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EDITORIAL

Suppression of Ventricular Arrhythmias After Myocardial Infarction by AT1 Receptor Blockade: Role of the AT2 Receptor and Casein Kinase 2/Kir2.1 Pathway

Editorial to: "Valsartan Upregulates Kir2.1 in Rats Suffering from Myocardial Infarction Via Casein Kinase 2" by Xinran Li et al.

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Abbreviations

AAD	Antiarrhythmic drug
AngII	Angiotensin II
AT_1R	AngII type 1 receptor
AT_2R	AngII type 2 receptor
ARB	AT_1R blocker
CK2	Casein kinase 2
ICD	Implantable cardioverter-defibrillator
IK1	Inward rectifier K+ current
LV	Left ventricular
MI	Myocardial infarction
PES	Programmed electrical stimulation
PVC	Premature ventricular complex
RAAS	Renin-angiotensin-aldosterone system
SCD	Sudden cardiac death
VAs	Ventricular arrhythmias
VT	Ventricular tachycardia
VF	Ventricular fibrillation

Ventricular arrhythmias (VAs) after myocardial infarction (MI) have been a source of concern for decades because they contribute to mortality in the post-MI survivors. Common VAs, spontaneous or programmed electrical stimulation (PES) induced, include premature ventricular depolarizations or complexes (PVCs), couplets, triplets, non-sustained ventricular tachycardia (VT) and ventricular fibrillation (VF) or VT/VF. Without doubt, major advances have been made in therapy for their control and prevention, with the development of pharmacologic and electrophysiological approaches including antiarrhythmic agents, beta-adrenergic drugs, catheter ablation, and the implantable cardioverter-defibrillator (ICD). In parallel, an added benefit of renin-angiotensin-aldosterone system (RAAS) blockers introduced for therapy of post-MI left ventricular (LV) remodeling and dysfunction, including the angiotensin II (AngII) type 1 receptor (AT_1R) antagonists or blockers (ARBs), has been the suppression of VAs and sudden cardiac deaths (SCDs) as well as "final" deaths and their contribution to improved survival and outcome [1–7]. However, the precise molecular mechanism for the ARB-induced suppression of VAs has been elusive. A major goal of translational research has therefore been to not only unravel the underlying molecular mechanisms for post-MI VAs in general, but also to identify the precise molecular mechanisms and novel pathways resulting in their suppression so that they may be specifically targeted. There is a definite need for new therapies because a significant percentage of post-MI survivors continue to develop VAs resulting in SCD or "final" death despite optimal therapy including reperfusion [4, 7].

The electrical mechanisms of post-MI VAs have been extensively studied in experimental models since the 1980s. The traditional concept for VA induction in both MI and non-MI hearts has revolved around reentry, triggers and substrates [8–12]. Most cardiology students are familiar with the simple form of re-entry due to an anatomic obstacle described by Mines in 1913, and the classic Schmitt-Erlanger model of unidirectional block and re-entry proposed in 1929. However, MI is rather unique in that it results in variable degrees of regional remodeling of myocardial structure, matrix, morphology, topography and electrophysiological

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properties including ionic, metabolic and electrical (Fig. 1). The marked regional heterogeneity and anisotropy promotes the vulnerable substrate for re-entry. As expected, because of the dynamic nature of the evolving MI and remodeling processes, and different degrees of heterogeneity and ischemia/reperfusion, the substrate and mechanism of VT/VF and VA differ between acute, subacute, chronic and remote MI. In a simple construct, increased automaticity in impaired but ischemia-resistant His-Purkinje fibers and focal re-excitation, due to current flowing between myocardial fibers, result in ectopic repolarizations and triggered activity in areas of ischemia and lead to VAs during acute MI [12]. In contrast, impaired regional excitability and conductivity of ischemic zones and infarct borders (containing islands of ischemic tissue especially after coronary reperfusion), and patches of scar tissue during the subacute healing/repair phase offer the fertile arrhythmogenic substrate for reentry and sustained VA [12 for review]. Studies suggest that the dominant mechanism for VA is re-entry in ischemia and triggered activity in reperfusion [12]. Of note, experimental studies in the 1980s established that post-MI bradycardia triggers PVCs and VT/VF in the dog model, suggesting the need for aggressive prevention and treatment of bradyarrythmias. Intramural re-entry leading to sustained rapid VT can result in circulatory collapse and shock due to just ionic and electrical remodeling [10, 12]. Polymorphic VT that degenerates into VF can lead to SCD or "final" death. The highest risk for SCDs is during the first 30 days after MI [5].

The clinical management of MI and associated VAs has evolved dramatically since the 1980s [12–14]. Although early myocardial reperfusion reduces early mortality from VAs with sustained VT/VF and SCD [12], reperfusion itself results in profound electrophysiological remodeling with increased VT/VF depending on the duration of prior ischemia [11] and various modulators of arrhythmogenesis (Fig. 1). Additionally, late reperfusion is associated with reperfusion damage, necrosis, and structural and matrix remodeling [15] that may lead to VAs, and late presenters after acute MI remain at increased

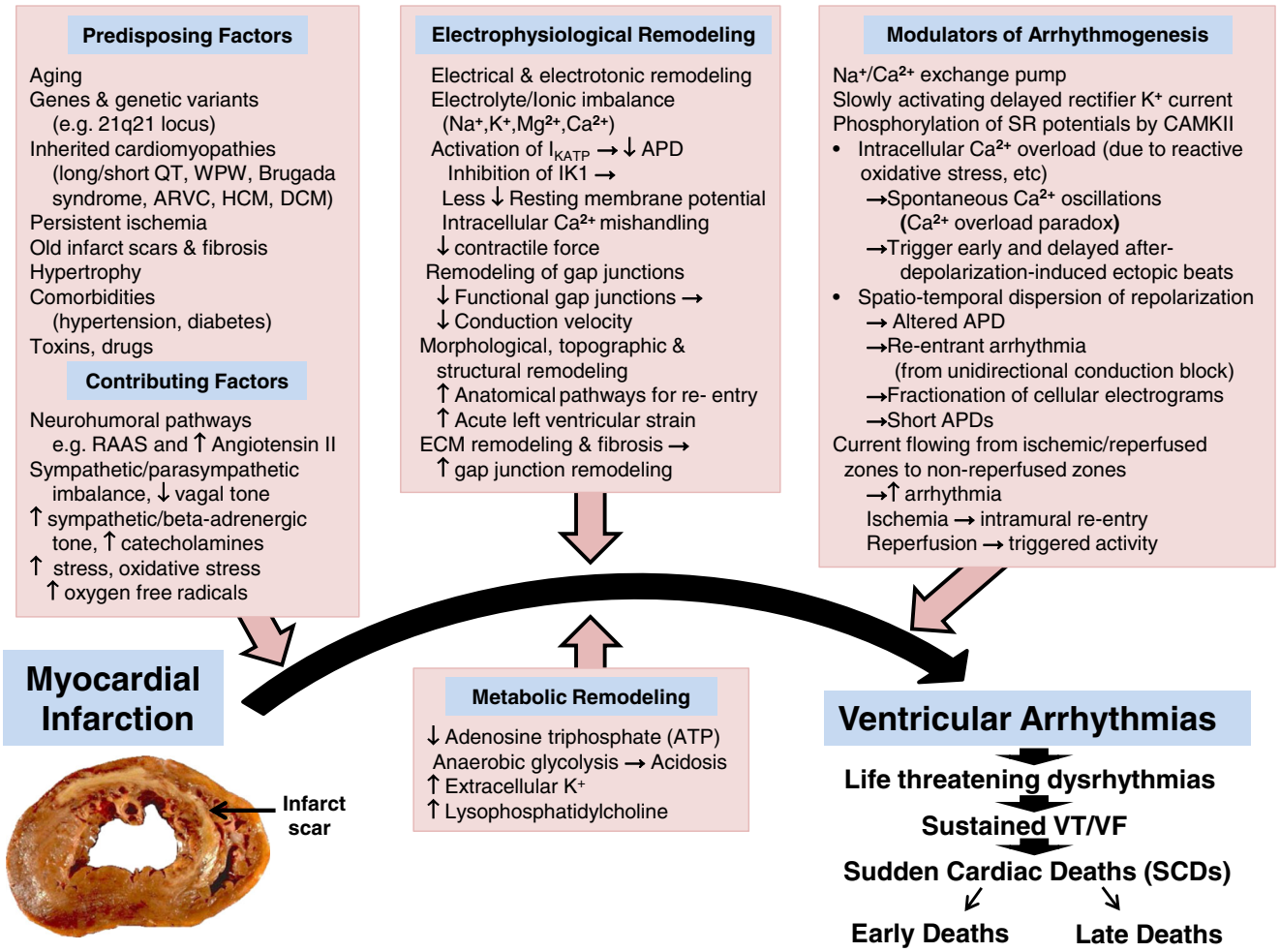

Fig. 1 Factors in genesis of ventricular arrhythmias after myocardial infarction. ↑, increase; ↓, decrease; *APD* action potential duration; *ARVC* arrhythmogenic right ventricular cardiomyopathy; *CAMKII* calcium and calmodulin-dependent protein kinase 2; *DCM* dilated cardiomyopathy; *ECM* extracellular matrix; *SR* sarcoplasmic reticulum; *HCM* hypertrophic cardiomyopathy; *WPW* Wolf-Parkinson-White syndrome. Other abbreviations as in text

risk of VA. Despite thrombolytic therapy in an early reperfusion trial [16], sustained VT/VF impacted negatively on outcome at 1 year; 30-day VT/VF mortality was 44.5 % and 1-year VT/VF mortality was 48.4 %, while 1-year mortality of 30-day survivors was 7.1 % [16]. Although revascularization procedures, infarct-limiting and anti-remodeling therapies, and beta-blockers have contributed to lower the incidence of sustained VAs within the first 48 h of MI, randomized trial data show that sustained VAs still develop in about 6 % of patients during that interval [12]. VT/VF occurs in ~6 % patients undergoing primary percutaneous coronary intervention and was associated with 3-fold higher 90-day mortality, and the risk was higher late than early VT/VF [12]. Antiarrhythmic drugs (AADs) in acute MI remain controversial and their use for prophylaxis has been discouraged [12]. In the dog model, the defibrillation threshold is higher for spontaneous VF than PES-induced VF in acute MI hearts with or without reperfusion, underscoring the different metabolic or pathologic derangements in causation that need to be considered in assessing AAD therapies and designing of ICDs to control VT/VF [17].

Since the 1980s, evidence has been trickling in concerning the contributions of infarct size, infarct expansion and both infarct and structural ventricular remodeling in the acute MI phase, and further remodeling during the subsequent subacute healing/repair and chronic phases to VAs [18]. During infarct healing, focal fibrosis can either block or delay conduction; in infarct centers where damage is more homogeneous, block dominates whereas in infarct borders where damage is patchy, fibrosis widens the separation between muscle bundles and provides new, stable, anatomical channels for reentry circuits and monophasic VT given the appropriate trigger, such as sinus rate change (bradycardia or tachycardia) or PVCs. Reperfused infarcts have more patchy infarct centers and borders and spared epicardial rims, providing potentially more tracts for reentry, thereby increasing the risk for VT/VF. Infarct-limiting therapies that salvage epicardial rims may buttress against remodeling but provide the vulnerable substrate for reentry and VT/VF. Studies suggest that increased anisotropy in the epicardial border zone of healing canine infarcts contribute to reentrant circuits and VT by slowing transverse conduction due to decreased side-to-side coupling between myocytes independent of connexin43 gap junctional protein expression [19]. Post-MI survivors remain at risk for monophasic VT, but this risk (or that of sustained spontaneous or inducible VT) has decreased in those receiving recommended therapies, including AT_1R antagonists or ARBs as well as ICDs for recurrent VT and catheter ablation in those refractory to AADs. However, the 5-year mortality risk is still significant, and the risk remains high in patients with large MIs or unsuccessfully reperfused MIs.

Studies of molecular correlates of potassium current remodeling underscored the multiple cellular and molecular mechanisms underlying the downregulation of potassium currents in failing hearts [10]. For example in the rapid-pacing-induced heart failure rabbit model, reduced inward-rectifier K^+ (IK1) current occurs without decrease in Kir2.1 mRNA level, implying that the reduced current results from post-translational modification of the channel protein [10]. In the rapid-pacing-induced heart failure dog model, moderate myocardial dysfunction was associated with significant electrophysiological abnormalities and VF, but no changes in myocardial cell morphology or intercellular connections, or expression of gap junction proteins connexin43 and connexin45, suggesting a dominant functional abnormality in cell-to-cell communication [20]. In the isolated perfused dog heart, spatiotemporal resolution mapping of optical transmembrane potentials detected erupting rotors that emit reentrant waves during early VF, and "evolved" or deteriorated into a pattern lacking the spatiotemporal features of epicardial rotors [21]. Whether such mapping may capture chaotic impulse propagation in the heterogeneous substrate of MIs and transition to more chaotic VT/VF and contribute to discovery and development of new therapies for post-MI VAs needs study.

Various mechanisms for the suppression of post-MI VAs by RAAS blockade including AT_1R antagonists such as valsartan have been postulated (Fig. 2). Increased AngII after MI and the arrhythmogenic effect of AngII acting via AT_1R are well documented [6, 22–24]. The postulated mechanisms have centered around limitations of infarct size, adverse post-MI infarct zone and structural LV remodeling [6, 18, 24] and electrical remodeling [1–7]. Recent experimental studies with valsartan post MI documented decreased AT_1R expression, decreased fibrosis and restored connexin43 in the border zone and reduced PES-induced VAs [25], and reduced transmural dispersion of repolarization and electrical heterogeneity with preserved the density of the outward potassium current (Ito) [26]. In this issue of Cardiovascular Drugs and Therapyl, Li et al. explored the effect of valsartan on the suppression of casein kinase 2 (CK2) and remodeling of the inward rectifier potassium current (IK1) via Kir2.1 protein after MI in the rat model [27]. They treated young Wistar rats with valsartan or saline for 7 days between day 1 and day 8 after MI, and used standard Western blot and PCR techniques to measure regional myocardial CK2 and Kir2.1 protein and mRNA levels, respectively. They also overexpressed CK2 in neonatal rat ventricular myocytes by transfection using the H9c2 rat embryonic ventricle cell line. They performed 6 sets of experiments in logical sequence and report 6 main findings. First, increased CK2 expression in the infarct border was associated with reduced IK1/Kir2.1 protein levels. Second, CK2 overexpression suppressed the KCNJ2/Kir2.1 expression. Third, CK2 inhibition enhanced KCNJ2/Kir2.1 expression. Fourth, compared to saline controls in vivo, valsartan reduced CK2 and increased Kir2.1 expression post MI. Fifth, hypoxia increased CK2 expression whereas valsartan inhibited CK2

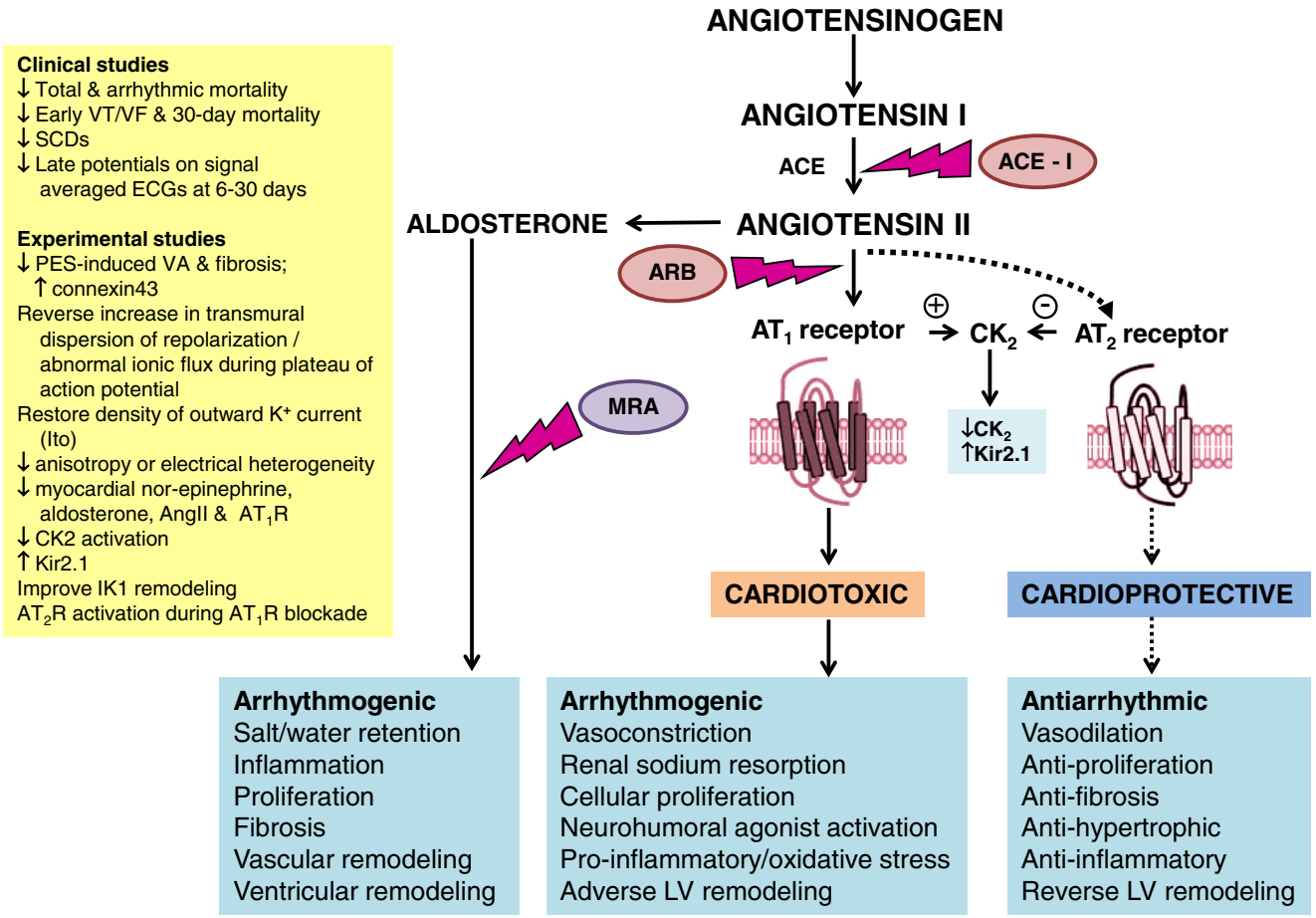

Fig. 2 Mechanisms of suppression ventricular arrhythmias after myocardial infarction by AT_1R blockade and other RAAS antagonists. Enzymatic cascades and key receptor activation pathways in the RAAS with the proposed new AT_2R/CK2/Kir2.1 pathway. ↑, increase; ↓, decrease; *ACE* angiotensin-converting enzyme; *ACE-I* ACE-inhibitor; *Ang* angiotensin; *AT_1R and AT_2R* Ang-II type 1 and type 2 receptor, respectively; *ARB* angiotensin receptor blocker; *MRA* mineralocorticoid receptor antagonist. Other abbreviations as in text

expression in vitro. Sixth, CK2 overexpression in valsartan-treated neonatal rat ventricular myocytes abolished its beneficial effect on KCNJ2/Kir2.1 in those cells. Together, these findings suggested that valsartan reduces CK2 activation, increases Kir2.1 expression and modifies IK1 remodeling after MI in the rat model.

The new finding that AT_1R blockade after MI may contribute to reduced susceptibility to VAs during the healing/repair phase by modulation of IK1 remodeling via the CK2/Kir2.1 pathway in that study [27] has at least six important implications. First, it provides supportive and incremental data on the important topic of modification of electrical remodeling and suppression of VAs after MI by AT_1R blockade. Second, it endorses the idea of an arrythmogenic effect of increased AngII during healing after MI. Third, it provides an additional explanation and new molecular mechanism for the beneficial effect of AT_1R blockade on reducing susceptibility to VAs during healing after MI. Fourth, it supports the use of AT_1R blocker therapy for suppressing post-MI VAs after MI and improve survival with a favorable outcome. Fifth, the CK2/Kir2.1 pathway per se may provide a potential therapeutic target for suppressing post-MI VAs. Sixth, the discovery of this new molecular mechanism of arrhythmia suppression after MI involving the RAAS underscores the need for research into other molecular mechanisms and potential targets.

The mechanism for the AT_1R blocker induced inhibition of CK2 expression deserves comment. It is known that AT_2R plays a counterregulatory role opposing AT_1R functions, as in the case of enhanced vasodilation via unopposed AT_2R activation and downstream AT_2-mediated signaling [28]. A recent editorial suggested that CK2 may be activated by AT_1R and inactivated by AT_2R-activated SHP-1 [29] in the context of Rho inhibition via AT_2R resulting in vasodilation [30]. Another report suggested that AngII induces CK2-α -dependent kinase activity in the context of cardiomyocyte hypertrophy [31]. Also in a hypertrophy model, AngII was shown to differentially inhibit inward rectifier K^+ (Kir) channels in coronary vascular smooth muscle cells associated with increased AT_1R but not AT_2R [32]. Here, the provocative suggestion that CK2 is activated by AT_1R and inactivated by AT_2R [27] further expands the counterregulatory role of AT_2R in AT_1R functions (Fig. 2). AT_1R blockade with unopposed or

enhanced AT_2R activation appears to have resulted in net CK2 downregulation and upregulation of Kir2.1, but evidence for this putative AT_2R/CK2/Kir2.1 signaling pathway needs study.

Every study has its limitations. Here, establishment of cause and effect still remains to be shown using genetic models as mentioned by the authors [27]. Clear demonstrations of reduced VAs in vivo need to be shown with research translation in mind. Confirmation in large animal models is also needed. Since the animals were young, confirmation in older animals is needed because significant remodeling of the RAAS and other pathways occur with aging [24] and may involve post-MI electrical remodeling as well. There is extensive evidence that significant structural remodeling occurs during the acute as well as the subacute healing/repair phase after MI depending on infarct size as well as adequacy of healing/repair. Since this study really focused on the effect of AT_1R blockade during the dynamic subacute healing/repair phase, when significant structural infarct and non-infarct remodeling are known to occur with regional infarct expansion and global LV dilation/dysfunction (dependent on infarct size), beneficial effects on infarct size and structural remodeling may have contributed to reduced electrical remodeling. However, chronic and remote post-MI phases were also not studied. Finally, measurements of KCNJ2/Kir2.1 expression were not made during the acute or subacute phases of MI on myocytes from survivors of earlier electrical remodeling. Both spatial and temporal factors should be considered in post-MI electrical remodeling.

In conclusion, the finding that AT1 blockade during the healing/repair phase after MI reduces CK2 activation, which in turn increases Kir2.1 expression and ameliorates IK1 remodeling and thereby contributes to reduced susceptibility to VAs in this study [27] is important and deserves confirmation. The AT_2R/CK2/Kir2.1 and CK2/Kir2.1 pathways may be potential therapeutic targets for suppression of VAs post-MI.

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Conflict of Interest None.

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