Beta-blocker therapy in pediatric heart failure: 50 years lost to improve pharmacotherapy of a deadly disease

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A simplified picture from different sources about the global burden of pediatric heart failure will help us to identify the specific problems in this age group:

- Two-thirds of children who die from heart failure are infants
- The main cause of pediatric heart failure in Europe and the US are congenital heart defects (80% overall, 40% left-to-right shunts, and 20% complex heart defects)
- Besides congenital heart disease, causes of pediatric heart failure in the developing world include acquired heart disease (such as rheumatic heart disease), anemia, and infections
- With respect to these etiologies, left ventricular dysfunction is a minor problem in most children with heart failure. It is mostly explainable by hemodynamic reasons, neurohormonal activation, and autonomic dysregulation.

As a young resident, I introduced propranolol therapy in infants with severe heart failure due to congenital heart disease in 1996. The clinical improvement in the first six infants was so impressive that none of the doctors involved doubted its effectiveness. The main cause of mortality in patients with congenital heart disease is heart failure and the mortality of heart failure in infancy is very high. Hence, we could anticipate a larger potential benefit from this new therapy comparable to what was shown in adults with heart failure in randomized control trials in the late 1990s. However, the opinion leaders in pediatric cardiology declined propranolol therapy in infants with congenital heart disease for unknown reasons, despite a proven efficacy in a prospective randomized trial.[1] Without any support from the national and international societies, this promising new therapy was used only by a few "fearless" pediatric cardiologists.[2]

However, in the context of a real-world scenario in India, as in many parts of the world, a large number of infants with ventricular septal defects (VSD) need cheap and effective pharmacotherapies, whereas awaiting surgery due to nonavailability, or saturated pediatric cardiac surgical units.[3] Colleagues from the All-India Institute of Medical Science anticipated the benefit of propranolol in this group of infants and performed the VSD PHF (propranolol for heart failure) study, a prospective randomized trial[4] to evaluate the efficacy and safety of propranolol in infants with heart failure due to moderate to large VSD and published their results in an abstract in 2013[5] and a full-length article in this issue.[4] The number needed to treat was four to prevent one hospitalization!

Over the years, the journals have failed to present a broad discussion of the results and the use of this therapy, at least in the developing world. However, do we really need no effective pharmacotherapy for infant's heart failure in the US and Europe? In 2012, the single ventricle reconstruction trial showed, for the first time, the high interstage mortality in the best cardiac surgery centers in the world, mostly due to heart failure.[6] However, the proposed pharmacotherapy with enalapril was ineffective.[7] In this trial, 230 of the 533 eligible infants were recruited, and 31 died. The overall 1-year mortality of all infants with a single right ventricle was even higher (30%).

In 2002, we wrote the ethical protocol for the "Pro-Fontan-Study" to study the effect of propranolol in infants with univentricular hearts. However, despite a grant to perform this study, the university's decision-makers did not support the project any further. Recently, a single-center experience in 51 newborns with hypoplastic left heart showed an improvement of inter-stage mortality using beta-blocker after a hybrid approach.[8]

Today, 25 years later, I am about to retire and I still cannot believe that the history of Finn Waagstein repeats itself in pediatric cardiology: In 1972, he successfully used a beta-blocker for the first time in a person with severe heart failure and for over 20 years he was insulted by many of his colleagues.[9]

There is overwhelming evidence that drug treatment with beta-blockers + mineralocorticoid receptor antagonists and a combination of angiotensin receptor-neprilysin inhibitors significantly reduce mortality (odds ratio [OR] 0.372; 0.189–0.647) in adult patients with chronic heart failure with reduced ejection fraction, but not with angiotensin-converting enzyme inhibitors (OR 0.831; 0.661–1.011), or with angiotensin receptor blockers (OR 0.77; 0.606–1.261).[10] However, guidelines for pediatric heart failure do not recommend beta-blocker or

angiotensin-neprilysin inhibitors as prospective studies in children are not available. Many children with heart failure have died within the past 25 years, whereas we are waiting for these studies.

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