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Possible Donor-Dependent Differences in Efficacy of Fresh Frozen Plasma for Treatment of ACE Inhibitor-Induced Angioedema

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To the Editor:

Angiotensin converting enzyme (ACE) inhibitors are among the most important and widely prescribed drugs. Unfortunately, their use carries the risk of causing upper airway angioedema that can progress to life-threatening respiratory compromise requiring intubation or a surgical airway. Deaths have occurred due to the difficulty in securing a patent airway in patients with angioedema and from complications of mechanical ventilation.

Attempts at developing a definitive treatment to reverse or at least block progression of ACE inhibitor-induced angioedema have been unsuccessful. Since bradykinin, an inflammatory mediator that is normally degraded by ACE, is elevated in patients with ACE inhibitor-induced angioedema[1,2], it had been thought that elevated levels of bradykinin underlie ACE inhibitor-induced angioedema. However, the bradykinin receptor antagonist icatibant was ineffective in the two largest randomized trials performed to date[3,4]. Hence it has been proposed that other ACE-degraded inflammatory mediators, such as substance P[1,2] and des-Arginine9-bradykinin[5], also contribute to ACE inhibitor-induced angioedema.

In this regard, it is notable that there are case reports and case series in which ACE replacement through transfusion of fresh frozen plasma (FFP) was effective in treating ACE inhibitor-induced angioedema[6]. However, FFP is not uniformly effective and it has even

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been reported that FFP can worsen ACE inhibitor-induced angioedema[7]. One possible explanation for this variability that has not been considered in the literature is the potential variation in ACE activity levels between FFP units from different blood donors—indeed, it is likely that a number of donors take ACE inhibitors. Therefore, to begin to understand the variability in the efficacy of FFP, we assessed the circulating ACE activity levels among a typical group of Midwestern U.S. blood donors.

ACE activity in serum samples from 330 blood donors in the American Red Cross Missouri/Illinois Blood Services Region was quantitated using the ACE kinetic test (Buhlmann Laboratories). Serum ACE activity levels correlate strongly with plasma ACE activity levels[8]. The association between sex and ACE activity levels was assessed by the Mann-Whitney test. The association between age and ACE activity levels was assessed by Pearson correlation coefficient analyses. Analyses were performed using GraphPad Prism 8.0. The American Red Cross Institutional Review Board determined that this is not human studies research.

The frequency distribution of ACE activity levels among the donors (170 [51.5%] female; median age 41 years, interquartile range 25-58 years, range 16-77 years; 310 White, 10 Black, 4 Asian, 3 Hispanic, 1 Native-American, 2 Other) is shown in the Figure. (median 37.65 U/L, interquartile range 27.1-48.8 U/liter, range <5-109.6 U/liter). No association between sex and ACE activity level was detected ($p = 0.6446$). There was a weak inverse correlation between age and ACE activity level ($r = -0.1302$, $p = 0.0179$). Notably, thirty-nine (11.8%) donors had ACE activity levels of ≤ 20 U/liter, levels that are 95% specific for full compliance with ACE inhibitor use[9].

These results demonstrate that there can be greater than a 20-fold difference in ACE activity levels between different units of FFP from an unselected group of blood donors. This strongly suggests that the variability of the reported efficacy of FFP for treatment of ACE inhibitor-induced angioedema is at least in part due to a wide variation of ACE activity levels between different units of FFP. Furthermore, the results provide an explanation for how FFP transfusion could worsen an episode of angioedema or lengthen its time course (an effect that would not be recognized): FFP contains HMW-kininogen and kallikrein, the substrate and enzyme that generate bradykinin, therefore transfusion of FFP with low ACE activity could increase a recipient's bradykinin levels.

The importance of developing an effective and safe treatment for ACE inhibitor-induced angioedema will further increase with the increasing use of ACE inhibitors as metabolic syndrome becomes more prevalent and the population ages. The ready availability and low cost of FFP make it an appealing potential therapy. Although several case reports and case series have suggested that FFP is efficacious, randomized controlled trials to prove its benefit are imperative. Our findings indicate that these trials should utilize FFP that contains high levels of ACE activity.

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Clinical Implications

Fresh frozen plasma has been used to treat ACE inhibitor-induced angioedema, but outcomes have been variable. The data presented suggests that a component of the variability is due to differences in the ACE activity content of fresh frozen plasma from different donors.

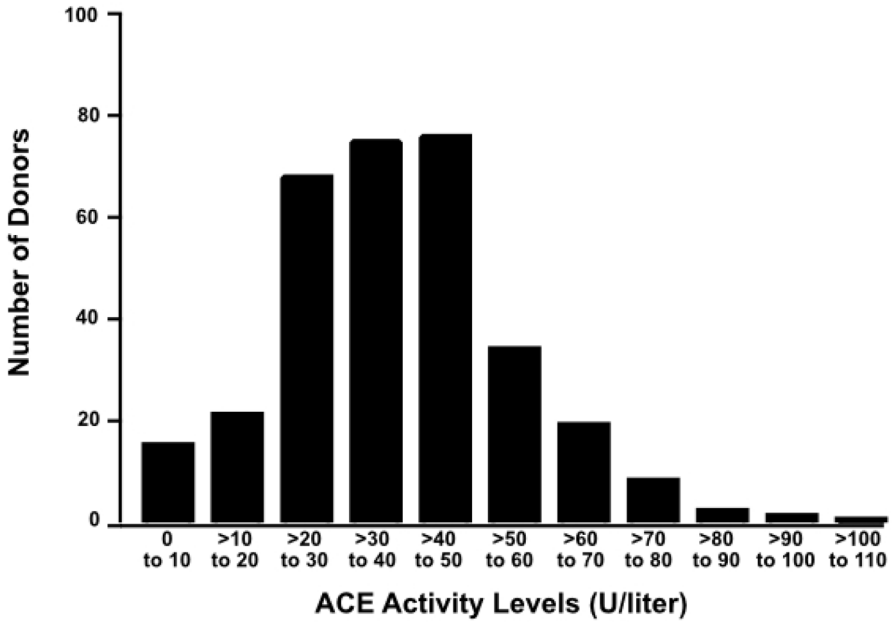

Figure.
Frequency distribution histogram of ACE activity levels in blood donors