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J. J. Brugts
C. A. Den Uil

ACE insertion/deletion polymorphism in sepsis and acute respiratory distress syndrome

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Correspondence

With great interest, we read the article by Villar et al., who investigated the angiotensin-converting enzyme insertion/deletion (ACE I/D) polymorphism in relationship to sepsis and acute respiratory syndrome (ARDS) in over 300 Spanish patients. The authors did not find an association between this polymorphism and susceptibility, and outcome in either severe sepsis or ARDS [1]. In our opinion, the authors' explanation for this lack of association is not sufficiently discussed and we hope to open the discussion on this topic by raising several issues. First, the authors correctly noted that ACE is an important enzyme involved in cardiovascular homeostasis [2]. We are disappointed that the authors investigated only one (non-functional) polymorphism in the ACE-gene. Instead of investigating one polymorphism, we would have preferred analysis of common variation in the complete ACE-gene, which would have been easy and feasible in such a relatively small population. This would have significantly strengthened any associations between ACE-genotypes and sepsis. In addition, it is good to realize that the ACE I/D polymorphism is only responsible for less than 20% variation of plasma ACE levels. It is hard to believe that such a single polymorphism accounts for a significant causal effect on endpoints such as sepsis and ARDS, which are probably syndromes that are highly influenced by microbial characteristics and polygenetic factors. Second, the authors reported a statistical power of 76–85% using a sample size of 212 septic and 120 ARDS patients. An adequate study size and statistical power are necessary to exclude false negative or positive association studies. An important review article in this field recently addressed that a number of 2,000 patients with sepsis would be required to detect a mortality relative risk of 1.5 from any polymorphism [3]. Third, the authors did not fully explain why the ACE I/D polymorphism could be important in sepsis, since individuals who have the DD-genotype usually have higher ACE levels relative to controls, whereas in septic ARDS patients markedly decreased plasma ACE levels have been observed [4, 5]. In this respect, it would have been nice if the authors would have correlated their findings to plasma ACE levels.

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J. J. Brugts · C. A. Den Uil (✉)
Department of Cardiology, Thoraxcenter, Erasmus Medical Center, Room V-017, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands
e-mail: c.denuil@erasmusmc.nl
Tel.: +31-10-7035019
Fax: +31-10-7032890