International Journal of Cardiology 279 (2019) 62–63

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Editorial

Renin–angiotensin–aldosterone system blockade in systemic right ventricle☆

Margarita Brida [a,b,c,*], Gary Webb [d]

[a] Adult Congenital Heart Centre and National Centre for Pulmonary Hypertension, Royal Brompton Hospital, London, UK
[b] National Heart and Lung Institute, Imperial College, London, UK
[c] Division for Adult Congenital Heart Disease, Department of Cardiovascular Medicine, University Hospital Centre Zagreb, Croatia
[d] Cincinnati Children's Hospital, Cincinnati, USA; University Health Network, Peter Munk Cardiac Centre, Toronto Congenital Cardiac Centre for Adults, and University of Toronto, Canada.

ARTICLE INFO

Article history:
Received 15 December 2018
Accepted 2 January 2019
Available online 6 January 2019

Unlike other areas in cardiovascular medicine, drug therapy in adults with congenital heart disease (ACHD) is based on scarce clinical data and remains largely empiric [1].

Currently, an important knowledge gap exists in the role of pharmacological therapy for ventricular dysfunction and heart failure in patients with a systemic right ventricle (SRV), namely congenitally corrected transposition of the great arteries (CCTGA) and transposition of the great arteries after atrial switch repair (TGA).

Renin–angiotensin–aldosterone system (RAAS) blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), represent the cornerstone of treatment in left ventricular failure [2]. RAAS blockers act by diminishing the effects of increased angiotensin II levels, slowing down the progressive deterioration of the left ventricle, and thus, improving morbidity and mortality. Therefore, these drugs have also been proposed for the treatment of patients with SRV dysfunction. The rational for potential benefit of RAAS blockade in SRV is based on similar angiotensin II receptor density in both the right and left ventricles as well as similar RAAS system activation in all patients with heart failure, irrespective of the morphology of the affected ventricle. However, to-date, little or no effect has been observed in consequent studies on RAAS blockade addressing SRV dysfunction (Table 1) [3–10].

In a recently published study, van Dissel et al. recruited an admirable number of patients with SRV on RAAS blockade therapy (n = 87) with the longest follow-up period (median of 8.3 years) published to-date [10]. Their study investigates the long-term outcome of patients with SRV after a randomized 3 year placebo-controlled trial on the effects of valsartan on SRV function [9]. Both the randomized controlled trial and the recently published retrospective study failed to achieve their primary end-point. There was no significant treatment effect of valsartan on SRV ejection fraction during the 3-year follow-up period; similarly, there was no long-term survival benefit after a mean period of 8.3 years. There is an emerging question here: are we chasing the right target in the quest for the 'holy grail' in the treatment of SRV?

Arguments against the treatment with ACE inhibitors and ARBs in the setting of SRV have also been postulated. Activation of the RAAS system could be a necessary compensatory mechanism in patients with pressure overloaded SRV, as is seen in patients with a pressure overloaded subpulmonary RV (e.g., patients with chronic cor pulmonale). Moreover, the underlying mechanism of SRV dysfunction and heart failure may involve different mechanisms, not necessarily present in systemic left ventricular failure. These differences include excessive ventricular hypertrophy not matched by a normal right coronary supply (i.e. demand ischaemia); SRV adaptation with predominant circumferential over longitudinal shortening without torsion (as is normally found in the systemic left ventricle); impaired atrioventricular transport due to rigid atrial baffles in TGA; increased myocardial fibrosis associated with ventricular dysfunction and arrhythmia propensity; systemic atrioventricular valve regurgitation (particularly in CCTGA); and SRV dysfunction due to other factors [11].

However, RAAS inhibitors may still have a role, as per emerging evidence of potential benefit in symptomatic patients with SRV. Unlike patients with stable SRV function, symptomatic patients, in general, have active neurohormonal and cardiac autonomic nervous systems. Therefore, blocking the RAAS might result in a better clinical outcome by suppressing their negative consequences. Indeed, previous studies showed a significant decline in NT-proBNP levels, as well as non-worsening of SRV ejection fraction in symptomatic patients treated with RAAS inhibitors [8,9]. The beneficial effect of RAAS inhibitors in this subgroup of patients was also present in the van Dissel et al. study. Valsartan significantly reduced the risk of events (i.e. supraventricular and ventricular arrhythmia, worsening heart failure, and tricuspid valve surgery) in symptomatic patients (HR 0.37, 95% CI 0.14–0.93) [10]. These findings are in concordance with the current

☆ M.B. was the recipient of the International Training and Research Fellowship EMAH Stiftung Karla VÖLLM, Krefeld, Germany.
DOI of original article: https://doi.org/10.1016/j.ijcard.2018.11.027.
* Corresponding author at: Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK.
E-mail address: margarita.brida@icloud.com (M. Brida).

https://doi.org/10.1016/j.ijcard.2019.01.003

Table 1
Summary of trials of RAAS blockade in patients with a systemic right ventricle.

N	Author	Reference	Year	Nb of patients	Study design	Follow-up	Symptomatic (NYHA > 1)	Drug	Results
1	Lester	Am J Cardiol	2001	7	Prospective	2 mths	N.S.	Losartan	Increase in RVEF and duration of exercise, decrease in EROA and RV on echocardiography
2	Hechter	Am J Cardiol	2001	14	Retrospective	18 mths	N.S.	Various ACEi	No effect on cardiopulmonary exercise, RVEF and SRV volume on MRI
3	Robinson	Pediatr Cardiol	2002	9	Prospective	12 mths	0	Enalapril	No effect on exercise capacity, cardiac index, and systemic vascular resistance during exercise
4	Dore	Circulation	2005	29	Prospective	3.5 mths	7	Losartan	No effect on exercise capacity and on NT-proBNP levels
5	Therrien	Int J Card	2008	17	Prospective	12 mths	1	Ramipril	No effect on RVEF, RVEDV and RVESV on MRI
6	Tutarel	Int J Card	2012	14	Retrospective	13 mths	14	Enalapril	No effect on maximum oxygen uptake and echocardiographic parameters. **Significant decrease in NT-proBNP**.
7	van der Bom	Circulation	2013	88	Prospective	3 yrs	26	Valsartan	No effect on RVEF on MRI, exercise capacity, quality of life. Larger increase in RVEDV and mass in the placebo group than in the valsartan group. **In symptomatic patients RVEF declined in placebo but remained unchanged in valsartan group**.
8	van Dissel	Int J Card	2018	87	Retrospective	8.3 yrs	26	Valsartan	No effect on survival and freedom from clinical events. **In symptomatic patients decreased risk of clinical events**.

ACEi = angiotensin converting enzyme inhibitor; EROA = Effective Regurgitant Orifice Area; MRI = Magnetic Resonance Imaging; mths = months; NT-proBNP = N-terminal proBrain Natriuretic Peptide; N.S. = not stated; NYHA = New York Heart Association class; RVEF = right ventricle ejection fraction; RVEDV = right ventricle end diastolic volume; RVESV = right ventricle end systolic volume; RV = regurgitation volume; SRV = systemic right ventricle; yrs = years. Bold text in results section represents the effect of RAAS blockade in symptomatic patients.

recommendations of the Working Group of Grown-Up Congenital Heart Disease and The Heart Failure Association, suggesting standard heart failure treatment, including RAAS blockers, also in symptomatic patients with SRV [12].

There are new pharmacological options for patients with heart failure emerging. One of them, a new compound (LCZ696) that combines the moieties of an ARB (valsartan) and a neprilysin inhibitor (sacubitril) has been shown to be superior to an ACE inhibitor (enalapril) in reducing the risk of hospitalization and death for left ventricular heart failure. Sacubitril/valsartan has been recommended to replace ACE inhibitors in ambulatory heart failure patients who remain symptomatic despite optimal therapy [2]. Maybe these new treatment options should be put in clinical trials for patients with SRV.

To conclude, pharmacological therapy in patients with SRV is still at its early stages. Thus far, recommendations are difficult to make and formalized guidelines on drug therapy are lacking. Large randomized clinical trials are clearly warranted to secure better levels of evidence.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

References

[1] M. Brida, G.P. Diller, H. Nashat, M. Strozzi, D. Milicic, H. Baumgartner, et al., Pharmacological therapy in adult congenital heart disease: growing need, yet limited evidence, Eur. Heart J. 0 (2018) 1–10.

[2] P. Ponikowski, A.A. Voors, S.D. Anker, H. Bueno, J.G.F. Cleland, A.J.S. Coats, et al., 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC, Eur. Heart J. 37 (27) (2016) 2129–2200.

[3] S.J. Lester, D.B. McElhinney, E. Viloria, G.P. Reddy, E. Ryan, W. Tworetzky, et al., Effects of losartan in patients with a systemically functioning morphologic right ventricle after atrial repair of transposition of the great arteries, Am. J. Cardiol. 88 (11) (2001) 1314–1316.

[4] S.J. Hechter, P.M. Fredriksen, P. Liu, G. Veldtman, N. Merchant, M. Freeman, et al., Angiotensin-converting enzyme inhibitors in adults after the Mustard procedure, Am. J. Cardiol. 87 (5) (2001) 660–663 (a11).

[5] B. Robinson, C.T. Heise, J.W. Moore, J. Anella, M. Sokoloski, E. Eshaghpour, Afterload reduction therapy in patients following intraatrial baffle operation for transposition of the great arteries, Pediatr. Cardiol. 23 (6) (2002) 618–623.

[6] A. Dore, C. Houde, K.L. Chan, A. Ducharme, P. Khairy, M. Juneau, et al., Angiotensin receptor blockade and exercise capacity in adults with systemic right ventricles: a multicenter, randomized, placebo-controlled clinical trial, Circulation 112 (16) (2005) 2411–2416.

[7] J. Therrien, Y. Provost, J. Harrison, M. Connelly, H. Kaemmerer, G.D. Webb, Effect of angiotensin receptor blockade on systemic right ventricular function and size: a small, randomized, placebo-controlled study, Int. J. Cardiol. 129 (2) (2008) 187–192.

[8] O. Tutarel, G.P. Meyer, H. Bertram, A. Wessel, B. Schieffer, M. Westhoff-Bleck, Safety and efficiency of chronic ACE inhibition in symptomatic heart failure patients with a systemic right ventricle, Int. J. Cardiol. 154 (1) (2012) 14–16.

[9] T. van der Bom, M.M. Winter, B.J. Bouma, M. Groenink, H.W. Vliegen, P.G. Pieper, et al., Effect of valsartan on systemic right ventricular function: a double-blind, randomized, placebo-controlled pilot trial, Circulation 127 (3) (2013) 322–330.

[10] A.C. van Dissel, M.M. Winter, T. van der Bom, H.W. Vliegen, A.P.J. van Dijk, P.G. Pieper, et al., Long-term clinical outcomes of valsartan in patients with a systemic right ventricle: follow-up of a multicenter randomized controlled trial, Int. J. Cardiol. (2018) https://doi.org/10.1016/j.ijcard.2018.10.078.

[11] M. Brida, G.P. Diller, M.A. Gatzoulis, Systemic right ventricle in adults with congenital heart disease: anatomic and phenotypic spectrum and current approach to management, Circulation 137 (5) (2018) 508–518.

[12] W. Budts, J. Roos-Hesselink, T. Radle-Hurst, A. Eicken, T.A. McDonagh, E. Lambrinou, et al., Treatment of heart failure in adult congenital heart disease: a position paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology, Eur. Heart J. 37 (18) (2016) 1419–1427.