CRITICAL CARE

LETTER

Cell-free DNA as a promising marker for risk stratification of pulmonary embolism

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Please see related research by Arnalich *et al.*, http://ccforum.com/content/17/3/R90

Arnalich and colleagues reported an interesting clinical study that evaluated cell-free plasma mitochondrial and nuclear DNA concentrations in patients with pulmonary embolism (PE) [1]. They found increased circulating mitochondrial and nuclear DNA levels, as well as alterations in other cardiac biomarkers (heart-type fatty acid-binding protein and troponin I) in patients with massive PE compared with those found in patients with submassive PE [1]. Importantly, all these biomarkers were found at higher concentrations in fatal massive PE than in non-fatal PE [1].

I would like to add experimental information associating cell-free DNA and acute pulmonary thromboembolism (APT). Experimental evidence showed that cell-free DNA concentrations increase in proportion to the severity of experimental APT [2]. In addition, these previous findings suggest that lysed cells from the thrombi are probably the major source of increased circulating plasma DNA in experimental APT. Supporting this idea, microsphere-induced PE causing similar pulmonary hypertension to that induced by APT did not result in increased plasma DNA concentrations. Moreover, blood clots release free DNA in a dose-dependent manner *in vitro* [2]. Although Arnalich and colleagues have not specified the main causes of PE in their study, it is possible that part of measured free DNA may derive from thrombi causing PE.

In conclusion, the clinical findings reported by Arnalich and colleagues align with previous experimental results showing that plasma DNA levels increase with severity of APT. While circulating DNA has emerged as a promising marker for risk stratification of PE, further investigations are needed to clarify the origins of free DNA.

Authors' response

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Dr Neto-Neves, in his letter on our paper published in the May issue of *Critical Care* [1], suggests correctly that a potential source of the high amounts of cell-free plasma mitochondrial DNA and nuclear DNA observed in our patients with massive PE could be thrombi obstructing the pulmonary vessels. With regards to his comment about the main causes of PE in our study, he does not realize that Table 1 indicates the main predisposing risk factors and shows that 16 patients developed deep venous thrombosis.

Although thrombi are probably the origin of increased circulating DNA concentration in the model of experimental acute PE reported by Uzuelli and colleagues [2], two main findings in our study indicate that acute right ventricular damage could more probably be the main source of DNA. Firstly, highly significant direct associations were found between plasma heart-type fatty acid-binding protein concentrations and both plasma mitochondrial DNA and nuclear DNA levels. Heart-type fatty acid-binding protein may be elevated in our patients as a consequence of right ventricular pressure overload, which increases wall stress resulting in right ventricular ischemia and infarction [3]. Secondly, the significant correlation between plasma soluble Fas values, an indirect marker of apoptotic cell death, and mitochondrial DNA concentrations observed in this study could be a direct consequence of the hypoxia-induced

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apoptosis of cardiomyocytes, which is known to occur mainly via the mitochondrial pathway of apoptosis [4]. Similarly, in bacteremic patients, a potential relationship between high plasma cell-free nuclear DNA concentration and apoptotic DNA fragmentation has been reported recently [5].

Abbreviations

APT: Acute pulmonary thromboembolism; PE: Pulmonary embolism.

Competing interests

The authors declare that they have no competing interests.

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