateau pressure exceeded 25 cm H_2O. When breathing efforts were noted, the switch to pressure support ventilation was made. During pressure support ventilation, the pressure support level was adjusted in order to obtain the target tidal volume, with a minimal level of support of 5 cm H_2O and maximal airway pressure of 25 cm H_2O. If with this support level the resultant tidal volume exceeded 6 ml/kg in the low tidal volume group or did not reach 10 ml/kg in the intermediate tidal volume group, this was accepted.[9] The respiratory rate was adjusted if necessary to prevent severe respiratory acidosis (pH less than 7.25) or alkalosis (pH greater than 7.45). In case of severe dyspnea, patient-ventilator asynchrony, a respiratory rate

greater than 35 per min, uncontrollable acidosis or increasing levels of discomfort, tidal volume could be increased in steps of 1 ml/kg predicted body weight per hour, with both volume-controlled and pressure support ventilation. The lowest possible level of positive end-expiratory pressure was used with a minimum of 5 cm H_2O. Recruitment maneuvers were allowed, when deemed necessary by the attending physician.

Before performing the transthoracic echocardiography, hemodynamic and respiratory data of patients were recorded. If an arterial blood gas was performed within 4 h of the transthoracic echocardiography examination, these data were also collected from the electronic patient data management system. Patients were positioned in a partial left lateral position taking special care of avoiding stress. Skin electrodes were attached to obtain a continuous cardiac rhythm on the echocardiogram with a minimum recording of three cardiac cycles of sinus rhythm or five cardiac cycles in case of atrial fibrillation according to guidelines.[17] The following order of the transthoracic echocardiography examination was systematically followed using six standard views: parasternal long-axis, parasternal short-axis, apical four-chamber, apical two-chamber, apical five-chamber, and subcostal.

The myocardial performance index was chosen as primary endpoint since it provides information about combined systolic and diastolic function,[18] can be calculated for the left ventricle and the right ventricle,[19,20] is obtainable in the presence of suboptimal two-dimensional images,[21] and is relatively independent of preload and afterload in nonacute conditions.[22] In contrast, other parameters such as stroke volume and ejection fraction are more load dependent and can vary upon the changes in left ventricular and right ventricular preload and afterload induced by tidal volume ventilation. The myocardial performance index is a nongeometric measurement as it is calculated through tissue Doppler imaging by adding the isovolumetric contraction time to the isovolumetric relaxation time and then dividing the sum by the ejection time. In case myocardial function deteriorates, the isovolumetric contraction and relaxation periods are lengthened and the ejection time shortens, resulting in a *higher* myocardial performance index value indicative of *decreased* myocardial function. Since myocardial performance index integrates isovolumetric indices besides the ejection phase, it can theoretically demonstrate myocardial dysfunction before a change in an ejection phase measure such as ejection fraction occurs.

A detailed description of all the other systolic and diastolic measurements obtained by the transthoracic echocardiography examination is provided in the Appendix.

Statistical Analysis

Up to date, only two studies specifically studied relatively load-independent parameters of myocardial function during changes in tidal volume.[15,23] However, these were experimental studies not taking into account the heterogeneity of critically ill patients on the ICU. For this observational study in humans, we estimated that enrollment of 17 patients in each study group would be sufficient to achieve a power of 80%, with a two-sided significance level of 0.05 to detect a 0.08 difference assuming an SD of 0.08 between the low tidal volume and intermediate tidal volume groups in the primary parameter myocardial performance index.[19,20] Therefore, we enrolled 42 patients, accounting for a safe margin of 20% dropouts due to insufficient acoustic windows. The images were obtained by an experienced cardiologist (either T.C. or W.L.), and analyzed offline using automated function imaging software (EchoPAC; GE Vingmed, Norway) by an observer (either B.B. or R.d.B.) blinded for the randomization group. Normality of distribution was assessed using the Shapiro–Wilk test. The comparison of continuous variables between the two groups was performed using the independent samples *t* test in case of a normal distribution, otherwise the Mann–Whitney U test was used. The comparisons of categorical variables between both groups was performed using the chi-square test. Analyses were performed using SPSS Statistics version 25 (IBM Corporation, USA). Categorical data are presented as number with percentage in parenthesis. Continuous data are presented as mean ± SD in case of a normal distribution, otherwise the median with interquartile ranges is used. Comparisons are shown with the mean difference and the 95% CI from the independent samples *t* test in case of a normal distribution, otherwise the Hodges–Lehmann estimate of the median difference and 95% CI was used. A two-sided P value < 0.05 was considered statistically significant with exact P values given unless $P < 0.001$.

Results

From November 2014 through November 2015, 90 patients were found eligible in the Amsterdam University Medical Center to participate in the PReVENT trial. After exclusion of patients not eligible for the echocardiography study, 42 patients received a full transthoracic echocardiography examination; one patient was excluded from analysis due to poor acoustic windows. In total, 41 patients were analyzed with 21 patients receiving low tidal volume and 20 patients subjected to intermediate tidal volume (fig. 1).

Baseline Characteristics

Baseline characteristics are presented in table 1. There were no significant differences between the low tidal volume and intermediate tidal volume groups, except for more aspiration/pneumonia in the intermediate tidal volume group. There were no significant differences with regard to reason for mechanical ventilation between the two groups (table 1). All but four patients were in sinus rhythm, with the patients in atrial fibrillation equally divided between both groups. Almost half of patients were sedated and received vasopressors, but none received norepinephrine greater than 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Thirty-three patients received pressure support

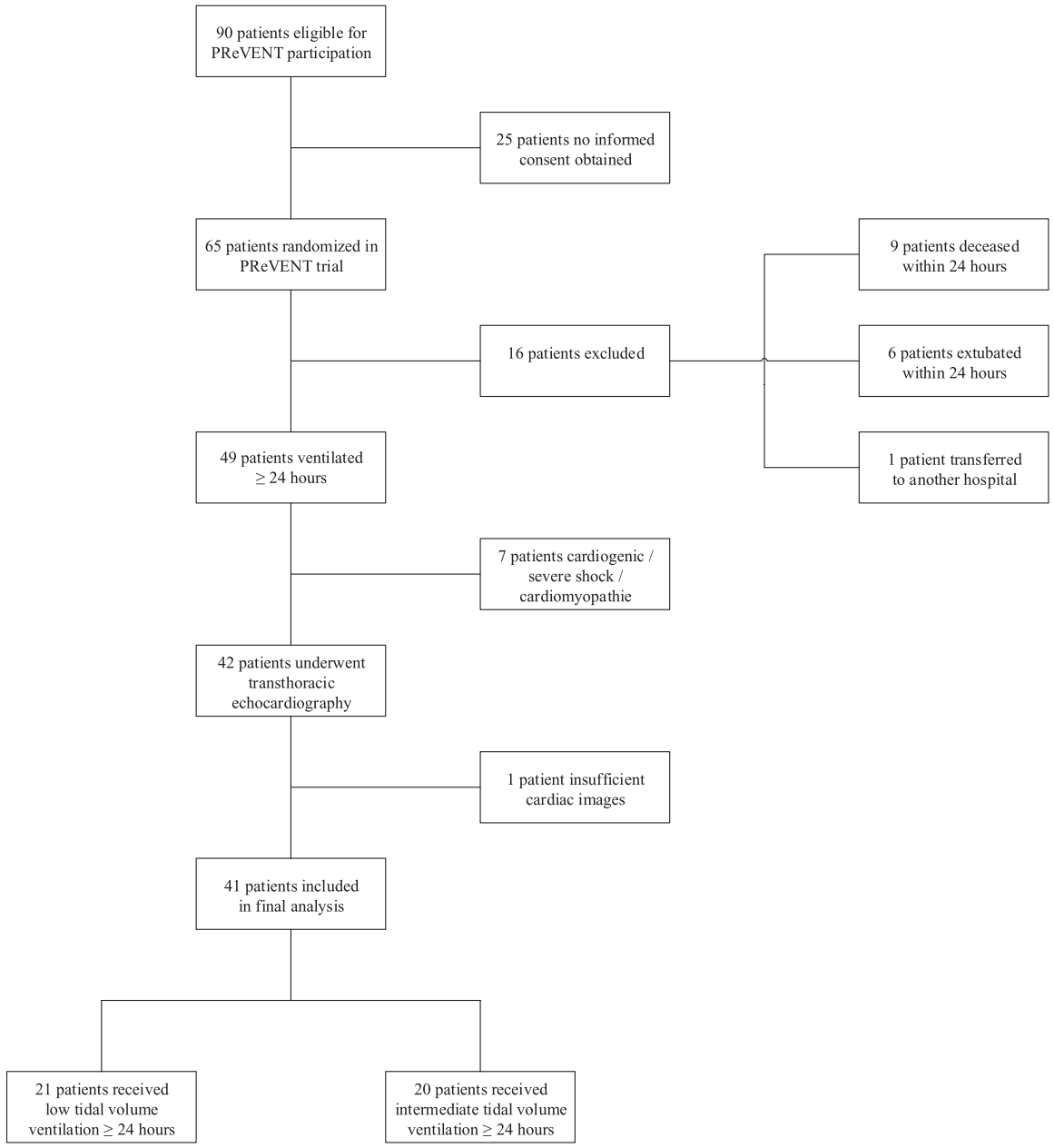

Fig. 1. Flow diagram of patient recruitment.

ventilation, with the remaining eight patients receiving volume-controlled ventilation, equally divided between both groups. All ventilatory settings and drug doses remained unaltered during the approximately 30 min entailing transthoracic echocardiography examination.

Respiratory and Hemodynamic Parameters

The respiratory and hemodynamic parameters are presented in table 2. Patients were mechanically ventilated according to the PReVENT protocol for a median of 27 h. Patients in the low tidal volume group received a mean tidal volume of 6.5 ± 1.8 ml/kg predicted body weight with the intermediate tidal volume group receiving 9.5 ± 1.6 ml/kg predicted body weight (mean difference, −3.0 ml/kg; 95% CI, −4.1 to −2.0; $P < 0.001$). All other respiratory and hemodynamic parameters did not differ between both groups. *Post hoc* analysis showed no difference in the administered tidal volumes in the patients with pressure support compared to the patients with volume-controlled ventilation (8.1 ± 2.3 ml/kg *vs.* 7.4 ± 2.2 ml/kg predicted body weight (mean difference 0.7 ml/kg; 95% CI, −1.1 to 2.5; $P = 0.458$) nor was there a difference in

Table 1. Baseline Patient Characteristics (n = 41)

Variable	Low Tidal Volume (n = 21)	Intermediate Tidal Volume (n = 20)	*P* Value
Age (yr), mean ± SD	58 ± 14	61 ± 16	0.447
Male, No. (%)	11 (52)	13 (65)	0.412
Height (cm), mean ± SD	173 ± 12	178 ± 11	0.187
Weight (kg), mean ± SD	77 ± 15	81 ± 17	0.554
Temperature (°C), mean ± SD	37.0 ± 1.0	36.9 ± 1.0	0.805
Sequential organ failure assessment, mean ± SD	8 ± 4	8 ± 3	0.811
Reason of ICU admission, No. (%)			
Abdominal sepsis	3 (14)	0 (0)	0.079
Aspiration/pneumonia	0 (0)	6 (30)	0.007
Cerebral vascular accident	2 (10)	2 (10)	0.959
Circulatory failure	5 (24)	3 (15)	0.477
Complicated kidney transplant	2 (10)	0 (0)	0.157
High energy trauma	3 (14)	3 (15)	0.948
Meningitis	0 (0)	2 (10)	0.137
Subarachnoid hemorrhage	2 (10)	3 (15)	0.592
Other*	4 (19)	1 (5)	0.169
Reason for mechanical ventilation, No. (%)			
Hypoxic respiratory failure	3 (14)	5 (25)	0.387
Hypercapnic respiratory failure	2 (10)	3 (15)	0.592
Airway protection†	16 (76)	12 (60)	0.265
Mechanical ventilation mode, No. (%)			
Pressure support	17 (81)	16 (80)	0.939
Volume controlled	4 (19)	4 (20)	0.939
Sedation, No. (%)			
Propofol	7 (33)	6 (30)	0.819
Midazolam	3 (14)	2 (10)	0.948
Vasopressor, No. (%)			
Norepinephrine	10 (48)	10 (50)	0.879
Dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$), median [IQR]	0.10 [0.10–0.33]	0.15 [0.09–0.33]	0.971
Valvulopathy, No. (%)	6 (29)	4 (20)	0.523
Sinus rhythm, No. (%)	19 (91)	18 (90)	0.959

Data are given as the mean ± SD when normally distributed, otherwise the median with interquartile ranges is used. Numbers are presented with (%).

*Acute abdominal aortic aneurysm, acute liver failure, gas gangrene, hypocalcemia, refractory epilepsy. †Postoperative, sedation, or coma.

ICU, intensive care unit; IQR, interquartile range.

respiratory rate (20 ± 7 breaths/min *vs.* 21 ± 10 breaths/min (mean difference, 1 breath/min; 95% CI, −9 to 8; $P = 0.898$).

Echocardiographic Evaluation

Moderate or severe mitral regurgitation was present in four patients, with nine patients having moderate or severe tricuspid regurgitation. None of the 41 patients exhibited significant aortic valvulopathy. The mean diameter of the vena cava inferior was 1.6 ± 0.6 cm and was not different between the low tidal volume and intermediate tidal volume groups.

Left and Right Ventricular Systolic and Diastolic Function

All left ventricular and right ventricular systolic and diastolic function parameters are depicted in table 3. No difference in indicators of right ventricular pressure or volume overload was found between both groups, with no difference in right ventricular afterload. The primary parameter myocardial performance index could be obtained in all 41 patients for the left ventricle, while this could not be acquired in 4 patients for the right ventricle, with the missing data equally divided between the low tidal volume and intermediate tidal volume group. Left ventricular and right ventricular myocardial performance index was higher in the intermediate tidal volume group, which is indicative of decreased combined systolic and diastolic function (fig. 2). All left and right ventricular systolic parameters were higher in the low tidal volume group compared to the intermediate tidal volume group, except for the left ventricular and right ventricular systolic maximal velocity, with a higher cardiac output in the low tidal volume group (table 3). All left ventricular and right ventricular diastolic parameters were similar between both groups.

Post hoc analysis showed no difference in myocardial function in patients on pressure support ventilation *versus* volume-controlled ventilation: the left ventricular myocardial performance index was 0.57 ± 0.21 *versus* 0.55 ± 0.09 (mean difference, 0.02; 95% CI, −0.08 to 0.11; $P = 0.733$) and the right ventricular myocardial performance index was 0.51 ± 0.17 *versus* 0.56 ± 0.22 (mean difference, −0.05; 95% CI, −0.19 to 0.10; $P = 0.516$) respectively.

When the six aspiration/pneumonia patients (all were in the intermediate tidal volume group) were excluded from the analysis, no attenuation in effect size on left ventricular myocardial performance index was seen: the left ventricular myocardial performance index was 0.50 ± 0.17 in the low tidal volume group *versus* 0.65 ± 0.22 in the nonaspiration/pneumonia intermediate tidal volume group (mean difference, −0.15; 95% CI, −0.28 to −0.01; $P = 0.031$), resulting in an increase of 0.02 in mean difference. The right ventricular myocardial performance index was 0.41 ± 0.13 *versus* 0.59 ± 0.16 (mean difference, −0.19; 95% CI, −0.29 to −0.08; $P = 0.001$) when the six aspiration/pneumonia patients were excluded, resulting in a small attenuation in effect size: the mean difference has decreased with 0.04, albeit with a remaining *P* value of 0.001.

Discussion

This is the first clinical study investigating whether tidal volume size affects myocardial function assessed by transthoracic echocardiography in non-ARDS patients randomized to a low tidal volume *versus* intermediate tidal volume strategy. Our data show that intermediate tidal volume ventilation resulted in a decline in myocardial performance with a lower cardiac output compared to low tidal volume ventilation, mainly caused by decreased left ventricular and right ventricular systolic function, while left and right ventricular diastolic function remained unaltered. Application of a low tidal volume strategy may reduce systolic ventilator-induced myocardial dysfunction in patients without ARDS.

Table 2. Respiratory and Hemodynamic Parameters at Transthoracic Echocardiographic Examination

Variable	Low Tidal Volume (n = 21)	Intermediate Tidal Volume (n = 20)	Point Estimate of the Difference (95% CI)	*P* Value
Time* (h)	27 [24–38]	27 [24–36]	0 [–4 to 3]	0.803
Respiration				
V_T (ml)	427 ± 117	681 ± 151	–254 (–339 to –169)	< 0.001
Predicted body weight† (kg)	66.9 ± 11.5	71.6 ± 11.0	–4.7 (–11.8 to 2.4)	0.190
V_T / predicted body weight (ml/kg)	6.5 ± 1.8	9.5 ± 1.6	–3.0 (–4.1 to –2.0)	< 0.001
PEEP (cm H_2O)	5 [5–8]	5 [5–7]	0 [0–2]	0.108
FIO_2 (%)	30 [23–40]	28 [22–39]	2 [–4 to 5]	0.690
RR (breaths/min)	22 ± 8	18 ± 6	4 (–1 to 8)	0.115
pH	7.41 ± 0.07	7.43 ± 0.06	–0.02 (–0.06 to 0.03)	0.459
$PaCO_2$ (mmHg)	38.2 ± 6.6	35.0 ± 6.0	3.2 (–0.9 to 7.3)	0.122
PaO_2 (mmHg)	75.8 [67.7–85.5]	81.0 [73.5–87.8]	–4.1 [–11.3 to 3.8]	0.296
Hb (mmol/l)	6.7 ± 1.6	6.7 ± 1.3	–0.1 (–1.0 to 0.9)	0.882
SaO_2 (%)	94 [93–95]	95 [94–96]	–1 [–3 to 0]	0.099
Hemodynamics				
HR (bpm)	88 ± 19	86 ± 18	2 (–9 to 14)	0.718
CVP (mmHg)	12 [9–17]	8 [4–17]	4 [–1 to 7]	0.110
SBP (mmHg)	132 ± 42	127 ± 30	5 (–18 to 28)	0.678
DBP (mmHg)	66 [60–78]	69 [60–82]	–2 [–10 to 8]	0.566
MAP (mmHg)	90 ± 21	89 ± 17	1 (–12 to 13)	0.926

Data are given as the mean ± SD when normally distributed, otherwise the median with interquartile ranges is used. Comparisons are shown with the point estimate of the mean or median difference, 95% CI and two-sided *P* value.

* Time after randomization to a low or intermediate tidal volume strategy according to the PReVENT trial. †Predicted body weight was calculated as 50 + 0.91 × (height [cm] – 152.4) for men and 45.5 + 0.91 × (height [cm] – 152.4) for women.

CVP, central venous pressure; DBP, diastolic blood pressure; FIO_2, fraction of inspired oxygen; Hb, hemoglobin; HR, heart rate; MAP, mean arterial pressure; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure; RR, respiratory rate; SBP, systolic blood pressure; SaO_2, arterial oxygen saturation; V_T, tidal volume.

Previous clinical studies have suggested that low tidal volume ventilation may prevent the development of ventilation-induced lung injury in non-ARDS patients.[24,25] Moreover, Lellouche *et al.* observed after multivariate analysis in postoperative cardiac surgery patients that high tidal ventilation was an independent risk factor for multiple organ failure.[26] Experimental studies in non-ARDS models had already demonstrated that ventilation with high tidal volumes induces the release of several inflammatory mediators into the circulation instigating distant organ injury including the heart.[10,11,14] Furthermore, increasing evidence has emerged correlating myocardial dysfunction to higher mortality rates.[27–29] This interaction may have contributed to the improved clinical outcomes observed in a meta-analysis reviewing the use of low tidal volume ventilation in patients without ARDS.[30]

It is well known that mechanical ventilation can induce hemodynamic compromise,[31] and that myocardial dysfunction and its sequelae are not properly reflected by conventional hemodynamic parameters.[32,33] Therefore in our study, left ventricular ejection fraction and tricuspid annular plane systolic excursion were considered as secondary parameters for left ventricular and right ventricular systolic function respectively, since both are affected by changes in loading conditions. As differences in tidal volume may induce changes in left and right ventricular preload and afterload affecting left ventricular ejection fraction and tricuspid annular plane systolic excursion as well as cardiac output, a change in these parameters does not necessarily reflect a change in myocardial function. Meanwhile, global longitudinal strain has shown to be superior to the more traditional two-dimensional echocardiographic measurement of left ventricular ejection fraction regarding detection of early systolic dysfunction, as well as prediction of mortality.[34] Additionally, the more recent usage of tissue Doppler imaging has provided more load-independent methods to assess systolic function such as the isovolumetric acceleration,[35,36] with the additional advantage that high quality two-dimensional images are no longer essential for reproducible recordings.[21] All left ventricular and right ventricular systolic parameters acquired through either traditional or newer techniques showed decreased function after ventilation for more than 24 h with intermediate tidal volume ventilation compared to the low tidal volume strategy, except for the left ventricular and right ventricular systolic maximal velocity ($P = 0.056$ and $P = 0.057$, respectively). A previous study showed a progressive decrease in systolic and diastolic function serially measured by pressure-volume loops in rats subjected to 19 ml/kg compared to 6 ml/kg.[15] In contrast, no difference in diastolic dysfunction was observed between both patient groups, possibly due to a less pronounced difference in applied tidal volumes compared to the experimental study. Furthermore, a time-dependent and reversible impairment of ventricular relaxation has been described in septic shock patients.[37]

Table 3. Left and Right Ventricular Systolic and Diastolic Function in Patients Subjected to a Low Tidal Volume *versus* Intermediate Tidal Volume Strategy

Left Ventricular Variables	Low Tidal Volume Ventilation (n = 21)	Intermediate Tidal Volume Ventilation (n = 20)	Point Estimate of the Difference (95% CI)	*P* Value	Right Ventricular Variables	Low Tidal Volume Ventilation (n = 21)	Intermediate Tidal Volume Ventilation (n = 20)	Point Estimate of the Difference (95% CI)	*P* Value
Primary parameter									
Myocardial performance index	0.50 ± 0.17	0.63 ± 0.19	−0.13 (−0.24 to −0.01)	0.030	Myocardial performance index	0.41 ± 0.13	0.64 ± 0.15	−0.23 (−0.32 to −0.14)	< 0.001
Systolic parameters									
Ejection fraction (%)	52 ± 10	44 ± 11	8 (1–15)	0.019	Tricuspid annular plane systolic excursion (cm)	2.3 ± 0.4	1.9 ± 0.5	0.4 (0.1– 0.7)	0.007
Global longitudinal strain (%)	−17.2 ± 3.9	−13.8 ± 3.7	−3.4 (−5.8 to −1.0)	0.007	Strain (%)	−19.0 ± 4.5	−15.1 ± 5.7	−3.9 (−7.5 to −0.3)	0.035
Isovolumetric acceleration (m/s²)	2.5 [1.7–2.8]	1.3 [0.9–2.6]	0.9 [0.2–1.4]	0.008	Isovolumetric acceleration (m/s²)	2.9 ± 1.3	1.8 ± 0.8	1.1 (0.3–1.8)	0.007
Systolic maximal velocity (cm/s)	10 ± 3	8 ± 2	2 (0 to 3)	0.056	Systolic maximal velocity (cm/s)	14 ± 5	12 ± 3	3 (0–5)	0.057
Diastolic parameters									
Early/Atrial velocity ratio	1.0 [0.8–1.3]	1.0 [0.8–1.3]	0.0 [−0.3 to 0.2]	0.916	Early/atrial velocity ratio	1.1 [0.8–1.2]	1.0 [0.9–1.5]	0.0 [−0.3 to 0.2]	> 0.999
Early maximal diastolic velocity (cm/s)	10 ± 4	9 ± 3	1 (−1 to 3)	0.272	Early maximal diastolic velocity (cm/s)	12 [10–15]	12 [8–16]	0 [−3 to 3]	0.851
General parameters									
Cardiac output (l/min)	5.3 [4.3–6.8]	3.8 [3.4–5.3]	1.3 [0.1–2.2]	0.045	Pulmonary acceleration time (m/s²)	12.7 ± 5.5	9.4 ± 2.9	3.2 (−0.3 to 6.8)	0.071
Eccentricity index	0.88 ± 0.20	0.99 ± 0.22	−0.12 (−0.27 to 0.02)	0.100	Right ventricle/left ventricle diameter*	0.84 ± 0.19	0.88 ± 0.17	−0.04 (−0.16 to 0.08)	0.484

Data are given as the mean ± SD when normally distributed, otherwise the median with interquartile ranges is used. Comparisons are shown with the point estimate of the mean or median difference, 95% CI, and a two-sided *P* value.
* Measured at end-diastole.

As a combined systolic and diastolic measurement may be more reflective of overall myocardial dysfunction, we used the myocardial performance index as primary parameter for the detection of ventilation-induced myocardial dysfunction. The myocardial performance index, formerly known as the Tei index, named after its inventor,[38] was higher in patients subjected to intermediate tidal volume ventilation compared to the low tidal volume strategy for both the left ventricle as the right ventricle, indicating global myocardial dysfunction. This is probably attributable to the difference in applied tidal volumes as other mechanical ventilator settings, respiratory parameters, or hemodynamic support did not differ between both groups (tables 1 and 2). The change in myocardial performance index may indicate a change in contractility and/or relaxation, although the latter seems less of a factor since no differences in diastolic function were found. The American Society of Echocardiography (Durham, North Carolina) and the European Association of Cardiovascular Imaging (Brussels, Belgium) regard a right ventricular myocardial performance index greater than 0.54 as the abnormality threshold,[17] suggesting significant myocardial dysfunction in the intermediate tidal volume group, but not in the low tidal volume group. The rise in myocardial performance index may therefore infer the use of inotropes as potential clinical implication, although this has not been investigated yet. While our data show the capability of tidal volume reduction to positively influence left ventricular and right ventricular function, positive end-expiratory pressure seems to have no direct effect on myocardial function.[39–41]

The development of ventilation-induced myocardial dysfunction upon intermediate tidal volume ventilation may in part be explained by ventilation-induced inflammation.[25,42,43] The injury to distant organs induced by ventilation-induced lung injury depresses myocardial function in a somewhat similar fashion as during sepsis.[44] Although our data suggest that low tidal volume ventilation may alleviate systolic ventilation-induced myocardial dysfunction, we did not measure inflammatory parameters so the contribution of inflammation cannot be determined. Interestingly, the main PReVENT trial did not show a difference in pulmonary outcome and survival. Gattinoni *et al.* note that the adverse effects of mechanical ventilation on the lung compared to the effect on the hemodynamics indeed differ.[45] While mortality and lung injury have shown to be associated with the mechanical power of ventilation,[46] which includes tidal volume size and respiratory rate among other ventilator parameters, the hemodynamic compromise mainly relates to the intrathoracic pressure.[31,41] It is therefore possible that intermediate tidal volume has deleterious effects on myocardial function mainly due to the changes in intrathoracic pressure, while the adverse effects of intermediate tidal volume on the lung are attenuated by a reduced respiratory rate. This may explain the same myocardial function observed in the patients on volume-controlled *versus* pressure support ventilation, as in both modes the changes

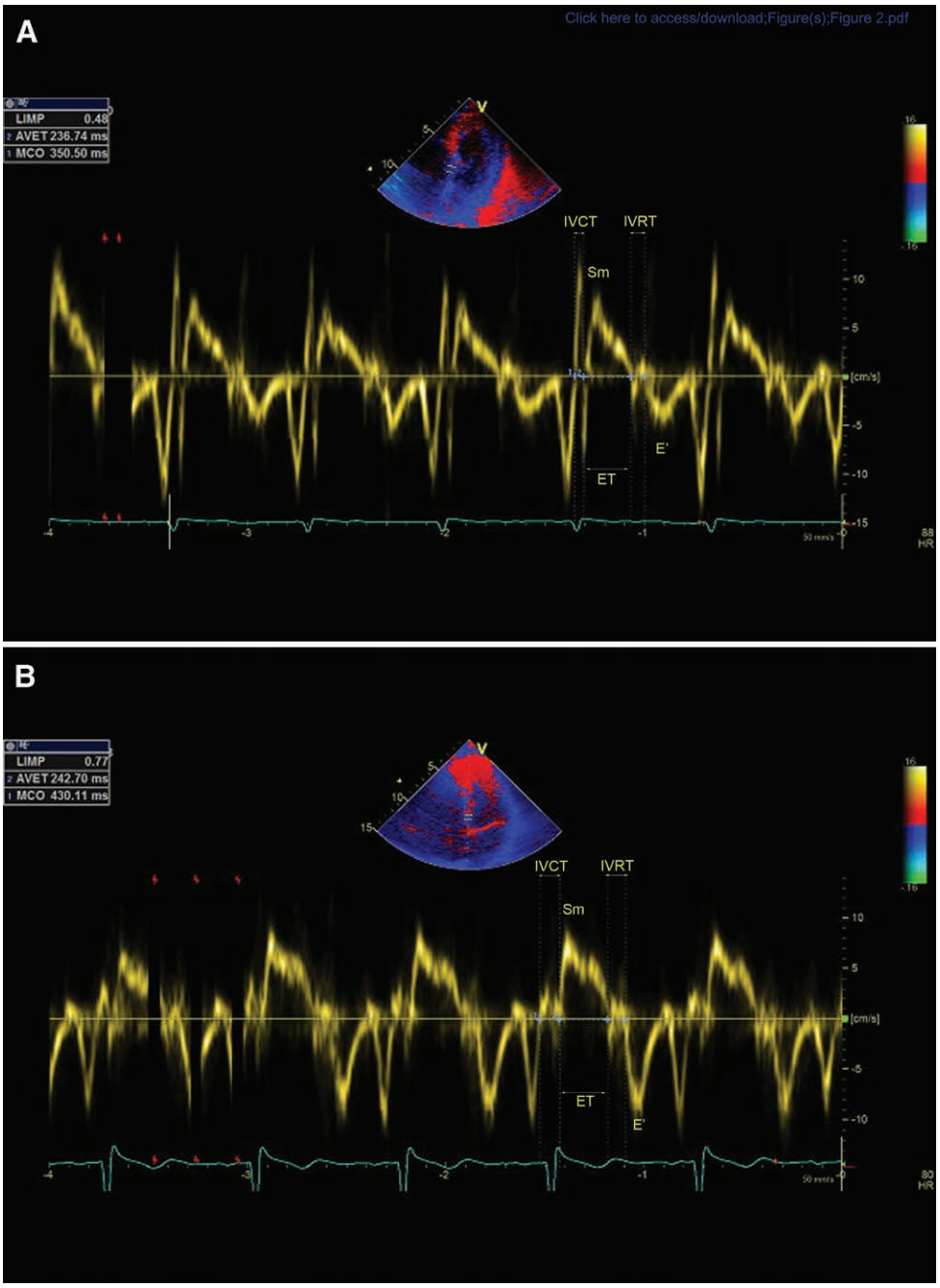

Fig. 2. Left ventricular myocardial performance index in patient A, who received low tidal volume ventilation, and patient B, who received intermediate tidal volume ventilation. The myocardial performance index is obtained using tissue Doppler imaging with an almost parallel ultrasound beam positioned at the septal annulus. The isovolumetric contraction time (IVCT) and isovolumetric relaxation time (IVRT) have a longer duration in patient B compared to patient A with a similar ejection time (ET) resulting in a higher myocardial performance index as this is calculated by (IVCT + IVRT) / ET, indicating decreased myocardial function. When the aortic valve ejection time (AVET) and mitral valve closure-to-opening time (MCO) are selected, the EchoPAC software automatically calculates the left ventricular myocardial performance index which is denoted as LIMP in the top left corners. The systolic maximal velocity (Sm) and early diastolic maximal velocity (E') are also shown.

in intrathoracic pressure are expected to be larger in the intermediate tidal volume group compared to the low tidal volume group.[31,41,47]

Several limitations of our study should be mentioned. First, we did not perform serial echocardiograms although a longitudinal study could have provided additional

information on myocardial dysfunction development. However, standard echocardiography shortly before intubation and mechanical ventilation was deemed unethical in patients experiencing dyspnea and/or with inadequate gas exchange. Furthermore, echocardiography directly after the start of mechanical ventilation could potentially result in a large variability in measurements as no steady ventilatory and/or hemodynamic state has presumably been reached. The myocardial performance index can be affected by rapid changes in preload,[23] and therefore a 24 h interval was chosen to enable the systematic performance of the transthoracic echocardiography examination in all patients in a relative stable setting on one hand, albeit before conceivable development of severe ARDS on the other hand.[25] Second, we acknowledge that our study could be underpowered as we recruited a limited number of heterogeneous patients in a single academic center partially limiting the external verification. However, we used echocardiographic measurements which are known to show small interindividual observer variability. We performed all echocardiograms using one ultrasound system and postprocessing software, with the same algorithms to calculate the parameters of myocardial function. Third, despite randomization there was a significant higher percentage of patients with aspiration/pneumonia at baseline in the intermediate tidal volume group compared to the low tidal volume group. Nevertheless, *post hoc* analysis did not demonstrate an attenuation in effect size on left ventricular performance when aspiration/pneumonia patients were excluded and only a modest decrease in effect size on right ventricular performance in our study. Fourth, blinding could not be performed due to the nature of the intervention. Nonetheless, all other respiratory parameters besides tidal volume size did not differ between both groups. Finally, the patients randomized to the higher tidal volume group "only" received a mean tidal volume of 9.5 ml/kg, and therefore were categorized as intermediate tidal volumes. Nevertheless, the difference with the low tidal volume group of 6.5 ml/kg is significant, with all other ventilator settings unmodified. It is important to note that the applied tidal volume sizes used in our study are in line with daily clinical practice on the ICU.[48] Further research must determine whether patients at higher risk of left ventricular and/or right ventricular systolic dysfunction may have additional benefit from a low tidal volume strategy.

Conclusion

Intermediate tidal volume ventilation induced left ventricular and right ventricular systolic dysfunction compared to a low tidal volume strategy. However, tidal volume size had no effect on left ventricular or right ventricular diastolic function.

Appendix

First, the parasternal long-axis view was obtained to assess left ventricular dimensions including the left ventricular outflow tract. Then, color Doppler was added to allow evaluation of aortic and/or mitral valvulopathy. All valve stenoses and/or regurgitations were graded as absent, mild, moderate, or severe, with the latter two classified as a significant valvulopathy.

Second, the parasternal short-axis view was obtained to assess the left ventricular eccentricity index calculated by the end-systolic anteroposterior diameter divided by the septolateral diameter providing an indicator of right ventricular pressure overload when the value exceeds 1.0.[49] Thereafter, at the level of the aortic valve, the pulsed-wave Doppler sample volume was positioned in the main pulmonary artery to obtain the pulmonary acceleration time as the peak velocity divided by the time to reach this peak. The pulmonary acceleration time was determined as a measure of right ventricular afterload, with a lower value indicating a higher pulmonary vascular resistance.[50,51]

Third, the apical four-chamber view was obtained to assess left ventricular and right ventricular dimensions. Acute *cor pulmonale* was defined as basal right ventricular end-diastolic diameter divided by basal left ventricular end-diastolic diameter as indicator of right ventricular volume overload when the ratio exceeds 0.6.[52] The apical four-chamber view was also used to calculate right ventricular free wall and left ventricular global longitudinal strain using the speckle tracking technique, with a more negative peak systolic global longitudinal strain value indicating improved systolic function relatively independent of loading conditions.[53] Then, color Doppler was added to allow evaluation of mitral and/or tricuspid valvulopathy. With the pulsed-wave Doppler sample volume positioned at the tips of the mitral valve and tricuspid valve, the left ventricular and right ventricular early/atrial velocity ratio was determined as measure for left ventricular and right ventricular diastolic function respectively. Subsequently, tissue Doppler imaging was performed with the pulsed-wave sampling volume positioned at the septal annulus to obtain a nearly parallel ultrasound beam to minimize measurement errors. Only in case of insufficient images was the pulsed-wave Doppler sampling volume positioned in the left ventricular lateral mitral annulus. For the right ventricle, the pulsed-wave Doppler sampling volume was positioned in the lateral tricuspid annulus. These recordings provided the systolic maximal velocity as a marker for systolic function and the early diastolic maximal velocity as a marker for diastolic function for each ventricle. The myocardial performance index was calculated by adding the isovolumetric contraction time to the isovolumetric relaxation time and then dividing the sum by the ejection time. The myocardial performance index is a nongeometric measurement and was chosen as primary endpoint since it provides information about combined systolic and diastolic function,[18] can be calculated for the

left ventricle and the right ventricle,[19,20] relatively independent of preload and afterload,[22] and can still be obtained in the presence of suboptimal two-dimensional images.[21] The isovolumetric acceleration was calculated as the maximal velocity of the isovolumetric contraction divided by the time to reach this maximum, assessing left ventricular and right ventricular systolic function in a less load dependent than traditional measurements.[35,36] M-mode was performed in the apical four-chamber view with the cursor through the right ventricular lateral tricuspid annulus providing the tricuspid annular plane systolic excursion.

Fourth, the apical two-chamber view was used together with the apical four-chamber view to calculate the left ventricular ejection fraction according to the modified Simpson rule.

Fifth, the pulsed-wave Doppler sample volume was positioned just below the aortic valve in the left ventricular outflow tract in the apical five-chamber view measuring the velocity time integral. By multiplying the velocity time integral with the square of the left ventricular outflow tract radius obtained from the parasternal short-axis view, stroke volume was obtained. Cardiac output was derived by multiplying stroke volume with heart rate.

Finally, patients were gently placed in supine position at the end of the examination. Then the subcostal view was obtained to allow evaluation of the vena cava inferior.

Competing Interests

Dr. Simonis received a grant supported by the Dutch organization for independent research ZonMw (The Hague, The Netherlands) to execute the main Protective Ventilation in Patients without ARDS (PReVENT) trial of which this project was a substudy. Dr. Gama de Abreu received financial support for research and lecture fees from Dräger Medical AG (Lübeck, Germany), Ambu (Ballerup, Denmark), and GE Healthcare (USA). Dr. Serpa Neto received personal fees from Dräger Medical AG. The other authors declare no competing interests.

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