Letter to the editor: Therapeutic options for systemic right ventricular failure

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The author’s reply

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TO THE EDITOR

In the recent paper presenting the latest insights into the therapeutic options for patients with systemic right ventricles, Winter et al.¹ argued that “the pragmatic use of angiotensin converting enzyme inhibitors and b blockers in these patients seems appropriate”. However, they also concluded that “the evidence base for the implementation of left ventricular failure treatment regimens in patients with a systemic right ventricle is poor” and that “most studies were underpowered, had short follow-up periods, or had a retrospective study set-up”.

There is, however, another important reason for the failure to demonstrate the efficacy of angiotensin converting enzyme inhibitors, angiotensin II and b blockers in patients with systemic right ventricles. The use of renin–angiotensin–aldosterone axis inhibitors with systemic right ventricles has been based on extrapolation from the results of classic heart failure trials, but these drugs were used indiscriminately in patients with systemic right ventricles in all published intervention studies, irrespective of the presence or absence of systolic dysfunction, of the patients’ symptoms, or the degree of neurohumoral activation.

The population of patients with a systemic right ventricle is heterogeneous, however. In our series,² only about half had impaired systolic function, a quarter had symptomatic right ventricular dysfunction and another quarter had asymptomatic right ventricular dysfunction. These finding were similar to those found by other authors and are concordant with the variable degree of neurohumoral activation in patients with systemic right ventricles. In our patients, about two-thirds had normal levels of angiotensin II and almost 40% had normal aldosterone levels (submitted for publication). These observations are comparable to those reported by Dore et al.³ and are not surprising, because normal renin–angiotensin–aldosterone axis activity is also seen in patients with asymptomatic left ventricular dysfunction and chronic stable heart failure.⁴

The majority of patients with systemic right ventricles are asymptomatic or mildly symptomatic and have minimal baseline activation of the renin-angiotensin-aldosterone system. They are therefore, in away, similar to patients with left
ventricular failure dysfunction participating, for instance, in the SOLVD trial. In this trial it was estimated, that the treatment of 1000 such patients with enalapril for about 3 years would prevent 56 premature deaths over 10 years. If this outcome was applied directly to the approximately 11,000 adult American patients with complete transposition of the great arteries, it would prevent about 600 deaths from right ventricular failure.

The important problem, therefore, is the need for appropriately defined population(s) of patients with systemic right ventricles, in which it is possible to distinguish the efficacy of pharmacotherapy in those who are symptomatic or asymptomatic, or who have preserved or impaired function of the systemic right ventricle. These matters can only be properly examined by a multicentre randomised trial.

Until the results of such a trial are available, it is pragmatic to use angiotensin enzyme converting inhibitors in patients with symptomatic and asymptomatic systemic right ventricular dysfunction as well as in patients with elevated and “high normal” blood pressure readings, irrespective of right ventricular function.


We thank Dr. Szymański for his critical review of our paper on the therapeutic options for patients with a systemic right ventricle. We agree with the author that studies on the effect of angiotensin converting enzyme (ACE) inhibitors, and angiotensin II receptor (AT-II) antagonists are hampered by the large heterogeneity of the patient population, and that strict definition of the study population is of key importance.

However, the largest impediment in performing trials in patients with a systemic right ventricle is to obtain sufficient power, due to the rarity of the condition. Dr. Szymański argues that patients with a systemic right ventricle resemble, in a way, patients with left ventricular failure as were studied in the SOLVD trial. Although the SOLVD investigators were able to set up two separate studies to investigate the effect of enalapril (in symptomatic (n=2500) and in asymptomatic (n=4600) patients with ventricular dysfunction), the number of patients with a systemic right ventricle does not allow for such specific population definition. Moreover, all patients with a systemic right ventricle are at increased risk of developing ventricular dysfunction. Therefore, the role of ACE inhibitors and AT-II antagonist should be clarified for all patients, irrespective of their current clinical condition.

Nevertheless, we agree with the author that a large-scale, multi-center, prospective randomized trial is urgently required to provide us with reliable information on the role of ACE inhibitors and AT-II antagonists in the treatment regimen of patients with a systemic right ventricle. Currently, we are engaged in such a trial, in which almost 100 patients with a systemic right ventricle are randomized to receive either valsartan of placebo for the duration of 3 consecutive years. Although we have chosen to use broad inclusion criteria for our study, extensive subgroup analyses will be performed which could overcome the problem of heterogeneity and identify those patients who are most likely to benefit from these medications.
Reference List