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EDITORIAL

Angiotensin II Receptor Blockers and Arrhythmias in Ventricular Hypertrophy

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Losartan was the first AT_1R (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,[1] and was rapidly followed by candesartan, eprosartan, irbesartan, valsartan, telmisartan, and olmesartan. All sartans bind the AT_1R with high affinity and negligible affinity to AT_2R (Ang II type 2 receptor).[2] Ang II signaling is mediated primarily via AT_1R, and AT+R activation is thought to counter the effects of AT_1R.[3] 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.[2] Ang II is a potent vasoconstrictor, and sartans are potent vasodilators, which leads to reduction of peripheral vascular resistance, cardiac afterload, and blood pressure.[4] 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 AT_1R.[4]

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The benefits of angiotensin receptor blockers were extensively studied in clinical trials for heart failure (HF) and a meta-analysis of HF (New York Heart Association class II–IV), including HF with preserved (2 studies with left ventricular ejection fraction ≥40%, 7151 patients) and with reduced ejection fractions (22 studies with left ventricular ejection fraction ≤40%, 17 900 patients). Findings revealed no reduction in mortality and morbidity compared with placebo,[5] and the antiarrhythmic properties have been well documented. Activation of AT_1R by Ang II or stretch has been shown to alter Ca^{2+} 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.[6] 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.[7]

ANTIARRHYTHMIC ACTIONS OF SARTANS

Premature beats, ventricular tachycardia, and ventricular fibrillation, are common in patients with heart failure with reduced ejection fraction,[8] which raises

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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 indirect effects through a reduction of inflammation, fibrosis, and myocardial stretch because of improved hemodynamics, pre- and afterload. Interestingly, clinical[11,12] and animal[13] studies implicate sartans as antiarrhythmic agents, particularly in HF with ventricular hypertrophy and hypertension. Valsartan reduced microvolt T-wave alternans, a harbinger of ventricular arrhythmias, which led the authors to propose that sartans reduced sudden cardiac death by improving repolarization abnormalities.[11] In hypertension and HF trials, sartans' beneficial effects were in part caused by reducing the occurrence of atrial fibrillation.[12] In rats with a myocardial infarct, there was corrected QT prolongation, a reduction of connexin 43, higher levels of collagen deposition, higher levels of AT_1R expression, and greater ventricular tachycardia/ventricular fibrillation induced by electrical stimulation. All were partly prevented by valsartan administered during development of the myocardial infarct.[13] In isolated rat cardiomyocytes, activation of AT_1R with Ang II resulted in a loss of Cav1.2 at T-tubules, a decrease of L-type Ca^{2+} current, $I_{Ca,L}$, and a marked decrease in Ca^{2+} transients during contractions, along with a faster repolarization of the action potential.[14] This suggests that sartans could prevent or reverse these effects of prolonged Ang II.

In the current issue of the *Journal of the American Heart Association* (*JAHA*), Chang and his colleagues investigate the antiarrhythmic mechanisms of action of candesartan cilexitil in a model of HF induced by an abdominal aorta banding.[15] They show that the abdominal aorta banding resulted in pressure overload, moderate to severe left ventricular (LV) hypertrophy and fibrosis, increased LV pressure and its decay time, and prolonged corrected QT interval, all of which were partially prevented by candesartan cilexetil treatment at the time of banding. Candesartan-treated (3 mg/kg per day for 5 weeks) banded rat hearts displayed shorter corrected QT intervals and lower vulnerability to atrial and ventricular tachyarrhythmias.

At the cellular and molecular level, candesartan prevented the banding-induced action potential prolongation, reduced the occurrence of triggered activity in papillary muscles isolated from the left ventricle, normalized the decay time of Ca^{2+} transient in LV myocytes from candesartan-treated banded rats, prevented the decrease in SERCA2a (sarcoplasmic reticulum Ca^{2+}-Mg^{2+}-ATPase) expression in LV tissues, and the depressed transient outward K^+ current (I_{to}) 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 Ca^{2+} current, $I_{Ca,L}$, and the steady-state activation and inactivation kinetics were not significantly altered by candesartan, likewise the I_{ss} and I_{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_{Na}, is the main determinant of the upstroke of the cardiac action potential and did not significantly change in the kinetic properties of peak I_{Na} and protein level of Nav1.5, whereas the I_{Na} density tended to be less in banded rat LV preparations, which may account for the slightly lower *V*max of the action potential in the banded rat. The authors found no change in sodium-calcium exchange function in banded myocytes, consistent with no changes in sodium-calcium exchange protein expression. Despite decreased Ca^{2+} uptake to sarcoplasmic reticulum, the unchanged amplitudes of Ca^{2+} transient, sarcoplasmic reticulum Ca^{2+} content, and contraction after aortic banding, could be explained partly by the prolonged action potential and slower repolarization, which may indirectly slow $I_{Ca,L}$ decline and counteract the activity of forward-mode sodium-calcium exchange, thereby maintaining the sarcoplasmic reticulum Ca^{2+} 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 AT_1R 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_{Kr} and I_{Ks}, drive repolarization.[16] The distribution of AT_1Rs 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_1Rs were activated by local stretch associated with the pressure overload. This raises an interesting question: Both Ang II and stretch can activate AT_1R, but do they have the same downstream effects? When Ang II is used as an agonist of AT_1R 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.[14] In contrast, pressure overload did not alter the same parameters.[15] Long-term activation or inhibition of AT_1R 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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