Scorpions, snakes, and Fontan failure: The dawn of a new ERA?

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It never ceases to amaze us how often the most fascinating mysteries of evolution intertwine with our routine surgical practice in subtle and unexpected ways. Relentless work of evolution over millions of years has resulted in venom peptides that rapidly incapacitate both prey and predators. The most dangerous scorpions and snakes have evolved to produce highly potent venom that induces severe coronary vasoconstriction and almost immediate ventricular fibrillation. It is remarkable that the most toxic component of this venom, sarafotoxin, is structurally very similar to another 21-residue peptide—endothelin (ET)—a natural compound of the human vascular system.¹

The family of ETs consists of 4 peptides that are converted from a common precursor, preproendothelin, by ET-converting enzyme in endothelial cells (Figure 1). The major isoform in the human vascular system is ET-1. ET-1 causes vasoconstriction and cell proliferation via activation of ET_A and ET_B receptors on vascular smooth muscle cells.² Stimulation of endothelial ET_B receptors causes vasodilatation via nitric oxide and prostacyclin pathways.³ Furthermore, ET_B receptors in the pulmonary endothelium are a major route for the clearance of ET-1.⁴ In patients with congestive heart failure, increased ET-1 level correlates with adverse outcomes. The main source of ET-1 in congestive heart failure appears to be the pulmonary vascular bed and it contributes significantly to increased pulmonary vascular resistance.⁵ Negating ET-1-induced pulmonary vasoconstriction would be of utmost importance in patients with failing Fontan circulation, particularly, because the majority of these patients have preserved systolic ventricular function, yet elevated pulmonary vascular resistance and impaired ventricular relaxation.⁶ Elevated pulmonary vascular resistance in patients with failing Fontan circulation is, at least in part, due to decreased nitric oxide production and elevated plasma ET levels.^{7,8} Current medical management of patients with Fontan failure is extremely limited and, at its very best, may somewhat delay a steady decline in functional

Vascular actions of endothelin-1.

Central Message

Endothelin receptor antagonists may be helpful in decreasing pulmonary resistance and improving functional capacity in patients with failing Fontan circulation.

See Article page 1468.

capacity of patients with a failing Fontan circulation. The current mainstay of treatment for patients with Fontan failure is cardiac transplantation, yet transplantation is challenging in these patients and, due to its complexity, limited donor supply, and substantial waiting list mortality, may not be readily available to most patients.⁹ Thus far, only a few small studies have examined the effects of pulmonary vasodilators on patients with a Fontan circulation. Two small, randomized trials have shown that that sildenafil could improve cardiac index, pulmonary blood flow, oxygen consumption, and ventilatory efficiency in patients with a Fontan circulation who underwent cardiopulmonary exercise testing.^{10,11} Results for endothelin receptor antagonists (ERAs) have been equivocal, with 2 small randomized trials showing improvement exercise capacity, oxygen consumption, and functional class,^{11,12} whereas a third trial showed no benefit.¹³

A very interesting article by Agnoletti and colleagues¹⁴ describes the effects of ERAs in patients with raised pulmonary vascular resistance and a Fontan circulation. In this small, nonrandomized trial they treated 24 patients with 2 different types of ERAs (bosentan for children, including adolescents, and macitentan for adults). They demonstrated that over a 6-month period, the use of ERAs was associated with a decrease in pulmonary resistance, improvement in cardiac output, and spirometric parameters. Furthermore, cardiopulmonary exercise testing

FIGURE 1. Vascular actions of endothelin-1. ECE, Endothelin converting enzyme; ERA, endothelin receptor antagonist; ET, endothelin; NOS, nitric oxide synthetase; COX, cyclo-oxygenase; cGMP, cyclic guanylyl triphosphate; cAMP, cyclic adenylyl monophosphate.

showed improvement in both younger children and adolescents, but not in adults.

There are several key findings in this study. This is the first demonstration that ERAs do not only decrease pulmonary vascular resistance, but also improve hemodynamic and respiratory parameters in patients with a Fontan circulation. Furthermore, they observed that functional improvement was essentially limited to children and adolescents, although significant decrease in pulmonary vascular resistance occurred in all patients. This could be because of a more advanced and often multifactorial circulatory failure in adult patients with long-standing failure of Fontan circulation. This may also explain why some trials, which enrolled older patients, have shown no benefits of ERAs in patients with Fontan failure. Alternatively, because adults received macitentan, whereas minors received bosentan, this may reflect the differential efficacy of drugs within the ERA class. It should be remembered that although both are dual ERAs, macitentan has a 50-fold increased selectivity for the ET_A subtype compared with the ET_B subtype.¹⁵ Because there are higher numbers of ET_A receptors than ET_B receptors in smooth muscle cells of the pulmonary arteries, blocking the ET_A receptors would appear more important in the treatment of pulmonary hypertension.¹⁶ Furthermore, macitentan has a high receptor occupancy half-life (17 minutes) compared with that of bosentan (70 seconds), and this essentially makes macitentan act as a noncompetitive antagonist of ET receptors, whereas bosentan remains a competitive antagonist.¹⁶ At least in theory,

macitentan would block the vasoconstriction effect of ET_A receptors and yet preserve, to some extent, vasodilation and clearance effects of ET_B receptors. Why then was macitentan not effective in improving functional capacity in adults? Provided that there were no issues with sample size, the more advanced multifactorial failure of Fontan circulation would be a logical explanation. It should also be said that although ET_B receptors mediate vasodilation in healthy individuals, ET_B receptors may cause vasoconstriction in patients with heart failure.¹⁷

Although the true influence of ERA on management in patients with failing Fontan circulation remains unclear, the study by Agnolletti and colleagues¹⁴ is an important step forward because it is the first study to clearly demonstrate beneficial effects of ERA in Fontan patients with increased pulmonary resistance. One can only hope that such profound effects on pulmonary resistance will be confirmed in randomized controlled trials and will result in long-term benefits. The path of least resistance may truly prove to be the path of the winner!

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