EDITORIAL

Angiotensin II Receptor Blockers and Arrhythmias in Ventricular Hypertrophy

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Losartan was the first AT₁R (angiotensin II [Ang II] type 1 receptor) blocker or sartan (short for selective angiotensin receptor antagonist) to be approved by the Food and Drug Administration for hypertension in 1995, and was rapidly followed by candesartan, eprosartan, irbesartan, valsartan, telmisartan, and olmesartan. All sartans bind the AT₁R with high affinity and negligible affinity to AT₂R (Ang II type 2 receptor). Ang II signaling is mediated primarily via AT₁R, and AT₁R activation is thought to counter the effects of AT₁R. Of the many sartans, candesartan, and for unclear reasons valsartan, stood out as more beneficial in clinical trials, but unfortunately there are no head-to-head comparisons between sartans. Ang II is a potent vasoconstrictor, and sartans are potent vasodilators, which leads to reduction of peripheral vascular resistance, cardiac afterload, and blood pressure. Sartans are more effective than angiotensin-converting enzyme inhibitors at lowering blood pressure because there are alternative pathways to convert Ang I to Ang II and to activate AT₁R.

ANTIARRHYTHMIC ACTIONS OF SARTANS

Premature beats, ventricular tachycardia, and ventricular fibrillation, are common in patients with heart failure with reduced ejection fraction, which raises the mortality and morbidity compared with placebo, and the antiarrhythmic properties have been well documented. Activation of AT₁R by Ang II or stretch has been shown to alter Ca²⁺ handling, repolarization, and ion channel expression. However, a new approach for the use of sartans to treat HF was conceived by combining valsartan with sacubitril, at a 1:1 stoichiometry, to form a new Novartis drug, Entresto, which represents the first Food and Drug Administration–approved drug for heart failure with reduced ejection fraction in decades. Sacubitril is a neprilysin inhibitor, and neprilysin is a neutral endopeptidase that degrades natriuretic peptides and other vasodilating peptides such as substance P and bradykinin, as well as vasoconstricting peptides such as endothelin and Ang II. Thus, neprilysin inhibition leads to increases in Ang II and must be combined with an angiotensin receptor blocker.

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the question of whether the combination therapy of sacubitril/valsartan reduces mortality by ≥20% by suppressing arrhythmias. Analysis of whether this drug treatment reduces the incidence of ventricular tachycardia/ventricular fibrillation in patients with heart failure with reduced ejection fraction remain inconclusive,9,10 which may be because of the lack of understanding of the mechanisms involved in the reduction of arrhythmia risk.

There is a lack of research on the possible antiarrhythmic actions of Entresto; one can speculate that there is a direct effect on ion channel remodeling or rhythmic actions of Entresto; one can speculate that loss of Cav1.2 at T-tubules, a decrease of L-type Ca2+ current, a reduction of connexin 43, higher levels of protein densities and protein levels of both Kv4.2 and Kv4.3 in banded rats. Other major cardiac ion channel currents were also investigated. The voltage-gated L-type Ca2+ current, \( I_{\text{Ca,L}} \), and the steady-state activation and inactivation kinetics were not significantly altered by candesartan, likewise the \( I_{\text{Na}} \) and \( I_{\text{K1}} \) densities and the corresponding Kv2.1 and Kir2.1 protein levels did not change and are unlikely to contribute to the corrected QT prolongation. The peak of the voltage-gated Na+ current, \( I_{\text{Na}} \) is the main determinant of the upstroke of the cardiac action potential and did not significantly change in sodium-calcium exchange function in banded myocytes, consistent with no changes in sodium-calcium exchange protein expression. Despite decreased Ca2+ uptake to sarcoplasmic reticulum, the unchanged amplitudes of Ca2+ transient, sarcoplasmic reticulum Ca2+ content, and contraction after aortic banding, could be explained partly by the prolonged action potential and slower repolarization, which may indirectly slow \( I_{\text{Ca,L}} \) decline and counteract the activity of forward-mode sodium-calcium exchange, thereby maintaining the sarcoplasmic reticulum Ca2+ content.

It is interesting to note that the model did not cause an increase in serum or tissue levels of Ang II, which leads to the speculation that AT1R is activated by pressure overload and stretch at the level of the receptors, and suggests that treatment with angiotensin-converting enzyme inhibitors is not likely to be as effective as sartans in this pathology. The study is a comprehensive analysis of cardiac ion channels using a whole-cell voltage clamp of myocytes from banded and banded rats plus candesartan, and thus provides compelling evidence that sartans suppress arrhythmias, both atrial and ventricular myocytes, through modification of cardiac ion channels.

The study is detailed, measures the relevant ionic currents, applies sound technical methods, and is consistent with clinical studies that report antiarrhythmic protection by sartans in patients with hypertension and structural injury (eg, ventricular hypertrophy). Nevertheless, these new insights carry important limitations. Candesartan was not tested as a therapeutic but as a possible prophylactic drug, which would tend to reduce its clinical significance and increases the likelihood that candesartan can prevent the effects of banding. The antiarrhythmic properties of the drug are demonstrated with a rodent model of ventricular
hypertrophy through its action on I_{to} and the channel proteins Kv4.2 and Kv4.3; however, I_{to} is not an important determinant of repolarization in the human action potential where the fast and slow components of the delayed rectifying K+ currents, I_{Ks} and I_{Kt}, drive repolarization.\textsuperscript{16} The distribution of AT_{1}R in the heart could be heterogeneous, which could contribute to repolarization abnormalities in banded animals.

Interestingly, the authors found that Ang II was not elevated in banded animals, either in the serum or ventricular tissue, which suggests that AT_{1}R were activated by local stretch associated with the pressure overload. This raises an interesting question: Both Ang II and stretch can activate AT_{1}R, but do they have the same downstream effects? When Ang II is used as an agonist of AT_{1}R in rat myocytes, there is a marked internalization of L-type Ca^{2+} channels, reduction of I_{Ca,L}, Ca^{2+} transients, and force of contraction.\textsuperscript{14} In contrast, pressure overload did not alter the same parameters.\textsuperscript{15} Long-term activation or inhibition of AT_{1}R causes considerable cardiovascular remodeling as well as genomic modifications of cardiac ion channels. Yet despite decades of research, the link between these receptors and changes at the transcriptional level are largely speculative. An elucidation of these mechanisms will be essential in the quest for effective therapies for cardiovascular diseases.

### ARTICLE INFORMATION

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**Disclosures**
None.

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