

COMMENTARY

Does low angiopoietin-1 predict adverse outcome in sepsis?

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See related research by Mankhambo et al., <http://ccforum.com/content/14/3/R91>

Abstract

Endothelial injury has emerged as a crucial early event in the pathogenesis of microcirculatory dysfunction, capillary leakage and multiorgan dysfunction syndrome. The endothelial-specific angiopoietin (Ang)/Tie2 ligand-receptor system has been identified recently as a nonredundant regulator of endothelial responsiveness. Ang-1 is a Tie2 agonist and promotes endothelial stabilization and quiescence, whereas Ang-2 is a Tie2 antagonist and promotes endothelial activation, destabilization, and inflammation. While the mediator function of both Ang-1 and Ang-2 has been well established in preclinical research, only Ang-2 has been identified as a clinically useful biomarker in the critical care arena. In the previous issue of *Critical Care*, Mankhambo and colleagues report on angiogenic factors in Malawian children with severe bacterial infection. Among those children, diminished levels of the vessel-protective factor Ang-1 remained a significant predictor of outcome after multivariate adjustment. Whether low Ang-1 represents an important risk factor of adverse outcome in critically ill adults remains to be seen.

Not until the nineteenth century was it generally agreed that arteries and veins are connected by capillaries and that these capillaries indeed have a cellular wall, the so-called endothelium. At this point in time, one was convinced that the endothelium was a passive inner layer of blood vessels, not participating in any kind of active processes. Nowadays, better understanding of physiological processes involving the endothelium (for example, coagulation, hemostasis, and so forth) has led to

appreciation of the endothelium as an independent and active organ system. During the past decade, endothelial injury has attracted much attention – being a crucial event in the pathogenesis of experimental septic organ dysfunction. As a consequence, several circulating factors released by the activated endothelial cells, neighboring support cells (such as vascular smooth muscle cells and pericytes), or platelets have been identified as biomarkers of outcome in sepsis.

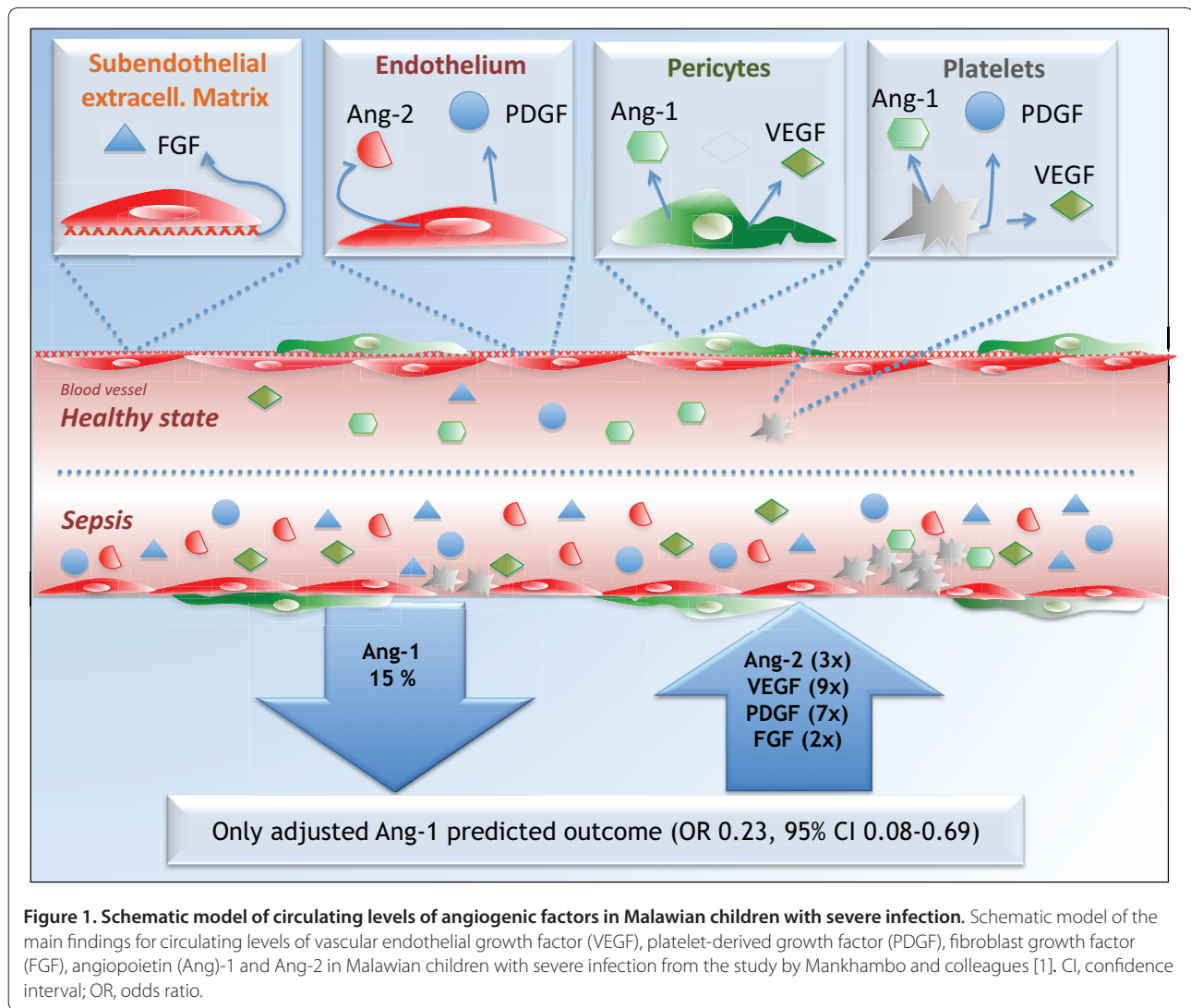
In the previous issue of *Critical Care*, Mankhambo and colleagues report on circulating levels of vascular endothelial growth factor (VEGF), platelet-derived growth factor, fibroblast growth factor, angiopoietin (Ang)-1 and Ang-2 in Malawian children with severe infection [1]. They found robust increases in VEGF, platelet-derived growth factor, fibroblast growth factor and Ang-2 levels (twofold to ninefold), whereas Ang-1 was modestly decreased by only 15% (not significant). Survivors had lower Ang-2 and higher platelet-derived growth factor and Ang-1 levels, respectively (Figure 1). Only (low) Ang-1, however, was significantly associated with mortality after multivariate adjustment.

In 1996 the Ang/Tie2 ligand-receptor system was discovered as the second class of vascular-specific receptor tyrosine kinases (the first being the VEGF/VEGF-receptor system). Classically thought of as an important regulator in vessel maturation and remodeling, recent studies demonstrated that the Ang/Tie2 system not only regulates angiogenesis but also controls endothelial inflammation in a nonredundant manner [2]. Ang-1 and Ang-2 are antagonistic ligands that bind to the extracellular domain of the Tie2 receptor, which is almost exclusively expressed by endothelial cells. Binding of the agonist Ang-1 maintains vessel integrity, inhibits vascular leakage, suppresses inflammatory gene expression, and prevents recruitment and transmigration of leukocytes [3]. In contrast, binding of Ang-2 to Tie2 disrupts protective Ang-1 signaling and facilitates endothelial inflammation, most probably via preventing Ang-1 from phosphorylating Tie2 [4]. Ang-2 was identified recently as a strong and independent predictor of outcome in early and later stages of critical illness in adults [5-9].

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Clinical data from children with severe infection or sepsis are still very limited. Giuliano and coworkers were the first to report that Ang-2 levels were significantly elevated and Ang-1 levels were significantly decreased in children with septic shock compared to children with either systemic inflammatory response syndrome or sepsis [10]. Only circulating Ang-2, however, correlated with disease severity and outcome. The same investigators analyzed Ang-2 release in children after cardiopulmonary bypass surgery [11]. They identified a close correlation of Ang-2 with surrogate markers of capillary leakage and found a relevant role of Ang-2 in predicting the intensive care unit length of stay. In contrast to septic children of the aforementioned study, circulating Ang-1 levels were normal or even elevated after cardiopulmonary bypass. Finally, recent data coming from Ugandan children indicate that Ang-2 might

serve as a biomarker to discriminate uncomplicated malaria from cerebral malaria [12].

While the mediator function of both Ang-1 and Ang-2 has been well established in preclinical research, only Ang-2 has been established as a clinically useful biomarker in the critical care arena [13]. Speculation is tempting, however, on the disturbances in the Ang/Tie2 system during sepsis being a shift from the more protective Ang-1 to the more vascular disruptive Ang-2 [13]. While some authors found elevated Ang-1 levels, others detected low Ang-1 concentrations in intensive care unit patients. This finding might be explained by differences in the samples used for analysis. Unlike Ang-2, which is exclusively stored in endothelial cells, Ang-1 is not exclusively expressed by the vascular wall (Figure 1) – a high amount of Ang-1 (and VEGF) is also found in platelets [14]. False positive Ang-1 levels can

therefore result from the *ex vivo* activation of platelets within serum tubes, a problem recognized only recently.

The article by Mankhambo and colleagues adds knowledge to our current understanding of Ang-1 in critical illness. Plasma Ang-1 levels were not different between patients and controls, but low Ang-1 was independently associated with poor prognosis. Therefore it is reasonable to assume that a very small decrease in circulating Ang-1 has a huge impact on outcome, and that low Ang-1 is probably not associated with mortality in a linear fashion. One might speculate that low Ang-1 *per se* represents an important risk factor for adverse outcome in children with sepsis. Unfortunately, the authors neither investigated the correlation between plasma Ang-1 and clinicopathologic features of multiorgan dysfunction syndrome, nor reported the sensitivity and specificity of specific Ang-1 cut-off values in predicting outcome.

With regard to the value of circulating Ang-1 as a biomarker in sepsis, several questions remain open. What is the role of Ang-1 in platelets and does platelet-derived Ang-1 correlate with outcome? Is it possible to quantify Ang-1 in a compartment-specific fashion (that is, true circulating Ang-1 vs. platelet-derived Ang-1)? Is there a specific all-or-nothing cut-off value for Ang-1, or is the ratio between Ang-1 and Ang-2 critical for outcome prediction? All of these questions remain an active focus in several laboratories, including our own.

Abbreviations

Ang, angiopoietin; VEGF, vascular endothelial growth factor.

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Competing interests

The authors declare that they have no competing interests.

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