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### Achievement of Steady State Optimizes Results When Performing Indirect Calorimetry

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ABSTRACT. Background: The use of steady state as the endpoint for performance of indirect calorimetry (IC) is controversial. We designed this prospective study to evaluate the necessity and significance of achieving steady state. Methods: Patients with respiratory failure placed on mechanical ventilation in a short- or long-term acute care unit at any 1 of 3 university-based urban hospitals were eligible for the study. The 24-hour total energy expenditure (TEE) was determined by a Nellcor Puritan Bennett 7250 continuous IC monitor. Measured gas exchange parameters were obtained and averaged every 1 minute for the initial hour and then every 15 minutes for the next 23 hours. Over the initial hour, resting energy expenditure (REE) was averaged for intervals over the first 20, 30, 40, and 60 minutes, and for various definitions of steady state where oxygen consumption  $(Vo_2)$  and carbon dioxide production  $(Vco_2)$  changed by <10%, 15%, and 20%. Coefficient of variation (CV) was calculated for Vo<sub>2</sub> over the first 30 minutes of study. Results: Twenty-two patients (mean age, 52.8 years, 59% male, mean Acute Physiology and Chronic Health Evaluation (APACHE III) score 42.0) were entered in the study. The best correlation between shortterm "snapshot" REE and the 24-hour TEE was achieved by the steady-state period defined by the most stringent criteria (change in  $Vo_2$  and  $Vco_2$  by <10%). The average REE for all steady-state and interval periods correlated significantly to TEE with no significant difference in the absolute values for REE and TEE. Adding 10% for an activity factor to the average REE for each steady-state and interval period again correlated to TEE in a similar fashion with the same *R* value, but the absolute values for REE + 10% for all steady-state and interval periods were significantly different than the corresponding TEE. In those patients with less variation (CV for  $Vo_2 \leq 9.0$ ), the REE obtained for the steady-state period defined by the most stringent criteria still had the best correlation, but similar correlation could be obtained by interval testing of  $\geq$ 30-minute duration. In those patients with greater variation (CV for  $Vo_2 > 9.0$ ), interval testing of at least 60 minutes or more was required to attain levels of correlation similar to that achieved by the steady-state period defined by the most stringent criteria. Conclusions: These data support the use of steady state, best defined as an interval of 5 consecutive minutes whereby  $Vo_2$  and  $Vco_2$ change by <10%. The mean REE from this period correlates best to the 24-hour TEE regardless of CV. IC testing can be completed after achievement of steady state. Activity factors of 10% to 15% should not be added to the steady-state REE, because this practice significantly decreases the accuracy. In patients who fail to achieve steady state, the CV helps to determine the appropriate duration of IC testing. In those patients with a low CV ( $\leq 9.0$ ), 30-minute test duration is adequate. In patients with CV >9.0, test duration of at least 60 minutes may be required. These latter patients should be considered for 24-hour IC testing. (Journal of Parenteral and Enteral Nutrition 27:16-20, 2003)

Indirect calorimetry (IC) studies obtained by the metabolic cart have been used by intensivists and clinical nutritionists to determine energy expenditure, degree of metabolism, and nutritional requirements in hospitalized patients.<sup>1-3</sup> Both continuous and consecutive intermittent measurements of resting energy expenditure (REE) in these patients have shown a wide variation over 24 hours of testing.<sup>2-4</sup> Because of this variability in REE, any measurement over a short-term period of time ( $\leq 60$  minutes), which is then

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extrapolated to represent the 24-hour total energy expenditure (TEE), may introduce significant error.  $^{5,6}$ 

To improve the degree to which a "snapshot" shortterm (20 to 60 minutes) IC study accurately reflects TEE in a 24-hour period, the concept of steady state (SS) was introduced into the methodology of IC testing.<sup>5,7–9</sup> Designated as the end-point of IC testing, the steady-state interval has been variably defined as a single 5-minute period during which average minute oxygen consumption ( $Vo_2$ ), carbon dioxide production ( $Vco_2$ ), and respiratory quotient (RQ) change by less than a predetermined percentage range.<sup>7–10</sup> The steady-state interval purportedly represents the baseline physiologic state in which measurements should reflect substrate use and the true REE.<sup>7,9,10</sup> Achieving SS during IC testing is recommended to assure validity and reduce error from artifactual influences.<sup>5,7,9,10</sup>

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The use of SS, however, is controversial. Not all metabolic laboratories use SS criteria, choosing instead to perform IC testing for a preset time interval of variable duration.<sup>3,11</sup> SS is variably defined in the literature.<sup>7–9</sup> Attempts to achieve SS may unnecessarily prolong the duration of IC testing. Reducing stringency in the criteria for SS by increasing the degree of "allowable" variation in  $Vo_2$  and  $Vco_2$  may not significantly change the overall validity of the test. A steady-state interval by any of the currently proposed criteria may be difficult to attain in the more acutely ill unstable patients.<sup>7</sup>

Therefore, we designed this prospective study to evaluate the necessity and significance of achieving SS (compared with simple interval testing), to determine the optimal SS criteria that would best correlate to the 24-hour TEE, and to help identify those patients who might need 24-hour IC testing.

### METHODS

Patients with respiratory failure on mechanical ventilation, hospitalized at 1 of 3 university-affiliated urban facilities for short-term (University of Louisville Hospital, Jewish Hospital) or long-term acute care (Kindred Hospital Louisville), were eligible for the study. Patients were required to be hemodynamically stable in a plateau phase of their ventilatory support, with the anticipation that ventilator settings would not be changed during the ensuing 24-hour period. Patients were excluded from the study if there was evidence of medical/surgical instability, demonstration of a measured RQ out of physiologic range, or if there were conditions that may have prohibited IC testing such as poor cooperation, fraction of inspired oxygen  $(Fio_2) > 0.80$ , or a positive end-expiratory pressure  $(PEEP) \ge 20 \text{ mm Hg.}$ 

All patients were placed on a Nellcor Puritan Bennett 7200 ventilator (Nellcor Puritan Bennett, Pleasanton, CA). Indirect calorimetry was done prospectively by the Nellcor Puritan Bennett 7250 continuous IC monitor (Nellcor Puritan Bennett, Pleasanton, CA). Gas exchange parameters including  $Vo_2$ ,  $Vco_2$ , and REE were obtained and averaged each minute for the initial hour (to simulate routine "snapshot" IC testing) and then every 15 minutes for the remaining 23 hours of the study. RQ was defined by the ratio of  $V_{CO_2}/V_{O_2}$ and was calculated by the metabolic monitor. The 7250 IC monitor was hooked in series to a laptop IBM compatible personal computer, allowing continuous downloading of gas exchange parameters (1328 data points collected on each patient) into a text file in Excel format. Coefficient of variation (CV) was calculated for the  $Vo_2$  over the first 30 minutes of the study. Patients were then arbitrarily defined as having low CV if  $\leq 9.0$ or high CV if >9.0. Total energy expenditure (TEE) was defined as the cumulative energy expenditure derived for the entire 24 hours by the 7250 IC monitor. Patients receiving nutrition support by the enteral or parenteral route were fed by continuous infusion throughout the study.

Three SS periods were defined as follows for consecutive 5-minute periods whereby (Fig. 1):

## METHODS



FIG. 1. Designation of steady-state (SS) and interval (INT) periods obtained from initial 60 minutes of indirect calorimetry testing. REE, resting energy expenditure.

 $[SS10] = Vo_2: Vo_2$  change by  $\leq 10\%$ 

 $[SS15] = Vo_2: Vco_2$  change by  $\leq 15\%$ 

 $[SS20] = Vo_2: Vco_2$  change by  $\leq 20\%$ 

Four separate time intervals were defined by initial consecutive timed intervals as follows (Fig. 1):

[INT20] = Initial 20 minutes

[INT30] = Initial 30 minutes

[INT40] = Initial 40 minutes

[INT60] = Initial 60 minutes

For each of the 7 "snapshots" (3 SS periods and 4 time intervals), the Pearson correlation coefficient between the "snapshot" REE value and the TEE value for each subject was calculated. Steiger's method<sup>12</sup> was used to determine whether the correlations of different "snapshots" with the TEE were significantly different from each other. Paired t tests were used to compare the mean REE for each "snapshot" with the mean TEE.

### RESULTS

Of 25 patients initially entered into the study, 3 patients were excluded for failure to obtain a full 24 hours of IC data. The 22 patients who completed the study were a mean age of 52.8 years (range, 16 to 84 years), were 59% male (13 of 22), and had a mean Acute Physiology and Chronic Health Evaluation (APACHE III) score of 42.0 (range, 12 to 77). All 22 patients were on mechanical ventilation, with 63.6% (14 of 22) in a short-term acute care unit at University of Louisville Hospital or Jewish Hospital and 36.4% (8 of 22) in a long-term acute care unit at Kindred Hospital Louisville. Primary reasons for mechanical ventilation included closed head injury in 8, chronic obstructive pulmonary disease in 6, cerebral vascular

TABLE I Comparison of mean resting energy expenditure values from short-term "snapshot" steady-state and interval periods to mean 24-hour total energy expenditure for all study batients

SS and interval period	REE		$\mathrm{REE}~+~10\%$		Correlation	Significance
	Mean	SEM	Mean	SEM	(R  value)	(p  value)
INT20 $(n = 22)$	1988	84	2186	92	.838	<.001
INT30 $(n = 22)$	1980	85	2179	94	.868	< .001
INT40 $(n = 22)$	1972	84	2170	93	.873	< .001
INT60 $(n = 20)$	1957	87	2152	95	.929	< .001
SS10 (n = 16)	1999	100	2199	110	.943	< .001
SS15(n = 21)	1957	94	2152	94	.912	< .001
SS20 (n = 19)	1960	92	2156	102	.817	< .001

\*Mean 24-hour TEE =  $1999 (\pm 90)$  kcal/d.

INT, interval; SS, steady state; CV, coefficient of variation; REE, resting energy expenditure; TEE, total energy expenditure.

accident in 4, and pneumonia in 4. Continuous enteral feeding was provided for 77.4% of patients, continuous total parenteral nutrition (TPN) in 13.6%, and continuous nutrition support by both routes in 4.5% of patients. No nutrition therapy was provided in 4.5% of the study patients.

Table I shows overall results for the study population. Of the 22 study patients, 16 achieved steady state by the most stringent criteria (SS10). All 22 patients achieved steady state by either the SS15 or SS20 criteria. The mean REE for all SS definitions and INT periods correlated significantly with the 24-hour TEE, with no significant difference in means by paired ttests. The mean REE + 10% for all SS and INT periods also correlated significantly with the 24-hour TEE in an identical fashion with the same R values. However, the actual value obtained for the REE + 10% for all SS and INT periods was significantly different from the 24-hour TEE (p < .05 by paired t test).

Overall, the best correlation to 24-hour TEE was observed when the mean REE was obtained from the steady-state period defined by the most stringent criteria (SS10; R = .943). Correlation to 24-hour TEE diminished as less stringent criteria for the steadystate interval was used, with a significant decrease in correlation when comparing the most stringent criterion (<10% change) with <20% change (R = .943 versus R = .817, p < .001). Results obtained by timed intervals indicated that similar correlation to 24-hour TEE was obtained for the mean REE from the initial

TABLE IIComparison of mean resting energy expenditure values from short-term"snapshot" steady-state and interval periods to mean 24-hour total energy<br/>expenditure for patients with low variation in  $Vo_2$  ( $CV \leq 9.0$ )

	-	2		
SS and interval period	REE Mean SEM		Correlation with TEE* (R value)	Significance (p value)
$\frac{1}{1000}(n-11)$	9199	107	920	
INT30 (n = 11) INT30 (n = 11)	2122 2131	107	.920	<.001
INT40 $(n = 11)$	2119	106	.925	< .001
INT60 $(n = 10)$	2074	110	.928	<.001
SS10 (n = 11) SS15 (n = 11)	2084 2084	110	.942 891	<.001
SS20 (n = 8)	2150	91	.831	.001

\*Mean 24-hour TEE =  $2142 (\pm 118)$  kcal/d; mean CV =  $4.9 (\pm 0.4)$ . INT, interval; SS, steady state; CV, coefficient of variation; REE, resting energy expenditure; TEE, total energy expenditure. 60-minute interval (INT 60; R = .943 versus R = .929, p = .329). Shortening the interval testing to 40 minutes (INT40) or less yielded significant decreases in correlation (R = .929 for INT60 versus R = .873 for INT40, R = .868 for INT30, and R = .838 for INT20, p < .001 for each comparison).

Tables II and III demonstrate the effect of variation in gas exchange parameters on the correlation of the short-term "snapshot" REE values and the mean 24-hour TEE. Table III shows that the definitions of steady-state criteria and use of short-term interval testing become more clinically important in those patients with greater physiologic variation and high CV values for Vo<sub>2</sub>. Again, for this subset of patients, the best correlation between 24-hour TEE and mean REE was obtained from the steady-state period defined by the most stringent criteria (SS10, R = .960). The correlation decreased dramatically, as the steady-state criteria were defined less stringently (SS15, SS20), with a significant decrease in correlation when comparing the most stringent criterion (<10% change) with 20% change (R = .960 versus R = .772, p < .001). In these patients with high variation (CV > 9.0), only the mean REE with 60-minute interval (INT60) had similar correlation with the 24 hour TEE (R = .960versus R = .937, p = .212). Using the mean REE from any interval shorter than this duration (INT40, INT30, INT20) resulted in significantly less correlation to 24-hour TEE (R = .937 for INT60 versus R = .795 for INT40, R = .788 for INT30, and R = .729 for INT20;

TABLE III Comparison of mean resting energy expenditure values from short-term "snapshot" steady-state and interval periods to mean 24-hour total energy expenditure for patients with high variation in  $VO_2$  (CV > 9.0)

	1	8	2	
SS and interval	REE		Correlation with TEE*	Significance
period	Mean	SEM	(R  value)	(p value)
INT20 $(n = 11)$	1853	120	.729	.011
INT30 $(n = 11)$	1830	120	.788	.004
INT40 $(n = 11)$	1825	119	.795	.003
INT60 $(n = 10)$	1839	129	.937	< .001
SS10 (n = 5)	1811	200	.960	.009
SS15 (n = 10)	1816	118	.917	< .001
SS20 (n = 11)	1821	133	.772	.005

\*Mean 24-hour TEE =  $1857 (\pm 125)$  kcal/d; mean CV =  $15.0 (\pm 1.7)$ . INT, interval; SS, steady state; CV, coefficient of variation; REE, resting energy expenditure; TEE, total energy expenditure. p < .001 for each comparison; Table III). Table II shows the results in the subset of those patients with low variation ( $CV \le 9.0$ ). The best correlation was still seen with the SS10 period of most stringent criteria (R =.942), but the mean REE obtained from almost any interval (INT20, INT 30, INT40) resulted in similar correlation ( $R \ge .920$ , p < .001 for all comparisons; Table II). Mean REE for less stringent steady-state periods (SS15, SS20) resulted in decreasing degrees of correlation, with a significant decrease in correlation when comparing the most stringent criterion (<10%change) with <20% change (R = .942 versus R = .831, p = .022). Of interest is the fact that variation in the gas exchange parameters could not be anticipated by the degree of critical illness, in that the mean APACHE III score was significantly higher in those patients with a low CV compared with those with higher CV (47.1  $\pm$ 7.1 versus  $37.4 \pm 5.7$ , p = .002).

### DISCUSSION

Continuous or consecutive intermittent measurements by IC testing in critically ill patients have shown wide variation in energy expenditure over a prolonged period of study. Factors such as severity of illness, circadian rhythm, sedation, nutrition therapy, nursing care, motor activity, and pain often lead to alterations in energy expenditure resulting from clinical fluctua-tions in the physiologic state.<sup>3,4,11,13–16</sup> Throughout a 24-hour period, energy expenditure may range from 10% below to 23% above a single measured "snap-shot" REE.<sup>3</sup> The mean coefficient of variation in 1 study in critically ill patients over 24 hours of testing was shown to be 13.5% (range, 10.8% to 15.2%).<sup>6</sup> The more critically ill the patient, the greater the variability in energy expenditure. In a different study, critically ill patients early in their hospital course demonstrated a mean daily variability of 46.0% in the REE (range, 37%) to 56%), which was thought to be caused by abrupt changes in metabolism related to sepsis, emergency surgery, and carbohydrate excesses from TPN.<sup>17</sup> Later in their hospital course, as the same patients stabilized, variability in energy expenditure decreased to a mean of 12% (range, 4% to 18%).<sup>17</sup> A large portion of the variability in energy expenditure has been shown to be attributable to alterations in minute ventilation. respiratory rate, heart rate, and systolic blood pressure, suggesting that the cardiopulmonary system plays a large role in the amount of energy consumed by critically ill patients.<sup>6</sup> Variability in energy expenditure does not necessarily correlate to higher or lower total energy expenditure measurements and cannot be entirely accounted for by patient activity or nursing care procedures.<sup>6</sup> Unfortunately, some variability in energy expenditure may be attributed to artifactual influences related to technique in performing IC studies, arising from error introduced by leaks, changes in calibration, and fluctuations in the fraction of inspired oxygen.<sup>6</sup>

Because of this variability in energy expenditure, short-term "snapshot," intermittent, or "window" IC studies in unstable critically ill patients with fluctuating metabolic rates have been criticized as not accu-

rately reflecting the 24-hour TEE.<sup>6,9</sup> The cost of respiratory therapy technicians and equipment and the need for maximum time efficiency in performing IC studies contribute to the fact that most studies in the critical care setting are less than 1 hour in length.<sup>6</sup> To reduce sampling error and to improve the correlation between short-term REE and the 24-hour TEE, a number of investigators recommend that all IC measurements be taken while the patient is in "steady-state" condition or metabolic "equilibrium."<sup>5-7,9,10,18,19</sup> Surprising emphasis is placed on meticulous techniques and a "rigid approach,"<sup>5</sup> suggesting that performing IC studies and extracting data only from the steady-state period insures confidence that the "snapshot" energy expenditure measurement truly represents the patient's total energy expenditure.<sup>5,7,10</sup> To improve the accuracy of this snapshot REE, activity factors of 10% to 15% are often added by clinicians to account for the fact that measurements made during the SS period of rest may not accurately reflect or include increased energy expenditure associated with routine nursing care occurring at other times of the day (activity factors are only used for short-term "snapshot" IC studies, not for 24-hour measurements of TEE).<sup>15,19</sup> These same reports suggest that failure to achieve steady state represents a period of true metabolic instability, that the validity of the IC measurements is questionable, the data should not be used, and the IC study should be aborted.5,7,10

Unfortunately, metabolic "equilibrium" has been poorly defined, and the need to achieve steady state during IC testing is controversial. This controversy is reflected in a lack of consensus for the methodology in performing IC testing. Strong proponents of the concept specify the identification of a steady-state period before completion of the IC test.  $^{7-10}$  The actual criteria for steady state, however, are variably defined as a 5-minute interval during which either average minute  $Vo_2$  and  $Vco_2$  change by <10%,<sup>8,10</sup>  $Vo_2$  and  $Vco_2$  vary about their mean values by  $\le5\%$ ,<sup>9</sup> or that the coefficient of variation for both  $Vo_2$  and  $Vco_2$  is  $\leq 5\%$ .<sup>7</sup> Other investigators provide more clinically oriented, nonspecific criteria for steady state defined "where the patient is lying motionless with eyes open and responding to surrounding events."<sup>19,20</sup> Investigators less concerned about the specifics of steady state refer vaguely to testing patients in a "resting state" for  $\geq 30$  minutes<sup>18</sup> or simply perform IC measuring  $Vo_2$  and  $Vco_2$  over a 30-minute period (in a thermoneutral environment after an overnight fast) without reference to basal or steady-state conditions.<sup>5,21</sup>

Results of the current study with 1328 data points per patient support the clinical importance of achieving steady state when performing IC testing. The average REE for the steady-state period defined by the most stringent criteria correlated best to the measured 24-hour TEE, regardless of the variation in gas exchange parameters. This steady-state REE was superior to that REE obtained by any interval testing up to and including 60 minutes in duration. Lessening the stringency for defining steady state resulted in decreasing degrees of correlation. Extrapolating the steady-state REE to the 24-hour TEE had such a high degree of accuracy that no further adjustments needed to be made for patient or nursing care activity. The issues related to steady state become even more important with greater variation in energy expenditure and metabolic instability. Metabolic instability may not always be evident clinically. Achieving steady state by the most stringent criteria in these patients may be more difficult but assures a continued high correlation and accuracy for the "snapshot" REE. In these patients, short-term interval testing or use of steadystate criteria of lesser stringency results in considerable deterioration in correlation and accuracy. Failure to achieve steady state does not necessarily invalidate the study but does signify the introduction of greater error and less accuracy in representing or extrapolating the short-term REE to the 24-hour TEE.

Although the results of this study help standardize the methodology for performing IC, the statistical differences between the various steady-state and interval criteria do not necessarily represent clinically important differences. Greater accuracy in designing nutrition support regimens for enteral tube feeding or TPN seems empirically important to reduce consequences from over- or underfeeding. However, it is beyond the scope of this study to determine what degree of accuracy in determining caloric requirements is necessary to specifically reduce complications from artificial nutrition support.

Based on the results of this study, the following recommendations can be made regarding the methodology for performing IC testing. Steady state should be defined by change in  $Vo_2$  and  $Vco_2$  of <10% over a period of 5 consecutive minutes. IC testing may be terminated when the patient achieves this steady state. The values for the mean REE from this steadystate period, with no further adjustments (in the absence of fever), can be used as an accurate representation of the 24-hour TEE. In patients who fail to achieve steady state, interval testing for as little as 30 minutes may be adequate to provide an accurate REE if the CV for Vo<sub>2</sub> over the first 30 minutes of the testing period is  $\leq 9.0$ . For that patient who fails to achieve steady state and is metabolically unstable, more prolonged testing is required (minimum of 60 minutes), and 24-hour IC monitoring should be considered.

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