Journal of Clinical Monitoring and Computing (2004) 18: 275–281

WEANING FROM LONG-TERM MECHANICAL VENTILATION: A NONPULMONARY WEANING INDEX

L. Todorova[1] *and A. Temelkov, MD*[2]

Todorova L, Temelkov A. Weaning from Long-Term Mechanical Ventilation: A Nonpulmonary Weaning Index
J Clin Monit 2004; 18: 275–281

ABSTRACT. Objective. Despite the extensive investigations in the area of weaning, clinicians are still struggling with the question of when to begin the process of weaning. Clinical weaning indices designed to predict the weaning potential are most frequently based on pulmonary factors. However, many physiological, respiratory, and mechanical factors also have impact on weaning, but are often overlooked. We suggest a new "nonpulmonary weaning index" (NPWI), which assesses the influence of factors such as blood albumin and total blood protein on the weaning success. **Methods**. We assess the information value of 17 clinical and paraclinical indices in a retrospective study covering 151 patients on a long-term (at least 7 days) mechanical ventilation. The most informative of those 17 indices are used in the formulation of NPWI. Its threshold differentiates the successful from the unsuccessful weaning trials. **Results**. From all 17 indices the most significant are: total blood protein, blood albumin, PaO_2, hematocrit, lactate, the ratio PaO_2/FiO_2, hemoglobine, and RUE. The proposed index uses only two of them: blood albumin and total blood protein. It is easily calculated and can easily be tracked in time. It has high sensitivity and specificity. **Conclusions**. The results of this study suggest that in the decision whether to attempt weaning from long-term mechanical ventilation, more attention should be paid to the nonpulmonary factors.

KEY WORDS. Mechanical ventilation, weaning, readiness to wean.

INTRODUCTION

The use of intubation and mechanical ventilation in an ICU in the latest years mark a considerable advance. This is due to the common use of mechanical ventilation devices in every day practice, as well as their great variety. The rate of the patients, who recieve ventilatory support in circumstance of critical care, vary between 20 and 60% according to their clinical features, as 10–50% from mechanical ventilated patients require prolonged weaning procedure [1–3]. Our clinical experience show that endotracheal intubation with mechanical ventilation and application of ventilation circuits lead to potential complications and some unfavourable physiologic effects [4, 5]. Thus for instance, they are the most important risk factors, leading to development of nosocomial pneumonias in critical ill patients [6, 7]. In such patients the risk is several times higher, as some authors report, and it grows in proportion of the duration of breathing support. It is reported for cumulative frequency of pneumonias from 8.5% during first 3 days after beginning of ventilation, 21.1% during first 7 days, 32.4% to 14th day and 45.6% in cases with mechanical ventilation with duration over 14 days. Thus in these cases it is of critical significance that mechanical ventilation

From the [1]Department of Biomedical Informatics, Central Laboratory of Biomedical Engineering, Bulgarian Academy of Sciences, Acad. G. Bonchev Street, Block 105, 1113 Sofia, Bulgaria, [2]Centre of Acute Respiratory Insufficiancy, Alexandrov's University Hospital, Sofia, Bulgaria.

Received 09 October, 2003, and in revised form 15 April, 2004. Accepted for publication 10 June, 2004.

Address correspondence to Lyudmila Todorova, Department of Biomedical Informatics, Central Laboratory of Biomedical Engineering, Bulgarian Academy of Sciences, Acad. G. Bonchev Street, Block 105, 1113 Sofia, Bulgaria.
E-mail: lpt@clbme.bas.bg

should be withdrawn and patient be extubated in the earliest possible moment, when he is in a position to maintain spontaneous breathing. In many patients who need a short-term mechanical ventilation, weaning is quick and easy [8]. However, withdrawing of mechanical ventilation may be performed with considerable difficulty in patients who are ventilated mechanically for over 7 days. Besides that, medical care for this patients demands considerable expenditures.

The early determination of patients, able to breathe spontaneously, is one of the main problems for management by clinicians in ICU. Taking the decision how and when to begin the process of weaning from mechanical ventilation includes evaluation of prognostic parameters of ventilatory withdrawal, and (as well as) determine the integrative weaning predictive indices.

With the present study we seek to determine the information received from certain clinical and paraclinical indices, which are significant in realization of transition to spontaneous breathing after long-term mechanical ventilation. On this basis a new index for prediction of the beginning of weaning from mechanical ventilation is to be developed, which will assess the influence of nonpulmonary factors, which were, because of specifity of the process, up to this moment considered as insignificant. The purpose for development of this index is to be highly sensitive and specific, to be easy for calculation and not to demand any special equipment.

METHODS AND MATERIALS

A retrospective study, that covers 151 patients, admitted and discharged in the Centre of Acute Respiratory Insufficiancy, Alexandrov's University Hospital- Sofia, Bulgaria, for a period of 11 years (1989–1999). All the patients were on a long-term mechanical ventilation for more than 7 days (26.12 ± 11.09). In the history of these patients, we could not receive data for preceding chronic pulmonary disease or serious systematic illness for anybody, deteriorating the primary disease process. The ethiologic factors, leading to ARF (acute respiratory failure) with a necessity of long-term mechanical ventilation, are presented in Table 1. The average age of the patients in this study is 33.76 ± 18.25 years (2–59 years—Figure 1).

Table 1. The ethiologic factors, leading to ARF with necessary long-term mechanical ventilation

Polytrauma	57 (38%)
Isolated craniocerebral trauma	17 (11%)
Sepsis	17 (11%)
Thoracic trauma	15 (10%)
Pneumonia	11 (8%)
Cardiac arrest and cardiopulmonary resuscitation	10 (7%)
Postoperative acute respiratory failure	5 (3%)
Neuromuscular weakness	5 (3%)
Other	14 (9%)

The principle is carried for definitive withdrawal of mechanical ventilation, so that the patient is be able to breathe spontaneously without ventilatory support for more than 24 h [9–13]. The following clinical and paraclinical indices are used.

- clinical indices, connected with hemodynamics:
  - heart rate (Ps/min)
  - systolic arterial pressure (RRs./mmHg)

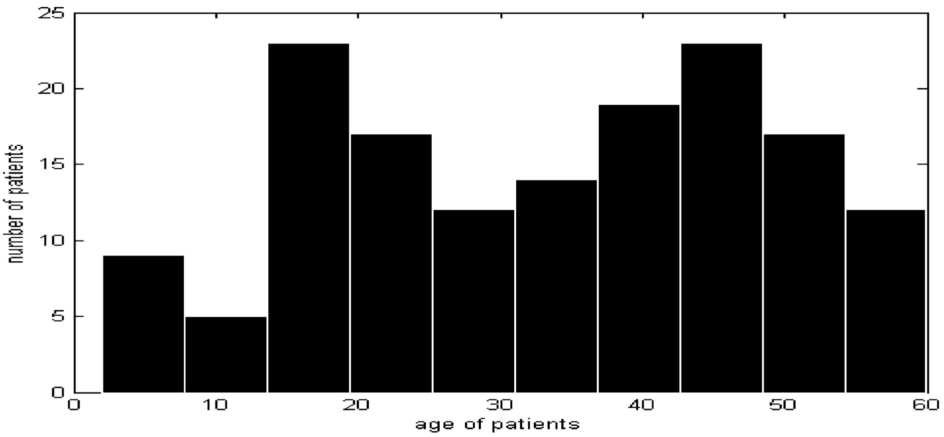

Fig. 1. Age distribution of the patients.

  - diastolic arterial pressure (RRd./mmHg)
  - mean arterial pressure (RRm./mmHg)

- paraclinical indices, connected with:
  - blood–gas analysis: pH, PaO_2, $PaCO_2$, PaO_2/FiO_2
  - nutrition: total blood protein (tbp), blood albumin (alb), blood sugar (bs), lactate
  - inflamation: fever, RUE, Leuc
  - hematologic indices: hemoglobine, hematocrit.

Two methods were used for statistical data analysis: the method of stepwise discriminant analysis and the method of stepwise logistic regression [14, 15]. For this analysis, each patient was represented with an n-dimensional vector (in our case, $n = 17$), i.e.:

$$X = (x_1, x_2, \ldots, x_n)'$$

stepwise discriminant analysis:

- stepwise discriminant analysis calculates two linear discriminant functions as follows:

$$F'(x) = \sum_{i=1}^{17} w_i' x_i + a'$$

$$F''(x) = \sum_{i=1}^{17} w_i'' x_i + a''$$

where w_i', w_i'' are discriminant coefficients and a', a'' are constants. It is assumed that the probability distribution is normal and the classes' covariance matrices are equal.

$F'(x)$ and $F''(x)$ define the class membership of each patient with vector X. If the first function $F'(x)$ is greater than $F''(x)$ then X belongs to class 1—"not ready for weaning", else—to class 2—"ready for weaning".

stepwise logistic regression:

- the assumption in stepwise logistic regression is that the difference between the logarithms of the conditional pdf of the two classes is linear with respect to $x_1, x_2, \ldots, x_n$, i.e.:

$$\log\left(\frac{p(x/\omega_1)}{p(x/\omega_2)}\right) = \beta_0 + \beta^{\mathrm{T}} x$$

or after the transformation:

$$\frac{p(\omega_1/x)}{p(\omega_2/x)} = \exp(\beta_0' + \beta^{\mathrm{T}} x)$$

where $\beta_0' = \beta_0 + \log(p(\omega_1)/p(\omega_2))$

This model is an exact description of a broad range of cases, including:

1. Cases, in which the distributions are multivariate normal with equal covariance matrices;
2. Cases in which multiple discrete distributions are described with log-linear models with identical interaction terms between classes;
3. Cases, which are combinations of 1 and 2, i.e. images are described from interval and categorical variables.

Obviously this method is applicable to a broad range of real problems, which may not involve data with normal distribution.

Discrimination between the two classes depends on the ratio $\frac{p(\omega_1/x)}{p(\omega_2/x)}$, whereby:

$$x \text{ is put into } \omega_1, \quad \text{if } \frac{p(\omega_1/x)}{p(\omega_2/x)} > 1;$$

$$x \text{ is put into } \omega_2, \quad \text{if } \frac{p(\omega_1/x)}{p(\omega_2/x)} < 1.$$

Equivalently,

$$\text{if } \beta_0' + \beta^{\mathrm{T}} x > 0, \ x \text{ is classified to } \omega_1;$$

$$\text{if } \beta_0' + \beta^{\mathrm{T}} x < 0, \ x \text{ is classified to } \omega_2.$$

In stepwise logistic regression, independent (predictive) variables are included or eliminated in a stepwise manner. In this paper stepwise forward regression is used, whereby new variables are added until the model reaches optrimal performance.

Statistics data processing is carried out both with absolute and normalized values. The normalization is accomplished according to the formula [16]:

$$\overline{p_{k,j}} = \frac{p_{k,j}}{p_{k,j} + p_{k',j}}$$

$$\overline{p_{k',j}} = \frac{p_{k',j}}{\hat{p}_{k,j} + p_{k',j}} \tag{1}$$

where $\hat{p}_{k,j}$ is the absolute value of the variable j for the k-th patient, measured one day before the beginning of weaning; $P_{k',j}$, the value on the day when weaning begins.

The purpose of normalization is to minimize the variance between the classes and to increase the distance between them.

RESULTS

All calculations are done with software for statistical biomedical data calculations—BMDP. By using the absolute values of variables (Table 2), the stepwise discriminant analysis rejected as insignificant the following variables: temperature, Lv, blood sugar, FiO_2, *$PaCO_2$*, Ps (pulse rate),

Table 2. Means and standard deviations of the clinical and paraclinical indices for both classes ($p < 0.05$ compared to successfully weaned group)

Index	Class 1	Class 2	p value
Total blood protein	66.99338 ± 3.34763	70.31000 ± 7.48041	1.0072×10^{-6}
Albumin	34.28344 ± 4.09322	40.06167 ± 3.19840	0
Blood sugar	5.11060 ± 0.87378	5.12427 ± 1.13765	0.9484
Lactate	1.41722 ± 0.35623	1.66133 ± 0.52658	3.8369×10^{-6}
Hb	107.73510 ± 10.80969	109.14000 ± 16.70029	0.3556
Hematocrit	0.33913 ± 0.03611	0.32593 ± 0.06246	0.0277
Temperature	37.91126 ± 0.29179	37.89067 ± 0.35903	0.6484
Lv	9.79470 ± 1.30603	9.52667 ± 2.32326	0.2127
RUE	54.31788 ± 10.99780	50.93333 ± 24.06358	0.1049
FiO_2	37.11921 ± 5.64025	34.84667 ± 6.98199	0.0020
PaO_2	88.38543 ± 6.60063	92.93066 ± 10.49082	1.0318×10^{-5}
$PaCO_2$	37.58941 ± 2.79116	36.13467 ± 3.67513	1.5208×10^{-4}
PaO_2/FiO_2	243.44900 ± 36.03651	275.77600 ± 55.95282	7.3593×10^{-9}
Ps	97.85497 ± 12.26595	97.66000 ± 11.75124	0.9348
RRs	126.25830 ± 10.16888	124.30000 ± 14.78061	0.1885
RRd	75.09933 ± 8.78389	72.13333 ± 10.78071	0.0095
RRm	96.29934 ± 8.89654	93.83334 ± 12.42719	0.0504
NPWI	101.2768 ± 5.36987	110.3717 ± 7.99148	0

Table 3. Values of coefficients and constants in the discriminant functions

	Coefficients of discriminant functions					
	Absolute values			Normalized values		
	Stepwise discriminant analysis		Stepwise logistic regression	Stepwise discriminant analysis		Stepwise logistic regression
Index	Class 1	Class 2		Class 1	Class 2	
Hb	0.45700	0.51136	−0.06266	202.51030	223.23640	–
Ht	−23.70619	−47.45654	24.30	46.07078	20.25119	68.17
Lv	–	–	–	–	–	224.2
Rue	0.21667	0.19582	0.01664	4.65760	−7.67940	110.7
tbp	1.96317	2.09009	−0.1024	1021.9540	1118.8230	−819.2
Alb	2.56822	3.02337	−0.4005	843.78170	960.53200	−1002
bs	–	–	–	34.96157	26.68681	182.0
Lakt	9.63244	10.87341	−1.336	54.61376	63.55532	−67.00
FiO_2	–	–	–	–	–	108.7
PaO_2	1.17468	1.24460	−0.07193	343.14720	362.00950	–
PaO_2/FiO_2	0.05703	0.06686	−0.01038	83.00468	91.29517	–
RRs	–	–	–0.04228	–	–	–
RRd	–	–	0.06827	–	–	33.50
Constant	−202.6389	−‘235.9702	31.24	−633.1895	−745.1941	580.7

Table 4. Sensitivity (SEN), specificity (SPE), positive predictive value (PPV), and negative predictive value (NPV)

Method	Sensitivity	Specificity	PPV	NPV
Stepwise discriminant analysis (absolute values)	0.84	0.81	0.82	0.84
Stepwise logistic regression (absolute values)	0.87	0.85	0.86	0.87
Stepwise discriminant analysis (normalized values)	0.95	0.95	0.95	0.95
Stepwise logistic regression (normalized values)	0.99	0.99	0.99	0.99
NPWI (absolute values)	0.76	0.77	0.77	0.76
NPWI (normalized values)	0.98	0.98	0.98	0.98

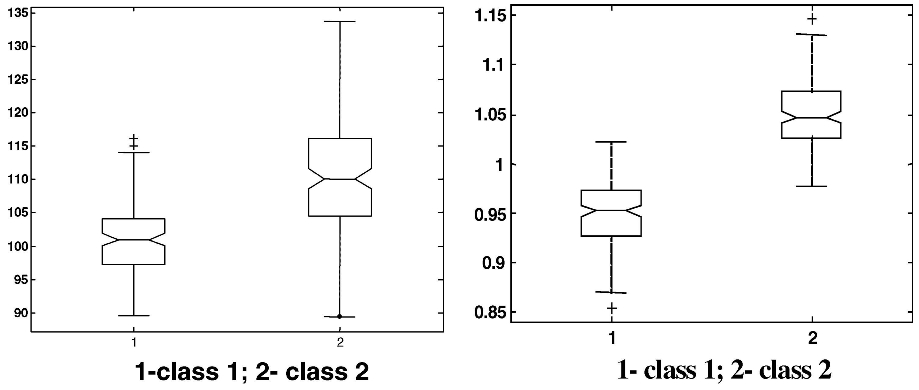

Fig. 2. Class separation with absolute (left) and normalized (right) NPWI values.

RRs, RRd, RRm. Statistically significant variables were found to be: albumin, PaO_2, total blood protein, hematocrit, lactate, the ratio PaO_2/FiO_2, Hb and RUE. The stepwise logistic regression finds as significant: albumin, the ratio PaO_2/FiO_2, lactate, total blood protein, PaO_2, Ht, Hb, RRd, RRs, RUE. Using the normalized values of the variables, the stepwise discriminant analysis includes as statistically significant: albumin, total blood protein, RUE, the ratio PaO_2/FiO_2, lactate, PaO_2, Ht, Hb and blood sugar. The stepwise logistic regression with normalized variables found as significant: albumin, total blood protein, RUE, RRd, Lv, FiO_2, blood sugar, hematocrit and lactate. The variables are given in the order of statistical significance. The values of the coefficients in discriminant functions and the constants are given in Table 3. In Table 4, the sensitivity (SEN), specificity (SPE), positive predictive value (PPV), and negative predictive value (NPV) are calculated according to the formulas:

$$\mathrm{SEN} = \frac{\mathrm{TP}}{\mathrm{TP} + \mathrm{FN}}$$

$$\mathrm{SPE} = \frac{\mathrm{TN}}{\mathrm{TN} + \mathrm{FP}}$$

$$\mathrm{PPV} = \frac{\mathrm{TP}}{\mathrm{TP} + \mathrm{FP}}$$

$$\mathrm{NPV} = \frac{\mathrm{TN}}{\mathrm{TN} + \mathrm{FN}}$$

where TP is true positives; FP, false positives; TN, true negatives; FN, false negatives.

Analysing the results of statistics analysis of the traditional indices and the correlation dependence between them, it is suggested a new index as a predictor of successful weaning, called "nonpulmonary weaning index " (NPWI):

$$\mathrm{NPWI} = \mathrm{alb} + \mathrm{tbp},$$

where the values of albumin and total blood protein are normalized in advance, according to the formula (1), where $p_{k',j}$ is the absolute value of the respective index, measured for the same day, and $p_{k,j}$ the identical value, measured the previous day. If NPWI has value, more than 1, then the patient has readiness to wean (he belongs to class 2), in the other case the patient belongs to class 1 (he does not have readiness to wean).

In Figure 2 the results are shown, received with the ANOVA 1 for the NPWI of two classes, with absolute and normalized values, respectively. In Figure 2 (left) it is seen that there is significant overlapping of two classes, while in case where the values of NPWI are normalized, the overlapping is insignificant. In Figure 2 (right) it is clearly seen that the threshold value for the NPWI is 1 ($p < 0.001$).

DISCUSSION

All examined patients belong to different nosologic units, but they are united by one general factor i.e. the acute respiratory failure, requiring long-term mechanical ventilation. This period is of different duration and depends on the duration, specificity and tendency of the reverse development of the disease. In 62 patients, this period is of duration about 25 days, and in the rest it is two-times longer. Data were collected from the patient's history, progress notes, intensive care documentations, blood–gas analysis and laboratory data, from the day preceding the beginning of weaning, and from the day on which weaning had been performed (i.e. the data according to which the clinician has taken the decision, "ready for weaning"). This make the results of the study more reliable than those obtained from studies based on the data collected from patients at the end of the process (ready for extubation), which are less informative for the readiness of the examined patients at the beginning of weaning.

The number of patients, included in this study, compared with the number from other [17, 18] studies, is sufficiently high, so the obtained results should be accepted as reliable.

Among the traditional weaning indices there is not any such one, whose values are to be rapidly changed (improved) in the discussed period of time, i.e. which could be informative for taking a decision at beginning of mechanical ventilation weaning attempts [19]. That is why the efforts of many investigators are directed for development of indices and integrating these parameters. However, on the basis of the specificity of the process, there are quite a few studies in which nonpulmonary factors are taken in consideration [20], and these factors are not often tested as prognostic indices in terms of taking a decision for beginning of weaning. The albumin is the most frequently used nonpulmonary factor [21–25]. The proposed index besides the albumin accounts for the influence of one more nonpulmonary factor, the total blood protein. The index is simple for calculation and secures assessment, which could easily be tracked in time. Its calculation does not require additional devices and measurements, which makes it acceptable for clinicians and convenient for use in daily practice. The values of the offered index are changed significantly in a 48–72 h interval before beginning of weaning from mechanical ventilation. The disadvantage of this index is the duration of this period, because it is important that the interval should not exceed 24 h. This is due to the fact that albumin and total blood protein pertain to slow varying parameters. This flaw is compensated by the high sensitivity and specificity of the index. The threshold of the NPWI, which is related with the assessment of weaning from mechanical ventilation is:

<1− predicts "no readiness to wean from mechanical ventilation";

>1− predicts "readiness to wean from mechanical ventilation".

The results of this study stress the importance of nonpulmonary factors such as albumin and total blood protein, considered in combination, for the process of weaning from mechanical ventilation. It is important as well that in the process of obtaining the values for the NPWI the subjective is avoided, which is often present in other studies [26]. The NPWI can be used in evaluation of the patient without any special equipment or use of computered devices. The proposed index can be successfully put into practice as one of indices (not alone but as an additional parameter in the complex evaluation of the clinical condition of the patients) in a particular computer application, designed to determine the moment of beginning of weaning attempts from mechanical ventilation or taking a decision whether it is possible weaning for a particular patient.

REFERENCES

1. Schachter EN, Tucker D, Beck CJ. Does intermittent mandatory ventilation accelerate weaning? JAMA 1981; 246: 1210–1214.
2. Thavanainen J, Salmenpera M, Nikki P. Extubation criteria after weaning from intermittent mandatory ventilation and continuous positive airway pressure. Crit Care Med 1983; 11: 702–707.
3. Tobin MJ, Perez W, Guenther SM, Semmens BJ, Mador MJ, Allen SJ, Lodato RF, Dantzker DR. The pattern of breathing during successful and unsuccessful trials of weaning from mechanical ventilation. Am Rev Respir Dis 1986; 134: 1111–1118.
4. Hillman DR. Physiological aspects of intermittent positive pressure ventilation. Anaesth Intensive Care 1986; 14: 226–235.
5. Lin ES, Oh TE. Which mode of ventilation? In: Dobb G, ed. Intensive care: Developments and controversies. Baillere's Clinical Anaesthesiology. London: WB Saunders, 1991: 441–473.
6. Brochard L, Rauss A, Benito S, Conti G, Mancebo J, Rekik N, Gasparetto A, Lemaire F. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. Am J Respir Crit Care Med 1994; 150: 896–903.

7. Fagon JY, Chastre J, Novara A, Medioni P, Gibert C. Respective influences of initial severity of illness and of mechanical ventilation in the development of ICU acquired pneumonia (abstract). Am Rev Respir Dis 1991; 143: A493.
8. Oh TE. Difficult weaning from mechanical ventilation. Annals Academy of Medicine Singapore 1994; 23: 503–509.
9. Chatila W, Ani S, Guaglianone D, Jacob B, Amoateng-Adjepong Y, Manthous C. Cardiac ischemia during weaning from mechanical ventilation. Chest 1996; 109: 1577–1583.
10. Chatila W, Jacob B, Guaglionone D, Manthous CA. The unassisted respiratory rate-tidal volume ratio accurately predicts weaning outcome. Am J Med 1996; 101: 61–67.
11. Holliday JE and Hyers TM. The reduction of weaning time from mechanical ventilation using tidal volume and relaxation biofeedback. Am Rev Respir Dis 1990; 141: 1214–1220.
12. Vassilakopoulos T, Zakynthinos S, Roussos C. The conventional approach to weaning from mechanical ventilation. Eur Respir Mon 1998; 8: 266–298.
13. Yang K, Tobin M. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. J Med 1991; 324: 1445–1450.
14. Fukunaga K. Introduction to statistical pattern recognition, Academic Press: New York and London, 1972: 206–232.
15. Tou J, Gonzalez R. Pattern recognition principles. Massachusetts: Addison-Wesley Publishing Company, 1974; 90–95: 125–136.
16. Atanassov K. Intuitionistic fuzzy sets. New York: Physica-Verlag, 1999: 126–136.
17. Burns SM, Clochesy JM, Goodnough Hanneman SK, Ingersoll GE, Knebel AR, Shekleton ME. Weaning from long-term mechanical ventilation. Am J Crit Care, 1995; 4(1): 4–22.
18. Clement J, Buck E. Weaning from mechanical ventilatory support. Dimensions Crit Care Nurs 1996; 15: 114–129.
19. Mitchell M, Miyasaki A, Langston D. Work of breathing as a weaning parameter in mechanically ventilated patients. Chest 1995; 108: 1018–1020.
20. Burns S, Fahey S, Barton D, Slack D. Weaning from mechanical ventilation: A method for assessment and planning. AACN Clin Issues 1991; 2: 372–387.
21. Schlossmacher P, Hasselmann M, Meyer N, Kara F, Delabranche X, Kummerlen C, Ingenbleek Y. The prognostic value of nutritional and inflammatory indices in critically ill patients with acute respiratory failure. Clin Chem Lab Med 2002; 40(12): 1339–1343.
22. Sapijaszko M, Brant R, Sandham D, Berthiaume Y. Nonrespiratory predictor of mechanical ventilation dependency in intensive care unit patients. Crit Care Med 1996; 24(4): 601–607.
23. Modawal A, Candadai NP, Mandell KM, et al. Weaning success among ventilator-dependent patients in a rehabilitation facility. Arch Phys Med Rehabil 2002; 83(2): 154–157.
24. Gluck EH. Predicting eventual success or failure to wean in patients receiving long-term mechanical ventilation. Chest 1997; 111(3): 836.
25. Hurford W, Favorito F, Wilson D. Serum albumin concentrations during the weaning of mechanical ventilator-dependent patients. Am Rev Respir Dis 1991; 143: A685.
26. Burns S, Burns J, Truwit J. Comparison of five clinical weaning indices. Am J Crit Care 1994; 3: 343–352.