Endothelin inhibitors lower pulmonary vascular resistance and improve functional capacity in patients with Fontan circulation

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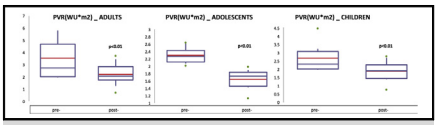
ABSTRACT

Objectives: To evaluate the effects of endothelin inhibitors (ERAs) on hemodynamic and functional parameters in patients post-Fontan procedure with high pulmonary vascular resistance (PVR).

Methods: Among our cohort of patients with Fontan circulation, 8 children, 8 adolescents, and 8 adults had PVR $\geq$2 WU*m^2. These patients were treated with ERAs (minors with bosentan, adults with macitentan) and reevaluated after 6 months. Pre- and posttreatment hemodynamic variables were assessed by cardiac catheterization. Functional capacity was evaluated by cardiopulmonary exercise testing (CPET). Our primary endpoint was to obtain a reduction of PVR; the secondary endpoint was to obtain an improvement of functional capacity.

Results: Under treatment, New York Heart Association class improved for adolescents and adults. PVR decreased ($P = .01$) in all groups: in children from the median value 2.3 (interquartile range 2.0-3.1) to 1.9 (1.4-2.3) WU*m^2, in adolescents from 2.3 (2.1-2.4) to 1.7 (1.4-1.8) WU*m^2, and in adults from 2.8 (2.0-4.7) to 2.1 (1.8-2.8)WU*m^2. In 71% of patients, PVR fell to less than 2 WU*m^2. Cardiac index increased in adolescents from 2.6 (2.4-3.3) to 3.6 (3.4-4.3) L/min/m^2, $P = .04$, and in adults from 2.1 (2.0-2.3) to 2.8 (2.3-4.7) L/min/m^2, $P = .03$. CPET showed that only adolescents displayed a significant functional improvement. Anaerobic threshold improved from 17 (13-19) to 18 (13-20) mL/kg/min, $P = .03$; oxygen consumption and VO_2 max increased from 1.3 (1.0-1.6) to 1.7 (1.1-1.9) L/min, $P = .02$ and from 25 (21-28) to 28 (26-31) L/min, $P = .02$, respectively. Oxygen pulse increased from 7.9 (5.7-10.4) to 11.2 (8.2-13.0) L/beat, $P = .01$.

Conclusions: This is the first study that assesses by cardiac catheterization and CPET the effects of ERA in patients with Fontan circulation with increased PVR. These results suggest that ERAs might provide most pronounced hemodynamic and functional improvement in adults and adolescents. (J Thorac Cardiovasc Surg 2017;■:1-8)



Endothelin inhibitors significantly decreased pulmonary vascular resistance in all 3 groups of patients.

Central Message

Our results suggest that endothelin inhibitors might be useful in patients with Fontan circulation and increased pulmonary vascular resistance. They provide the most pronounced hemodynamic and functional improvement in adults and adolescents (Video 1).

Perspective

We show that endothelin inhibitors normalize pulmonary vascular resistance in the majority of patients with Fontan circulation, increasing cardiac output. They improve ventilatory capacity and oxygen consumption. They induce most pronounced hemodynamic and functional improvement in adults and adolescents. We provide evidence that pulmonary vasodilatation with endothelin inhibitors might be useful in patients with Fontan circulation and increased pulmonary vascular resistance.

CONG

In patients with Fontan circulation, pulmonary vascular resistance (PVR) increases and indexed systemic output (QSI) slowly decreases with time since operation, eventually leading to Fontan failure and death.[1,2] It is known that patients with Fontan circulation display endothelial dysfunction,[3] characterized by decreased production of nitric oxide[4] and increased levels of endothelin.[5] Various authors have hypothesized that drugs that lower PVR through an endothelial action, such as endothelin receptor

Scanning this QR code will take you to a supplemental video for the article.

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Received for publication Aug 29, 2016; revisions received Jan 4, 2017; accepted for publication Jan 24, 2017.

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0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2017.01.051

Abbreviations and Acronyms

AT	= anaerobic threshold
CPET	= cardiopulmonary exercise testing
ERA	= endothelin inhibitor
FVC	= forced vital capacity
FEV_1	= forced expiratory volume in 1 second
NYHA	= New York Heart Association
PAH	= pulmonary arterial hypertension
PAP	= mean pulmonary arterial pressure
PVR	= pulmonary vascular resistance
QPI	= indexed pulmonary output
QSI	= indexed systemic output
SVR	= systemic vascular resistance
VD/VT	= volume dead/volume tidal
VE/VCO_2	= volume expired/volume CO_2 expired
VO_2	= oxygen consumption
VO_2 max	= maximal oxygen consumption

antagonists (ERAs) and phosphodiesterase-5 inhibitors, might improve symptoms and outcome of patients with Fontan circulation.[6-9] The results concerning the effects of ERAs on the functional capacity of this population are, however, controversial.[7-11] In particular, bosentan has been used in these patients with discordant results. Macitentan is a new ERA that was approved recently for the treatment of pulmonary arterial hypertension (PAH) in adult patients[12] but so far has not been used in patients who had Fontan procedure. To the best of our knowledge, there are no studies exploring the effects of ERAs on PVR in patients with Fontan circulation.

The aim of the present study was to measure hemodynamic and functional parameters in a group of patients with Fontan circulation and increased PVR before and after treatment with ERAs for a period of 6 months.

PATIENTS AND METHODS

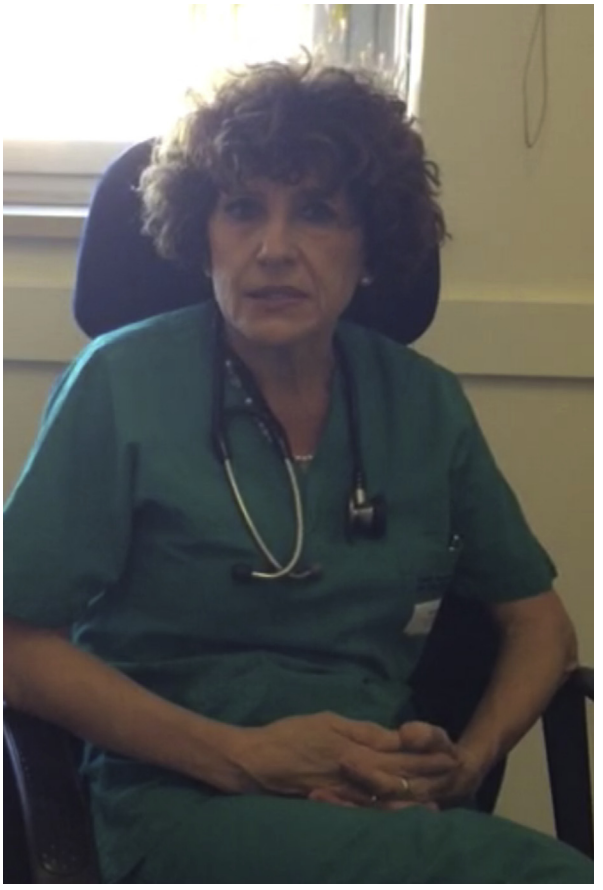
Study Design

The study was designed to explore the effect of a 6-month ERA treatment in patients who had Fontan procedure. Each patient was to act as case-control to test the impact of the ERA treatment. The primary end point was a reduction of PVR; the secondary end point was an improvement of functional capacity.

Study Population

The study population was derived from the pool of 64 consecutive patients who had Fontan procedure who were evaluated with cardiac catheterization and cardiopulmonary exercise testing (CPET) between March 2013 and December 2014 at our institution.[1]

Main inclusion criterion was PVR $\geq$ 2 WU*m^2. Exclusion criteria were active plastic bronchitis, protein-losing enteropathy, or cirrhosis confirmed by liver biopsy. Patients in stable clinical condition, even with previous history of plastic bronchitis, protein-losing enteropathy, or with cirrhosis-like fibrosis, were included. No exclusion criteria were applied concerning either age or sex.



VIDEO 1. PVR increases over time in patients with Fontan circulation, leading to hypoperfusion and poor functional capacity. The aim of the present study was to measure hemodynamic and functional parameters in a group of patients with Fontan circulation with PVR >2 Wu*m^2 before and after treatment with ERAs for a period of 6 months. Pre- and posttreatment hemodynamic variables were assessed by cardiac catheterization. Functional capacity was evaluated by cardiopulmonary testing. Our primary endpoint was to obtain a reduction of PVR; our secondary endpoint was to obtain an improvement of functional capacity. We show for the first time that ERAs have positive functional and hemodynamic effects in patients with Fontan circulation of various ages with increased PVR. ERAs improve physical ability, ventilatory capacity, and oxygen consumption. They lower PVR, increasing cardiac index. Although functional capacity remains below average, PVR becomes normal in the majority of patients. Our overall results provide evidence that pulmonary vasodilatation with ERAs might be considered a useful treatment in patients with Fontan circulation with increased PVR. Video available at: http://www.jtcvs.org.

Compliance to the study by adult patients or by parents of minors was strictly on a volunteer basis, following extensive information about its scope and procedures. Among the 26 of 64 (41%) patients who met the PVR $\geq$ 2 WU*m^2 condition, 24 of 26 (92%) entered the ERA study: 16 minors (age <18 years) and 8 adults (age $\geq$18 years).

Study Protocol

Although we aimed at administering macitentan to the entire population because of its improved receptorial binding,[12] both the local legislative authority and the ethic committee allowed its use only in adult patients. Thus, minors received oral bosentan 0.5 mg/kg twice daily for 4 weeks, followed