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Plasma catecholamines and oxygen consumption during weaning from mechanical ventilation

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Abstract. Previous studies on oxygen consumption ($\dot{V}_{O_2}$) during weaning from mechanical ventilation assumed that an increase in $\dot{V}_{O_2}$ ($\Delta\dot{V}_{O_2}$) reflected oxygen consumption by respiratory muscles ($\dot{V}_{O_2RESP}$), and proposed $\Delta\dot{V}_{O_2}$ as a weaning predictor. We measured $\dot{V}_{O_2}$ CO_2 production ($\dot{V}_{CO_2}$) and plasma catecholamines in 20 short-term ventilated patients during weaning by SIMV and CPAP. $\Delta\dot{V}_{O_2}$ as a percentage of $\dot{V}_{O_2}$ during spontaneous ventilation ($\Delta\dot{V}_{O_2}$%) ranged from 4.8% to 41.5%. $\dot{V}_{CO_2}$ also increased and correlated with $\dot{V}_{O_2}$. Plasma adrenaline and noradrenaline increased significantly to levels known to produce considerable increases in metabolic rate. Mean arterial pressure and heart rate concomitantly increased, but spontaneous minute ventilation decreased. Thus, since the increased plasma catecholamines are calorigenic, the assumption that $\Delta\dot{V}_{O_2}$ represents $\dot{V}_{O_2RESP}$ is incorrect. Although mean $\Delta\dot{V}_{O_2}$% of successfully weaned patients was significantly less than that of failure-to-wean patients, the wide scatter of individual values in the latter group excludes $\Delta\dot{V}_{O_2}$% as an accurate weaning predictor.

Key words: Weaning from ventilation – Oxygen consumption – Plasma catecholamines

Many patients develop respiratory failure when critically ill or following major surgery and require ventilatory support. Weaning from mechanical ventilation is undertaken when the patient has improved sufficiently, leading to extubation if adequate spontaneous ventilation is sustained. Some patients are not easily weaned from ventilatory support despite adequate nutrition and resolution of the underlying illness. Reinstitution of mechanical ventilation, even some hours after extubation, may be necessary with a high incidence of morbidity. The ability to predict whether a patient can be weaned off mechanical ventilation is thus of considerable importance.

Standard criteria used traditionally for weaning from ventilatory support are arterial blood gas (ABG) values, vital capacity, tidal volume, respiratory rate, minute ventilation ($\dot{V}_E$), and maximum inspiratory force. However, they are not accurate to predict successful weaning and extubation of intensive care patients [1–2]. Recently, there has been interest in the work of breathing as an indicator of successful weaning [1, 3–7]. Work of breathing can be expressed in terms of mechanical work (as denoted by the area under a pressure: volume loop), or indirectly by the difference in oxygen consumption while on mechanical ventilation and while breathing spontaneously.

Measuring oxygen consumption ($\dot{V}_{O_2}$) at the bedside is much less complex than measuring mechanical work, especially with the use of new portable metabolic monitors. It has been noted that $\dot{V}_{O_2}$ increases when patients are weaned from continuous mechanical ventilation (CMV) to spontaneous ventilation [3–7]. This increase in $\dot{V}_{O_2}$ ($\Delta\dot{V}_{O_2}$) has been attributed to increased respiratory muscle work, and has been proposed as an index of weaning ability [5, 7]. However, weaning may be physically and psychologically stressful, and plasma catecholamine levels are likely to be increased. Since catecholamines are potent calorigenic hormones [8–10], they can increase $\dot{V}_{O_2}$ significantly in their own right [11]. This study was undertaken to examine changes in $\dot{V}_{O_2}$ and catecholamine levels during weaning.

Material and methods

The study was approved by the Research Ethics Committee of the Chinese University of Hong Kong. Twenty consecutive ventilated adult patients in the ICU were studied (Table 1). All patients were receiving adequate nutrition. They were considered suitable for weaning by the attending intensivist independent of the investigators, and satisfied these criteria: haemodynamic stability, adequate oxygenation with an FiO_2 less than 0.4, vital capacity greater than 10 ml/kg, and (negative) maximal inspiratory force greater than -25 cmH_2O. Patients who required inotropic support or positive end expiratory pressure (PEEP) were excluded.

All patients were ventilated by Servo 900C ventilators (Siemens-Elema, Sweden) using the CMV mode. The ventilator's synchronized intermittent mandatory ventilation (SIMV) and continuous positive air-

Table 1. Details of patients and oxygen consumption

Pt. no.	Age	Sex	Diagnosis	Height (cm)	Weight (kg)	Duration of ventilation (days)	$\dot{V}_{O_2WEAN}$ (ml/min)	$\dot{V}_{O_2\ CMV}$ (ml/min)	$\%\dot{V}_{O_2WEAN}$	Outcome
1	80	F	COAD respiratory failure	155	38	3	235	149	36.5	failed
2	48	M	Post op (oesophagectomy)	170	70	1	295	277	7	weaned
3	38	F	Post op (oesophagectomy)	150	52	1	277	248	10.5	weaned
4	54	M	Post op AVR	165	52	1	287	237	17.4	weaned
5	69	M	COAD respiratory failure	160	50	3	308	181	41.2	failed
6	62	F	Post op (oesophagectomy)	155	44	1	210	181	13.8	weaned
7	66	M	Post op (oesophagectomy)	165	56	1	371	217	41.5	failed
8	60	M	Post op (pulmonary oedema)	172	67	4	312	288	7.6	failed
9	69	M	Post op (aneurysm repair)	168	60	2	246	185	15	weaned
10	57	M	Post op (CABG)	170	68	1	263	243	7.6	weaned
11	56	M	Post op (oesophagectomy)	170	53.3	1	242	225	7.2	weaned
12	24	M	Post op (spinal fusion)	170	70	1	323	267	17.3	weaned
13	76	M	COAD respiratory failure	162	50	2	220	200	10.7	weaned
14	46	M	Acute pulmonary oedema	165	46	1	207	164	20.7	weaned
15	69	F	Post op (oesophagectomy)	153	52.2	1	223	176	21.7	failed
16	80	F	Post op (bleeding gastric ulcer)	155	45	1	182	160	12.1	weaned
17	30	M	Near drowning	172	62	1	313	269	14	weaned
18	69	F	Post op (oesophagectomy)	152	51.5	2	230	218	5.21	failed
19	60	M	Post op (bleeding gastric ulcer)	165	65	2	272	209	30.1	failed
20	29	M	Post op (VSD repair)	170	62.5	1	395	377	4.8	weaned

COAD = chronic obstructive airways disease; op = operative; AVR = atrio-ventricular valve replacement; CABG = coronary artery bypass graft; VSD = ventricular septal defect

way pressure (CPAP) modes were used for weaning. Weaning was started with a SIMV rate 75% of CMV rate. This was changed at intervals of about 30–60 min, to SIMV rates of 50%, then 25% of CMV rate, and finally to CPAP of 5 cmH_2O. The study concluded after 60 min of CPAP.

Arterial oxygen saturation (Sa_{O_2}) and end-tidal CO_2 were monitored continuously throughout the study using a pulse oximeter (Ohmeda Biox 3700) and CO_2 analyzer (Datex Normocap CD 102). Baseline measurements of $\dot{V}_{O_2}$, CO_2 production ($\dot{V}_{CO_2}$), respiratory quotient (RQ), heart rate, mean arterial blood pressure (MAP), $\dot{V}_E$ and respiratory rate, were made while the patients were ventilated on CMV mode. These measurements were then repeated in the last 5–10 min of each SIMV and CPAP mode. With each set of measurements, blood was sampled from an arterial cannula for estimations of ABG and plasma catecholamines.

Patients were considered to have failed to wean if during the period of the study, they developed hypoxaemia (Sa_{O_2} less than 90% or Pa_{O_2} less than 8.0 kPa), hypercarbia (Pa_{CO_2} greater than 7.0 kPa), total respiratory rate over 25/min, tachycardia over 130/min, or clinical distress, as judged by the attending intensivist.

The metabolic variables were measured using the Deltatrac Metabolic Monitor (Datex, Finland). This is a microprocessorcontrolled indirect calorimetry device which measures $\dot{V}_{CO_2}$ and calculates RQ, $\dot{V}_{O_2}$ and REE at 1 min intervals. All variables were averaged using a 5 min running average, and expressed in STPD. The accuracy of the Deltatrac in measuring gas exchange has been validated previously in ventilated and spontaneously breathing patients [12, 13]. Plasma catecholamine concentrations were measured using high pressure liquid chromatography with electrochemical detection using a method modified from Causon [14]. The lower limit of detection was 25 pg/ml, with a coefficent of variation of 5.70% for noradrenaline and 9.07% for adrenaline. Sampling and measurements were undertaken at steady state during periods of minimal movement and stimulation. Baseline variables were those taken while on CMV (VAR_{CMV}) and variables taken on CPAP were denoted as VAR_{WEAN}. $\Delta\dot{V}_{O_2}$ was derived by subtracting $\dot{V}_{O_2CMV}$ from $\dot{V}_{O_2WEAN}$, and was also expressed as a percentage ($\Delta\dot{V}_{O_2}\%$ as $\Delta\dot{V}_{O_2}/\dot{V}_{O_2WEAN}$ %).

Statistiscal analyses were performed using a software package (SPSS/PC+Advanced Statistics V2–0, SPSS Inc, Chicago, USA). One-way repeated measures ANOVA was used to evaluate $\dot{V}_{O_2}$ at each weaning stage. Scheffe's test was used to evaluate $\dot{V}_{O_2}$ differences at various weaning stages. Student's *t*-test was used to compare weaned and failed-to-wean patients. VAR_{CMV} and VAR_{WEAN} variables were compared using paired *t*-test. Discriminant analysis was used to evaluate the ability of $\Delta\dot{V}_{O_2}\%$ to classify patients into weaned and failed-to-wean groups. A $p<0.05$ was considered significant. All data are presented as mean±SE unless indicated.

Results

Patient details, $\dot{V}_{O_2CMV}$, $\dot{V}_{O_2WEAN}$, and $\Delta\dot{V}_{O_2}\%$ are given in Table 1. Twenty patients, 14 males and 6 females aged 57.1±3.7 years were studied. Thirteen patients were successfully weaned from the ventilator and extubated. None of these patients required to be reintubated. The other 7 patients failed to be weaned and CMV was re-established. Three of these could not proceed past 50% SIMV weaning. Thus, their variables measured on 50% SIMV mode were taken as VAR_{WEAN}.

$\dot{V}_{O_2}$ increased during weaning (Fig. 1). Baseline $\dot{V}_{O_2CMV}$ of 226±12 ml/min was significantly less than $\dot{V}_{O_2WEAN}$ of 258±13 ml/min ($p<0.01$, Table 2). $\dot{V}_{O_2CMV}$ was also less than the $\dot{V}_{O_2}$ values of the other stages of weaning (significant at 95%). The differences between $\dot{V}_{O_2}$ values of the weaning stages were small and not significant (Fig. 1). Individual $\Delta\dot{V}_{O_2}\%$ values ranged from 4.8% to 41.5%. $\Delta\dot{V}_{O_2}\%$ of weaned patients (12.2±1.3%) was significantly less than that of failed-to-wean patients (26.2±5.7, $p<0.01$) (Table 3, Fig. 2).

There was good correlation between the increases in $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ during weaning ($r=0.92$, $p<0.005$). These measurements were averaged over a 5 min period. During this period, it can be assumed that the patient's metabolic status was stable. $\dot{V}_E$ decreased significantly

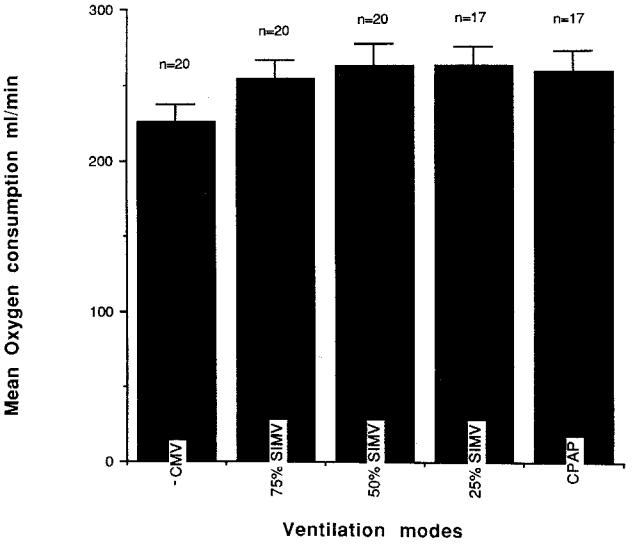

Fig. 1. Mean oxygen consumption during continuous mechanical ventilation (*CMV*) and during the weaning stages of decreasing synchronized IMV (*SIMV*) and continuous positive airway pressure (*CPAP*)

during CPAP weaning compared to CMV (7.73±0.40 l vs 6.90±0.40 l, $p<0.05$). This $\dot{V}_E$ difference can be explained by the hyperventilation used during CMV ($PaCO_2$ of 4.80±0.18 kPa) to suppress spontaneous respiratory activity. The decrease in $\dot{V}_E$ was reflected by a significant rise in $PaCO_2$ from 4.80±0.18 kPa to 5.58±0.19 kPa ($p<0.01$, Table 2).

Plasma catecholamine levels, MAP and heart rate during CMV and during weaning are shown in Table 2. No catecholamine result was available from 1 weaned patient, due to a technical fault in the assay. Plasma adrenaline levels during weaning (508±181 pg/ml) increased significantly from those during CMV (136±24 pg/ml, $p<0.05$, Table 2). This also occurred with plasma noradrenaline levels (1143±247 pg/ml vs 483 pg/ml, $p<0.01$). There was a significant correlation between plasma adrenaline and noradrenaline ($p<0.01$, $r=0.61$). The increase in plasma levels between weaned patients and failed-to-wean patients was significant for noradrenaline, but not for adrenaline (Table 3). MAP and heart rate both increased significantly during weaning, in parallel with the increased catecholamine levels (Table 2).

Table 2. Means ± SE of variables measured during CMV (VAR_{CMV}) and during weaning (VAR_{WEAN}) ($n=20$, except *when $n=19$)

	VAR_{CMV}	VAR_{WEAN}	p-Value
$\dot{V}_{O_2}$ (ml/min)	226 ±12	258 ±13	$p<0.01$
$\dot{V}_{CO_2}$ (ml/min)	176 ±8	201 ±10	$p<0.05$
$\dot{V}_E$ (l/min)	7.73 ±0.4	6.90 ±0.4	$p<0.05$
Adrenaline (pg/ml)*	136 ±24	508 ±181	$p<0.05$
Noradrenaline (pg/ml)*	483 ±65	1143 ±247	$p<0.01$
MAP (kPa)	10.91±0.67	13.03±0.67	$p<0.01$
Heart rate (beats/min)	90 ±4	106 ±7	$p<0.01$
$PaCO_2$ (kPa)	4.80 ±0.18	5.58 ±0.19	$p<0.01$

$\dot{V}_{O_2}$ = oxygen consumption; $\dot{V}_{CO_2}$ = carbon dioxide production; $\dot{V}_E$ = minute ventilation; MAP = mean arterial pressure

Table 3. Increase in oxygen consumption and plasma catecholamines in successfully weaned (weaned) and failure to wean (failed) patients

	Weaned *$n=13$ **$n=12$	Failed $n=7$	p-Value
$\Delta\dot{V}_{O_2}$% (%)*	12.2±1.3	26.2±5.7	$p<0.01$
Δ Adrenaline (pg/ml)**	288 ±219	516 ±279	NS
Δ Noradrenaline (pg/ml)**	244 ±64	1372±527	$p<0.05$

Mean ± SE values are shown. $\Delta\dot{V}_{O_2}$ = increased oxygen consumption as a percentage of total oxygen consumption during weaning; Δ Adrenaline and Δ Noradrenaline = increases in adrenaline and noradrenaline during weaning

Discussion

Studies on the $\dot{V}_{O_2}$ difference during weaning from controlled ventilation to spontaneous breathing ($\Delta\dot{V}_{O_2}$) have been reported on post-cardiac surgery patients [15, 16], patients with cardiopulmonary disease [3], multiple injuries, burns and sepsis [17], and those in ICUs [4–7]. Many of these studies assumed that $\Delta\dot{V}_{O_2}$ reflected oxygen consumption of respiratory muscles ($\dot{V}_{O_2RESP}$) primiarily. Thus, higher $\Delta\dot{V}_{O_2}$ values were proposed to result from increased work and decreased efficiency of respiratory muscles [3] and increased minute ventilation [17]. This assumes that oxygen metabolism of tissues other than respiratory muscles remains constant. However, other factors such as work of non-respiratory muscles and stress hormone secretion contribute to $\Delta\dot{V}_{O_2}$ and must be considered.

Catecholamines have known calorigenic actions, with adrenaline more than noradrenaline [8–10]. Plasma concentrations of catecholamines vary widely according to physiological and pathological conditions. Physiological plasma adrenaline and noradrenaline levels range respectively from about 30 and 200 pg/ml at rest, to over 400

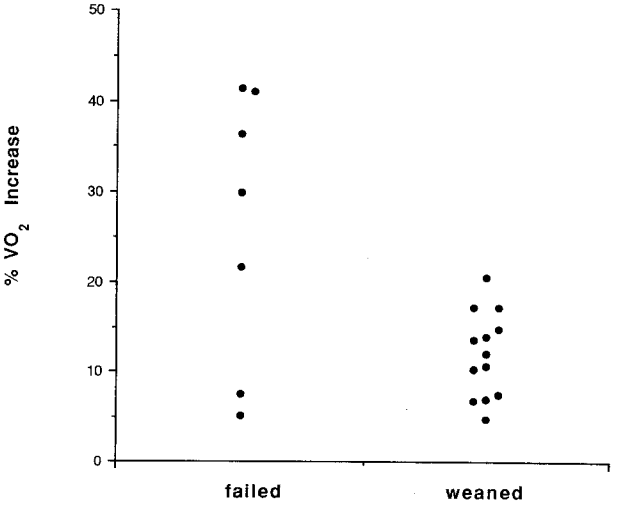

Fig. 2. Percent increase in oxygen consumption during weaning of patients who failed to be weaned and who were successfully weaned. Although the difference is significant ($p<0.01$), there is a wide scatter of values in the failed group

and 2000 pg/ml during heavy exercise [8]. Infusions of adrenaline to raise plasma levels to 450 pg/ml (2.2 nmol/l) in non-ventilated healthy subjects resulted in a 24% increase in metabolic rate [9]. Similarly, noradrenaline infusions to plasma levels of 1300 pg/ml (7.7 nmol/l) also increased metabolic rate up to 20% [9]. An increase in $\dot{V}_{O_2}$ of about 25% was observed following infusions of 1.2 μg/m²/min adrenaline [11].

Increased sympathetic activity during weaning have been documented [18–20]. Lemaire and co-workers [18], in a study on the haemodynamic effects of weaning, assayed plasma catecholamines in 8 patients, and found an increase in levels 10 min after starting weaning. Kennedy and co-workers [19] reported an increase in urinary catecholamines during weaning, although these measurements are poor indices of acute sympathetic activity. In our study, $\dot{V}_{O_2}$, plasma adrenaline and plasma noradrenaline levels increased during weaning, accompanied by increases in MAP and heart rate. Hence, our weaning levels of adrenaline of 508±181 pg/ml and noradrenaline of 1143±247 pg/ml would give rise to considerable increases in metabolic rate and non-respiratory $\dot{V}_{O_2}$, thus making a sizeable contribution to $\Delta\dot{V}_{O_2}$. This contribution of catecholamines to $\Delta\dot{V}_{O_2}$% during weaning was also suggested by Annat and colleagues [20], in a study of $\Delta\dot{V}_{O_2}$% during CPAP and pressure support ventilation. Systolic blood pressure increased significantly when their patients were changed from CMV to CPAP ventilation. In the present study, plasma noradrenaline levels were significantly higher in failed-to-wean patients, but adrenaline levels did not differentiate between these and weaned patients (Table 3). Hence, whether higher catecholamine levels are the cause or effect of failed weaning remains unanswered.

The $\Delta\dot{V}_{O_2}$ values in our study are consistent with those reported in the literature (vide supra). The similarity of $\Delta\dot{V}_{O_2}$ values of different patient groups from all studies, supports our observation that there is no uniform association between pulmonary disease and high $\Delta\dot{V}_{O_2}$ values (Table 1). This was also noted by Hubmayr and co-workers [6], suggesting that $\Delta\dot{V}_{O_2}$ does not reflect energy requirements of respiratory muscles primarily.

Some workers, on the assumption that $\Delta\dot{V}_{O_2}$ reflects $\dot{V}_{O_2RESP}$, have attempted to evaluate the use of $\Delta\dot{V}_{O_2}$ to predict weaning ability. Consequently, it was reported that patients who failed to be weaned exhibited significantly higher $\Delta\dot{V}_{O_2}$ values than those weaned successfully [5, 7, 21]. It was also proposed that 15% $\Delta\dot{V}_{O_2}$% was an accurate dividing reference point [5, 7], and that duration of weaning correlated with $\Delta\dot{V}_{O_2}$ [4]. Nevertheless, the usefulness of $\Delta\dot{V}_{O_2}$ as a predictor of successful weaning were not confirmed by other workers [6, 20, 22], and $\Delta\dot{V}_{O_2}$ could not be correlated with respiratory mechanical power output [6]. In the present study, $\Delta\dot{V}_{O_2}$% of failed-to-wean patients was significantly greater than that of weaned patients. However, there is a wide scatter of individual $\Delta\dot{V}_{O_2}$% values in the former group (Fig. 2). Discriminant analysis based on the data obtained failed to predict 2 of the 7 patients who failed to wean correctly (28.6% error). Any future predictions based on these data are likely to produce even less accurate results [23]. The ratio of between group variance to within group variance (Eigen value) was found to be 0.5363, indicating a poor discrimination. Larger Eigen values (>4) are associated with good discrimination.

There was a correlation between $\Delta\dot{V}_{O_2}$ and increase in plasma catecholamines, but consideration of the correlation is inappropriate, as increases in both variables are dependent on multiple factors. Extremely acute rises in catecholamines can occur and metabolic rates cannot follow proportionately. Indeed, this was seen in 3 patients in the present study.

For the purposes of this study, we defined failed-to-wean patients as those who could not be extubated following progressive weaning to spontaneous ventilation *on the first attempt.* There is no consistent definition of failed weaning from mechanical ventilation. Although it implies an inability to be extubated within a certain time period, this interval varies betweeen researchers [1, 5, 7]. All our failed-to-wean patients were able to be extubated over 1–3 days subsequent to the collection of data.

The longest period of mechanical ventilation in our series was 4 days. Consequently, the conclusions from this study may not be applicable to patients ventilated for prolonged periods. Nevertheless, plasma catecholamines are likely to increase in these patients when they are changed from CMV to spontaneous ventilation. This is suggested by the data of Annat and colleagues [20]. As all their patients had chronic obstructive pulmonary disease and were ventilated for 2–37 days.

In conclusion, $\dot{V}_{O_2}$ increase during weaning from mechanical to spontaneous ventilation is accompanied by 4-fold and 2-fold increases in plasma adrenaline and noradrenaline respectively, to levels known to produce considerable increases in body metabolism. Hence $\Delta\dot{V}_{O_2}$ cannot be equated primarily to oxygen consumption by respiratory muscles, and lacks sufficient accuracy to be a useful predictor of weaning ability.

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