CRITICAL CARE

COMMENTARY

Diagnostic potential of circulating cell-free DNA in patients needing mechanical ventilation: promises and challenges

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See related research by Okkonen *et al.*, http://ccforum.com/content/15/4/R196

Abstract

Circulating cell-free DNA (cf-DNA) mainly comes from apoptotic cells and can reflect the extent of cellular damage. Increased plasma levels of cf-DNA have been found in many acute disorders, including septic and clinically ill patients, and usually correlate well with clinical outcome. Acute respiratory failure, the most frequent organ failure in ICU patients, can be related to various acute diseases that may cause cell death and release of DNA into the bloodstream. In a recent issue of *Critical Care*, Okkonen and colleagues evaluate levels of cf-DNA in plasma as a prognostic marker in patients needing mechanical ventilation. They report that plasma cf-DNA was higher than normal in patients with mechanical ventilation, and even higher in patients who eventually died compared to survivors. However, its usefulness as a death predictor may be limited in the heterogeneous group of mechanically ventilated patients, probably due to confounding effects of co-morbidities, among other factors.

Circulating cell-free DNA (cf-DNA) fragments are small double-stranded molecules with a lower molecular weight than genomic DNA. High plasma cf-DNA concentrations have been documented in critically ill patients admitted to the ICU with a good correlation to patient outcome [1-8], suggesting this marker has prognostic value. The paper by Okkonen and colleagues [1] is the first study to assess levels of cf-DNA in plasma as a prognostic marker in critically ill patients needing mechanical ventilation.

Circulating cf-DNA can be detected in plasma or serum samples from healthy individuals at very low concentrations, ranging from 2.5 to 27.0 ng/ml in a recent meta-analysis [9]. The origin and the mechanisms whereby these fragments enter the bloodstream are not yet fully explained. Apoptosis and active cell release of newly synthesized DNA are the main sources of extracellular DNA under normal and pathological conditions other than cancer [9]. Results from sequence analysis of plasma cf-DNA indicate that the main origin of DNA fragments is apoptotic cells and not necrotic cells [10]. In addition to apoptosis, all normal and diseased living cells may actively release DNA fragments [11]. These fragments can form complexes with glycoprotein and act as messengers with signaling functions between cells and tissues. The elimination of nucleic acids from the blood is not dependent on renal clearance [12]. DNA binding to cell surface receptors and transport across the plasma membrane into many different cells for degradation to nucleotides or transportation into the nucleus seem to comprise the main mechanism for rapid clearance. Plasma nucleases have only a partial role in the removal of cf-DNA because these fragments circulate as nucleoprotein complexes, which protects them from degradation [9]

Three studies have evaluated the potential utility of cf-DNA measurement in predicting mortality in ICU patients [5-7], and another was specifically focused on septic patients [8]. All of these studies found higher plasma cf-DNA concentrations in the patients who died compared to survivors, and only one [5] demonstrated that DNA could predict the need for mechanical ventilation. Conditions of severe tissue hypoxia leading to a need for mechanical ventilation are associated with cell apoptosis and the release of DNA into the circulation. Okkonen and colleagues [1] performed a large prospective study in 25 Finnish ICUs evaluating plasma

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cf-DNA concentrations and their prognostic value for 90-day mortality in 580 patients with acute respiratory failure needing mechanical ventilation, 506 of whom required an invasive interface. Most of the patients (82%) had plasma cf-DNA concentrations higher than the upper normal limit of 4,000 GE/ml (26.4 ng/ml) according to a meta-analysis. The plasma cf-DNA concentration at admission was 1.6-fold higher in the 169 patients who died than in survivors. A DNA concentration over 16,000 GE/ml (105.6 ng/ml) was an independent predictor of 90-day mortality with a moderate discriminative power (positive likelihood ratio 1.72; adjusted odds ratio 2.16). Surprisingly, cf-DNA concentrations did not differ between the 47 patients fulfilling the diagnostic criteria for acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) and those who did not, despite the assumed higher degree of tissue damage and cell apoptosis in the ALI/ARDS patients. Unfortunately, the sample size was relatively small for the independent effect of ALI/ARDS on plasma cf-DNA concentration to be robustly analyzed.

Data from Okkonen and colleagues agree with previous reports on ICU patients but reflect differences in the plasma cf-DNA concentration used in predicting mortality. This was higher (127 ng/ml) in the study by Rhodes and colleagues [6] but lower in two other studies, 40.3 ng/ml [5] and 61.8 ng/ml [7]. In the series by Saukkonen and colleagues (the Finnsepsis Study Group) [8], which evaluated 255 patients with severe sepsis or septic shock, the best cutoff value for ICU mortality (79.2 ng/ml) was one-fourth lower than in the study by Okkonen and colleagues [1]. Methodological differences at various steps (blood sampling and processing, extraction methods, measurement principles), while not the only cause, are probably the main cause of this discrepancy in the values [9]. The development of a standardized and widely accepted protocol for cf-DNA analysis is warranted [9,11].

Novel methods and biomarkers in critically ill patients are necessary. Quantification of circulating cell-free mitochondrial and nuclear DNA may provide a platform for further investigation [13]. Circulating microRNAs (miRNAs), small non-coding RNAs that regulate gene expression, play important roles in normal and diseased cells. In sepsis, endothelial injury and leukocyte activation affect the expression level of some miRNAs, such as miR-126, which was identified in endothelial cells, and some others from leukocytes (miR-146a, miR-150, miR-223) [14]. Serum concentrations of miR-146a and miR-223 were found to be reduced in septic patients and they might serve as useful biomarkers for sepsis [15]. These and other miRNAs are promising novel diagnostic and prognostic tools in ICU patients.

Abbreviations

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; cf-DNA, cell-free DNA; GE, genome equivalent; miRNA, microRNA.

Competing interests

The authors declare that they have no competing interests.

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