# Acute Infection in Ventilated Patients in the Intensive Care Unit: Association Between Resting Energy Expenditure and C-Reactive Protein

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**ABSTRACT:** **Background:** Sepsis is a common cause of hospitalization, particularly in intensive care units (ICUs), and is a major cause of morbidity and mortality. Diagnosis is often difficult due to the absence of characteristic clinical signs (e.g., fever and leukocytosis); therefore, additional markers, in addition to C-reactive protein (CRP) and white blood cell (WBC) count, are needed.

**Objectives:** To prospectively link resting energy expenditure (REE) with CRP, WBC count, and sequential organ failure assessment (SOFA) scores in ICU patients. Such a correlation may suggest REE measurement as an additional parameter for sepsis diagnosis.

**Methods:** Our study comprised 41 ventilated consecutive patients › 18 years of age. Patient demographic data, height, actual body weight, and SOFA scores were collected at admission. REE was measured by indirect calorimetry. REE, CRP, and WBC measurements were collected at admission, on day three after admission, and 1 week later or as clinically indicated.

**Results:** Comparison of the REE and CRP changes revealed a significant correlation between REE and CRP changes ($r = 0.422$, $P = 0.007$). In addition, CRP changes also correlated with the changes in REE/REEp ($r = 0.36$, $P = 0.02$). Although no significant correlations in REE, WBC count, and SOFA score were found, a strong trend was observed.

**Conclusions:** To the best of our knowledge, this is the first study to link REE and CRP levels, indicative of severe infection. Further study is needed to establish these findings.

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**KEY WORDS:** C-reactive protein (CRP), calorimetry, intensive care unit (ICU), resting energy expenditure (REE), sepsis

Injuries, burns, and infections cause an array of metabolic responses in patients that affect the energy expenditure and the nitrogen balance. Sepsis is a common cause of hospitalization, particularly in the intensive care units (ICU) and is a major cause of morbidity and mortality [1-3]. The diagnosis of sepsis is ambiguous, as some patients do not present with characteristic clinical signs such as fever and leukocytosis [4]. Delays in diagnosis and treatment may increase the mortality rate. Therefore, efforts have been made to characterize additional markers, such as C-reactive protein (CRP), interleukin-6 and procalcitonin [5-10]. The clinical course of the infection is also correlated with the severity and number of organ dysfunctions and failure. One of the common severity scores is the Sequential Organ Failure Assessment (SOFA) score [11,12].

The indirect calorimetry method evaluates the patients resting energy expenditure (REE) by measuring oxygen consumption (VO2) and carbon dioxide production (VCO2) [13,14]. This technology is considered as the gold standard for determining patient energy expenditure [15]. In septic patients, following the insult, there is an increase in energy expenditure that is followed by a hypermetabolic state that is known to be associated with increased morbidity and mortality [16].

In this study, we aimed to determine, partially because of catabolism, the link between the REE of ICU patients and their CRP, WBC count, and SOFA score. Such a correlation may suggest REE measurements as an additional parameter for sepsis diagnosis.

## PATIENTS AND METHODS

### STUDY DESIGN AND PATIENT POPULATION

We conducted a prospective observational study of 41 ventilated stable ICU patients. Only patients older than 18 years of age were included. Due to the possible effect on CRP levels, patients with hepatic insufficiency were excluded from the study.

All patient demographic data was collected at admission, as was the patient's height and actual body weight. The SOFA score was obtained at admission to the ICU.

### INDIRECT CALORIMETRY AND REE MEASUREMENTS

REE measurements were made using an indirect calorimeter (CCM Express®, MGC Diagnostics, Saint Paul, MN, USA). After the calibration of the flow and gas sensors, the flow sensor was attached to the patient tube and REE was recorded for

30 minutes and the kcal value was obtained. The predicted REE (REEp) was calculated using the Harris–Benedict formula. REE measurements were made at admission, on the third day after admission, and 1 week later or as clinically required.

### CRP TESTS

Blood was collected in serum separation tubes and centrifuged at ×3000 G for 10 minutes. CRP concentrations were determined using the Integra chemistry analyzer (Roche Diagnostics, Switzerland). CRP levels < 5mg/L were considered normal.

### STATISTICAL ANALYSIS

Continuous parameters are presented as mean ± standard deviation. The aim of the study was to determine whether an increase in REE is associated with an increase in CRP, WBC count, and SOFA scores. For every patient, the change in each of the above parameters in a pair of consecutive tests was calculated (i.e., change in REE, change in CRP). These changes were then compared using Pearson's correlation.

These changes were also categorized according to their trend direction: upward (> 0), downward (< 0), or no change (= 0). The trends were then combined and grouped into three categories:

- Concordant trends: trends in both elements of the pair were identical (i.e., both up, both down, or both no change)
- Discordant trends of type A: trends were in opposite directions with the CRP trend downward and the REE trend upward
- Discordant trends of type B: trends were in opposite directions with the CRP trend upward and the REE trend downward

The research hypothesis stated that the probability of a concordant pair is greater than the two equal probabilities of discordant pairs. The chi-square test for the goodness of fit with the null hypothesis stating that all three categories have equal probabilities was used. $P < 0.05$ was considered significant.

### ETHICS AND INSTITUTIONAL REVIEW BOARD APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethics standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethics standards. For this type of study, formal informed consent was not required; nevertheless, an institutional review board approved this study.

## RESULTS

The study population comprised 41 ventilated patients admitted to the ICU. Patients were 50% male, with the age average of 78 ± 17 years. Outcome parameters are presented in Table 1.

### CHANGES IN REE CORRELATE WITH CHANGES IN CRP

One of the most clinically used markers of sepsis due to bacterial infection is CRP [4]. For each patient, several REE/CRP measurements were performed ($2 \leq n \leq 9$), according to clinical demands. The mean CRP value was 135 ± 101. To avoid patient bias, only two measuring points were considered for each patient: highest REE value and a measurement averaging 4–5 days before/after that peak (mean 4.35 ± 1.9 days between measurements).

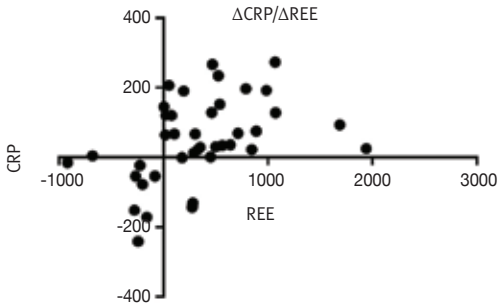
Comparison of the REE and CRP changes of these two points revealed a significant correlation ($r = 0.422$, $P = 0.007$) [Figure 1]. In addition, CRP changes also correlated with the changes in REE/REEp ($r = 0.36$, $P = 0.02$). Moreover, when taking all the measurements (n=131), the statistically significant positive linear correlation was maintained in both the REE and the REE/REEp ($r = 0.259$, $P = 0.003$, and $r = 0.221$, $P = 0.01$, respectively). Although significant, the correlation efficient was

**Table 1.** Patient outcome summary

| Parameter | Outcome |
|---|---|
| Number of patients | 40 |
| Age, years (mean ± SD) | 78 ± 16.6 |
| Gender, male/female | 20/20 |
| Patient condition (medical/surgical) | 35/5 |
| APACHE II (mean ± SD) | 26.3 ± 9.9 |
| BMI (mean ± SD) | 28.4 ± 6 |
| Length of ventilation, days, (range) | 25.3 ± 22.8 (2–96) |
| ICU length of stay, days, (range) | 20 ± 14.9 (2–78) |
| Hospital length of stay, days, mean (range) | 37 (3–184) |
| ICU mortality (%) | 30 |

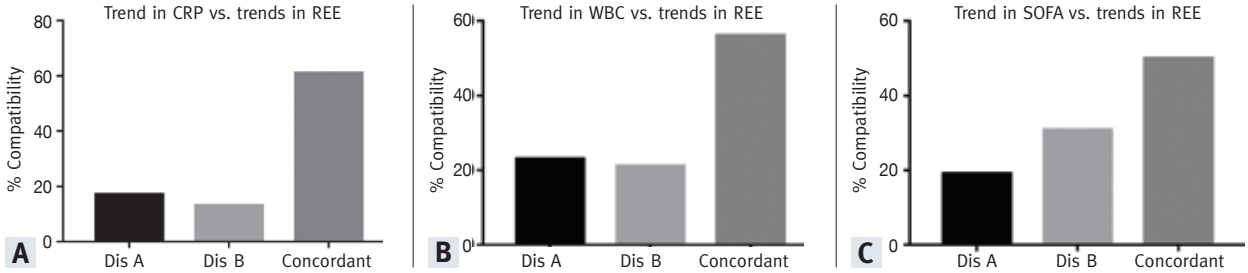
BMI + body mass index, ICU = intensive care unit, SD = standard deviation

**Figure 1.** The correlation between the change in (Δ) CRP and the change in (Δ) REE values. For each patient (n=41), two measurements were taken for each patient: the highest REE value and a measurement averaging 4–5 days before and after that peak. The difference in these values was calculated and a correlation test was conducted ($r = 0.42$, $P = 0.007$)




CRP = C-reactive protein, REE = resting energy expenditure

**Figure 2.** Trend associations between the REE, WBC count, and SOFA score. The percent of measurement pairs according to the trend association method between the change in REE value and CRP **[A]**, WBC count **[B]**, and SOFA score **[C]**




Concordant trend = both up, both down, or both no change
Discordant trend type A (Dis A) = REE same/CRP down, REE up/CRP down, REE up/CRP same
Discordant trend type B (Dis B) = REE same/CRP up, REE down/CRP same, REE down/CRP up
CRP = C-reactive protein, REE = resting energy expenditure, SOFA = sequential organ failure assessment, WBC = white blood cell

not high due to the high variability. Therefore, we performed a trend pattern association as described earlier. Indeed, a strong trend of association was found between the REE change and the CRP change (i.e., more concordant changes than not, $P < 0.0001$) [Figure 2A].

### CHANGES IN REE ARE ASSOCIATED WITH THE WBC COUNT AND SOFA SCORES

We similarly evaluated the correlation between the WBC and SOFA scores with the REE values at the same measuring points chosen earlier. The mean WBC value was 13.9 ± 6.3. However, there was no correlation due to high variability. We also analyzed the trend pattern association in all of the measuring point consecutive pairs (n=88) and found that the REE change was compatible with the WBC trend (i.e., more concordant changes). Moreover, the two types of discordant pairs showed equal occurrences [Figure 2B], suggesting a strong association ($P < 0.0001$). A similar pattern was observed for the SOFA score as well ($P < 0.004$) [Figure 2C].

## DISCUSSION

Sepsis is a common condition among ICU patients [17,18]. However, the clinical parameters for sepsis diagnosis, such as leukocytosis or fever are not always available [4]. Moreover, the presence of these symptoms does not necessarily indicate the presence of infection or of an inflammatory response. Therefore, there is a need for additional factors for accurate diagnosis.

Energy expenditure can be calculated by different formulas, but they have been shown to be less accurate for REE estimation [17,19]. The aim of this study was to test whether there is a correlation between changes in REE and CRP levels.

After the onset of the acute infectious or inflammatory process, blood CRP levels are elevated within 6 hours and therefore CRP belongs to the group of the acute phase reactants. A CRP level greater than 50 mg/L is suggestive of bacterial infection. Moreover, CRP levels correlate with the clinical course of the infection and the changes in its levels indicate patient improvement, or alternatively, provide information to the response to treatment [4,5,20], similar to the conventional severity score (i.e., the SOFA score). CRP values were also found to be indicative of other positively correlated inflammatory conditions, such as the need for a TNF inhibitor in psoriatic arthritis patients [21].

In fact, we found a significant correlation between CRP and REE changes. These findings show a possible link between changes in REE levels and the severity of infection. Thus, a reduction in REE levels may suggest that the patient is currently recovering from the severe infection.

REE measurement depends on various parameters like agitation, patient metabolism, high fever, or nutrition and thus, the variability between measurements is relatively large. In addition, other factors, such as genetics and liver function, can affect CRP values. This result can also explain the relatively low correlation rate and the weak results with the WBC and the SOFA score. Thus, a larger study population is needed to achieve more definitive results.

### CONCLUSIONS

To the best of our knowledge, this is the first study to link REE and CRP values to indicate severe clinical infection. Further study is needed to establish these findings.

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## Capsule

### Killer trifecta for leprosy

Cytotoxic granule proteins secreted by CD8+ T cells assist in the killing of both infected cells and intracellular bacteria. **Balin** et al. studied the ability of subsets of human CD8+ T cells that express different combinations of granule proteins to kill macrophages infected with *Mycobacterium leprae*. The CD8+ T cell subset with the highest efficiency of mycobacterial killing simultaneously expressed three granule proteins: granzyme B, perforin, and granulysin. Transcriptional profiling of CD8+ T cell subsets identified the natural killer (NK)-activating receptor NKG2C as a surface marker for identification and enrichment of these potent antimicrobial cells.

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Eitan Israeli

## Capsule

### Remodeling airway innervation in asthma

Asthma is a widespread chronic airway disease characterized by airway obstruction, inflammation, and hyperresponsiveness. In eosinophilic asthma, the most common form of asthma, eosinophils in the airway alter nerve function and exacerbate the disease. **Drake** and co-authors studied samples obtained by endobronchial biopsy from patients with severe eosinophilic asthma. They found that airway innervation was increased and positively correlated with symptom severity. In mice, eosinophilia increased airway innervation and triggered bronchoconstriction and airway hyperresponsiveness. Thus, structural remodeling of airway innervation contributes to symptom severity in eosinophilic asthma.

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Eitan Israeli

**"Anyone who has lost track of time when using a computer knows the propensity to dream, the urge to make dreams come true and the tendency to miss lunch"**

Tim Berners-Lee, (born 1955), also known as TimBL, English engineer and computer scientist, best known as the inventor of the World Wide Web