Heart Rate Variability Analysis during Weaning from Mechanical Ventilation: Models for Prediction of the Weaning Trial Outcome

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Abstract

This study estimates the activity of the autonomic cardiac control (ACC) in patients undergoing weaning from mechanical ventilation, aiming to predict the weaning outcome. ECG and AVEA ventilator data from 13 successfully and 14 unsuccessfully weaned patients were collected. Heart rate variability (HRV) profiles were estimated in non-sedated patients during 2 weaning phases: (1) PSV - pressure support ventilation at 12-25 cmH_2O; (2) SBT – spontaneous breathing trial at 8 cmH_2O. HRV indices in the time- and frequency-domain were analyzed on 5-min RR-interval episodes under stationary conditions during each weaning phase.

Our model for prediction of the successful weaning outcome considers 3 basic mechanisms for adequate ACC response on the weaning cardio-respiratory stress: (1) preserved ACC ability to maintain physiological adaptation; (2) modulated ACC activity by the breathing model; (3) mostly neurohumoral regulation of the blood circulation. The successful group model exhibits reduced total activity (TP, SDNN) with increased sympathetic (VLF/TP, LF/HF>1) and reduced vagal tone (HF/TP, RMSSD, pNN50), the latter related to the respiratory rate and tidal volume. Deviations from this HRV model are indicative for weaning failure detected with accuracy 92.6% (PSV), 81.5% (SBT), 96.3% (SBT-PSV).

Introduction

Mechanical ventilation (MV) of critically ill patients is associated with many risks and complications that lead to high morbidity, mortality, longer intensive care unit stay, and higher treatment costs [1]. Identifying the patient's readiness at the earliest time possible for successful weaning from MV is the primary target for patients with command breathing [2]. Discontinuation from MV is the process for a gradual reduction in ventilator support, to allow patients the ability to assume increasing levels of work to breathe until sustain spontaneous breathing. This weaning process occupies an average of 40% of the total duration of mechanical ventilation, with failure in over one third of MV patients. The consolidated evidence-based clinical practice guidelines of the American Thoracic Society (ATS) and the American College of Chest Physicians (CHEST) point out the process of MV liberation as an investigation priority [1].

Weaning from MV to spontaneous breathing has impact on 3 physiological mechanisms [3-5]:

1) Changes in the oxygen transport profile, which may provoke circulatory disturbances with a terminal result of weaning failure or other fatal complications (acute myocardial infarction, heart failure and cardiogenic pulmonary edema, rhythm disorders).
2) Haemodynamic alterations as a result of changes in the intrathoracic pressure (ITP), which is positively dependent on the tidal volume and modulated by MV breathing cycles [6]. The associated changes in the cardiac output, ventricular preload and afterload may result in acute alterations of cardiac mechanics and myocardial ischemia, manifested as arrhythmias.
3) Effects on the autonomic nervous system (ANS) activity, which is influenced by humoral changes in the intrathoracic cardiovascular system due to ITP changes. Therefore, ANS tries to compensate for these humoral changes by two mechanisms – increasing the sympathetic tone and decreasing the parasympathetic tone that affects the heart rate.

Heart rate variability (HRV) is the physiological phenomenon of inter-beat interval variation due to the joint action of the sympathetic and parasympathetic parts of the autonomic cardiac control (ACC) [7]. A number of studies on HRV changes at different phases during MV discontinuation have concluded that ACC status provides essential information on the pathophysiological imbalances reflected in the success or failure of weaning [3-5,8-13]. In failure patients, reduced HRV and vagal tone withdrawal have been reported [9,10,12]. This study aims to derive models for prediction of the weaning outcome by HRV, breathing and metabolic features, and to better understand the ACC role during MV weaning.

2. Materials and methods

2.1. Study population

Data from 27 patients undergoing weaning from MV (63% men, age 58±17 years, Simplified Acute Physiology Score SAPS II = 28.9±8.2) were collected with AVEA ventilator system in the intensive care unit of the Pirogov University Emergency Hospital, Sofia. According to inclusion criteria, the enrolled patients did not have cardiac arrhythmias, neurological diseases, did not take pre-medication with cardiovascular drugs, and received CMV for at least 72 hours prior the study. The decision to start weaning and weaning outcome has been made by the primary care physician following a weaning protocol approved by the local Ethics Committee, in concord to general weaning and extubation criteria [14].

The study considered two weaning phases in non-sedated patients:

1) Pressure support ventilation (PSV): titration of the inspiratory pressure support level from 25 down to 12 cmH_2O during about 30 min. All patients have successfully passed this phase.

2) Spontaneous breathing trial (SBT): PSV at 8 cmH_2O. SBT was terminated if the patient exhibited signs of poor tolerance.

The weaning outcome was estimated by the ability of the patient to maintain the SBT challenge for at least 2 hours, being successful (S=13 patients) and failed (F=14 patients).

2.2. HRV analysis

ECG signal (lead I, 500Hz) was continuously recorded. Time series of normal-to-normal RR-intervals (NN), deduced from adjacent normal sinus beats in stable artifact-free 5-min episodes under stationary conditions were extracted after the beginning of PSV and SBT. Standardized HRV indices [7] were calculated (Table 1):

- TIME-HRV from the time-domain NN-tachogram, dNN-tachogram (NN-intervals first differences) and NN-histogram (using standard discrete scale resolution of the bin equal to 7.8ms=1/128Hz).

- FREQ-HRV. Fourier Transform of NN interval time series resampled at 4Hz was applied to derive the power spectrum density components of HRV.

Table 1. Mean±standard deviation of time-frequency domain HRV, ventilatory and hemodynamic indices for failure (F, 14 patients) and successful group (S, 13 patients) during PSV and SBT. *: $p<0.05$ comparing F vs. S groups by T-test.

	Measurements	**PSV**		**SBT**		**SBT-PSV**	
		Success	**Failure**	**Success**	**Failure**	**Success**	**Failure**
TIME-HRV	**HR** (bpm) = 60/mean of NN-intervals	100±19	94±23	101±19	95±22	0.7±7.5	1.7±3.3
	SDNN (ms): std. deviation of NN-intervals	18±12	19±27	17±15	20±23	0.8±8.3	1.2±6.3
	MDNN (ms): mean deviation of NN-intervals	14±10	14±22	13±12	15±19	0.2±7	0.5±5
	SDNNd (ms): std. deviation of dNN	8±10	12±15	9±14	13±16	2.4±5.1	1.2±3.6
	MDNNd (ms): mean deviation of dNN	4±6	8±12	6±10	8±12	1.9±4.7	0.4±2.9
	pNN50 (%): proportion of dNN>50ms	1.0±3.2	5.4±14.5	2.1±6.6	5.5±15.8	1.1±3.5	0.1±3.5
	RMSSD (ms): root-mean square of dNN	10±11	17±23	12±16	19±25	3.4±6.5	1.9±5.3
	TRI: triangular index of NN-histogram	4.6±2.9	4.4±4.9	3.7±2.3	4.4±4.3	-0.5±0.8	0.1±1.2
FREQ-HRV	**TP** (ms^2): total power (0.015-0.4 Hz)	154±263	527±1593	207±369	546±1786	112±275	19±248
	VLF/TP (%): very low freq. (0.003-0.04 Hz)	53±17*	31±19*	47±23	37±25	-5±13*	6.8±15*
	LF/TP (%): low freq. band (0.04-0.15 Hz)	27±7	28±14	27±13	26±13	-1.9±11	-2.6±11
	HF/TP (%): high freq. band (0.15-0.4 Hz)	20±15*	41±26*	26±23	37±29	6.9±14	-4.2±20
	LF/HF ratio	3.3±2.6*	1.4±1.5*	3.6±4.2	1.9±2.1	-0.04±1.7	0.4±1.6
AVEA ventilator measurements	**SYS** (mmHg): systolic blood pressure	126±20	138±27	133±24	147±36	8±19	8.4±17
	DIA (mmHg): diastolic blood pressure	67±10	76±17	74±11	79±24	5±9	3.5±9.4
	SpO2 (%):oxygen saturation	97.1±1.8	95.9±3.0	95.9±2.6	93.7±3.4	-1.1±2.9	-2.1±2.5
	f (br/min): breathing frequency	18±6	23±8	27±6*	34±7*	9±4	11±8
	Vt (mL): tidal volume	542±120*	423±130*	379±92*	288±91*	-169±101	-136±113
	MV (L/min): minute volume	8.7±2.5	8.5±2.2	9.7±2.8	10.0±2.5	0.4±1.1	1.4±2.4
	RSBI=f/Vt: rapid shallow breathing index	37±24*	63±32*	76±26*	133±56*	40±21*	70±44*
	PETCO2 (mmHg): end-tidal carbon dioxide	35±8	34±8	32±6	33±7	-1.7±3.2	-0.6±3.0
	VO2 (mL): oxygen consumption	275±68	294±94	311±65	390±124	36±48	96±95
	VCO2 (mL): carbon dioxide elimination	213±56	231±74	231±44	250±83	17±35	19±33
	RQ: respiratory quotient	0.75±0.09	0.72±0.12	0.74±0.11	0.67±0.1	-0.01±0.1	-0.05±0.1
	EE (kCal): energy expenditure	1907±559	1949±520	2064±513	2316±673	177±270	367±633

2.3. Weaning outcome prediction model

Both HRV indices and AVEA ventilator measurements (Table 1) were processed in Matlab (MathWorks, Inc.) by forward stepwise linear discriminant analysis (SDA) to derive models for prediction of the weaning outcome. Models using different input vectors were trained, aiming to select the most powerful and non-redundant predictors, measurable during PSV, SBT, and the difference (SBT-PSV). The feature selection process was iterative, so that at each step, SDA was forced to include the predictor, which led to maximal classification accuracy:

$$Acuracy = \frac{TP + TN}{TP + FN + TN + FP},$$

where TP, FN are true positives and false negatives for detection of the weaning failure group (14 F-patients); TN, FP are true negatives and false positives for detection of the weaning success group (13 S-patients).

Leave-one-out cross-validation was applied to derive the maximal classification accuracy achieved by SDA. Moreover, to ovoid overtraining on the small size database, SDA was limited to include up to 7 features or the training stopped while reaching a plateau in the accuracy step-up trend for >2 steps.

3. Results and discussion

The statistical distributions (Table 1) show noticeable differences of S- vs. F-patients during PSV, SBT, SBT-PSV, although statistical significance was not confirmed due to the small cohort of patients. T-test highlights the most outstanding differences for HRV-FREQ (VLF/TP, HF/TP, LF/HF) and ventilator measures (RSBI, Vt, f).

The discriminant models (Figures 1, 2) rank the most powerful prognostic features to the weaning outcome:

- *PSV*: Vt (81%), VLF/TP (78%), LF/HF (78%); combined 6 HRV (92.6%) 2HRV+3AVEA (96.3%).
- *SBT*: HRV has the lowest prognostic value: 1 HRV (66%), combined 6 HRV (81.5%) vs. AVEA: RSBI (81.5%), f (78%), Vt (78%), RSBI+SYS (92.6%).
- *SBT-PSV*: RSBI (77%), VLF/TP (73%), TRI (73%); combined 6 HRV (96.2%) 6HRV+1AVEA (100%).

Our literature research finds inconsistent conclusions on ACC activity during MV weaning, considering that majority of studies have explored only frequency-domain HRV, i.e. neglecting time-domain HRV components [3,5,8-13], or analyzing only the couple (LF, HF) but neglecting VLF component [8-10,12,13]. This limitation suggests 3 potential sources for mislead interpretations:

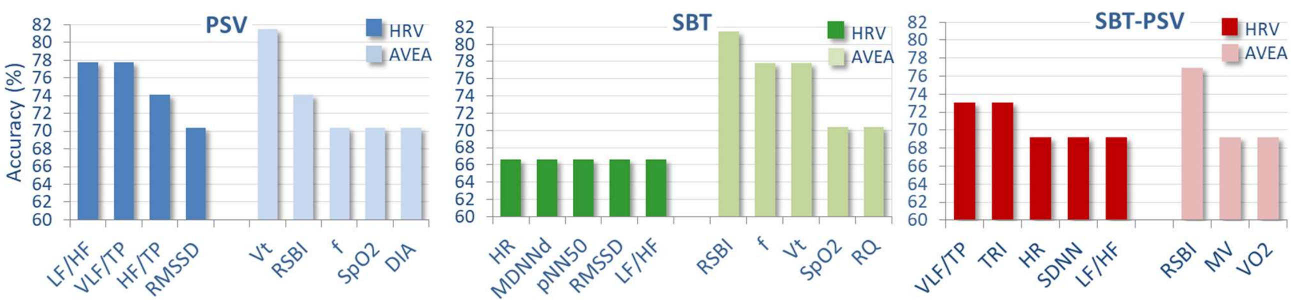
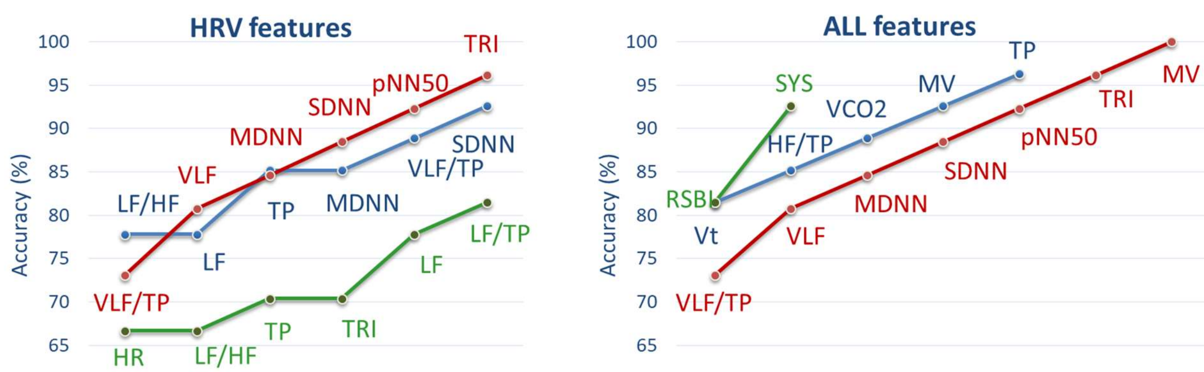


Figure 1. Top-ranked features (HRV, breathing, metabolic) in PSV, SBT, SBT-PSV for prediction of the weaning outcome.



Nb features	1	2	3	4	5	6
PSV	77.8	77.8	85.2	85.2	88.9	92.6
SBT	66.7	66.7	70.4	70.4	77.8	81.5
SBT-PSV	73.1	80.8	84.6	88.5	92.3	96.2

Nb features	1	2	3	4	5	6	7
PSV	81.5	85.2	88.9	92.6	96.3		
SBT	81.5	92.6					
SBT-PSV	73.1	80.8	84.6	88.5	92.3	96.2	100

Figure 2. Performance of 6 SDA models for prediction of the weaning outcome, showing the iteratively selected features (only HRV – left graph, all features – right graph) in PSV, SBT, SBT-PSV that lead to maximization of accuracy.

1) Risk for analysis of ACC profiles through only highly variable frequency-domain HRV indicators (mainly LF and HF). Especially for LF, in addition to the variability, a saturation effect can be observed at a significant sympathetic ACC tone, so the conclusions on the real cardiac autonomic balance (CAB) can be biased. We recommend always using the benefit of the time-domain HRV, whose dynamic scale covers the entire range of ACC tone activity. Our results (Table 1) show that LF/TP varies insignificantly within PSV and SBT for both S- and F-patients (mean value range 26-28%), while HF/TP has a significant rise in F- vs. S-patients (mean value 41% vs. 20% in PSV, 37% vs. 26% in SBT). This contradicts the hypothesis that the weaning failure is associated with reduced HRV and vagal tone withdrawal [9,10,12] and confirms increased vagal activity [3,8,11].

2) Missing mechanisms for control of the CAB activity evaluation by established strong correlations between pairs of time- and frequency-domain HRV indices, e.g.:

- SDNN vs. TP (r=0.85) shows that the increase in their values is positively associated with higher vagal activity, while the decrease – with lower vagal but increased sympathetic activity.
- RMSSD, PNN50 vs. HF (r=0.87; r=0.88) are indices for estimation of the vagal part in CAB.

The trends for proportional change of the linked time and frequency HRV indices are particularly important, because their presence or absence proves a respective reliability or uncertainty on the provided ACC activity interpretation. Table 1 confirms the consistency of our results, implying 1.6 to 5-fold higher tension of the vagal tone in F- vs. S-patients by agreement between pNN50 (5.4% vs. 1% in PSV, 5.5% vs. 2.1% in SBT), RMSSD (17 ms vs. 10 ms in PSV, 19 ms vs. 12 ms in SBT) and HF/TP (41% vs. 20% in PSV, 37% vs. 26% in SBT).

3) Ignoring the VLF component and analysis of an incomplete frequency-domain HRV model (TP=LF+HF), despite the emphasis on the neurohumoral regulatory mechanisms in MV and during MV weaning process [3]. Indeed, our results highlight the importance of VLF for prediction of the weaning outcome: S- vs. F-patients have significantly high VLF/TP during both weaning phases: 53% vs. 31% (SBT), 47% vs. 37% (SBT). The combination with significant increase of the sympathetic-vagal balance ratio LF/HF = 3.3 vs. 1.4 (SBT), 3.6 vs. 1.9 (PSV), emphasizes the positive role of the preserved ACC ability to maintain physiological adaptation by prevalence of the sympathetic activity during breathing stress, and its high prognostic value for successful weaning.

Our study confirms the hypothesis that the ACC status, estimated via HRV, related to the sympatho-vagal interactions in CAB can be a reliable prognostic method to the weaning outcome (96.2%) in critically ill patients. It is in agreement with similar conclusions by Orini et al [8], Briceno et al [13], while contradicts the opinion of Papaioannou et al [9].

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