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Review Article

Calcium-activated Ion Currents in Heart Failure and Ischemia: Point Counter Point

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Abstract

A fundamental principle of cellular electrophysiology is that certain ionic currents are activated (i.e. controlled) by the rise in and fall of cytosolic free calcium at the inner surface of the cell membrane during action potentials and the intervals between them. Knowledge about calcium-activated currents has developed in parallel with, and has been incorporated into emerging ideas about the mechanisms of cardiac arrhythmias and sudden death in patients with heart disease. Among the earliest discoveries in this field was the recognition that calcium- activated inward current through the sodium calcium exchanger can lead to early or late after-depolarization's (EAD's and DAD's) that trigger premature beats. More recently it has been found that calcium activated outward currents are more important in the heart than initially recognized because a group of calcium activated potassium channels known as SK channels is up-regulated in the ventricles during heart failure. Finally the idea that action potential shortening, which accompanies acute myocardial infarction, is a consequence of impaired calcium sequestration during ischemia, leading to increased outward potassium current, is supported by very recent research. The manner in which these different calcium activated ion currents in the heart regulate membrane potential and can cause – or in some cases prevent – arrhythmias is reconsidered in light of new evidence.

Keywords: Heart Failure; Ion Channels; Calcium Activated Potassium Currents; Myocardial Infarction; Ventricular Fibrillation; Sudden Death; Apamin

Introduction

Well known effects of chronic heart failure include prolongation of the cardiac action potential [1] which can lead to Early After Depolarization's (EAD's). EAD's are mediated in part by repetitive openings of the voltage-dependent (L-type) calcium channel and also by the sodium/calcium exchanger, which carries three sodium ions in ward for each calcium extruded. EAD's can be distinguished from Delayed After Depolarization's (DAD's) because they do not depend on calcium overload, or abnormal calcium release (calcium sparks) and because they occur earlier – before full repolarization of the plateau is fully achieved [2]. EAD's are thought to induce non-sustained arrhythmias (torsades de pointes) in patients with heart failure, which may lead to sudden death if they initiate ventricular fibrillation [3-5]. Maneuvers that defeat the control of intracellular calcium, such as low extracellular potassium (which raises $[Na]_i$), pharmacologic inhibition of the sodium/calcium exchanger, [4,5] and mutations that reduce calsequestrin (*Casq2*$^{+/-}$) can trigger ventricular arrhythmias in the mouse or rabbit heart [6].

Causes of a prolonged action potential in the presence of heart failure include up regulation of late sodium current channels or down regulation of major potassium currents, including $I_{to,}$ IK_s, IK_r IK_1, and I_{to} [7]. Single cardiac ventricular myocytes from patients with end stage heart failure have been shown to have abnormal intracellular calcium transients with a prolonged late component that is not normally present [8,9]. These abnormalities of the calcium transient may be a consequence as well as a cause of the prolongation of the action potential.

Lengthening of the action potential and torsades de pointes can also result from mutations in the fast sodium channel (SCN5A) or in the plateau potassium channel, IK_r (KCNH2). These effects do not depend primarily on changes in $[Ca]_i$, and can occur in hearts that are not failing. Prolongation of the plateau by any of these mechanisms can lead to additional upstroke(s) of the action potential (EAD's) due to re-activation of the L-type calcium channels without full repolarization.

Artificial Protective Mechanisms

A substantial fraction of cardiac deaths are due to lethal arrhythmias, which often occur in the setting of heart failure. Experience has shown that the benefits of treatment are not limited to patients with symptoms, but can be predicted from the presence of a low ejection fraction in an otherwise asymptomatic person. Implantation of an Internal Defibrillator (AICD) produces net survival benefit when the device is recommended for every patient with a substantially reduced ejection fraction, typically defined as below 35% or 30% [10,11]. The AICD is equipped with bradycardia detection, backup pacing, and overdrive pacing features. If overdrive pacing is unsuccessful, defibrillation shocks are delivered. Successful pace termination is common, and most monomorphic ventricular tachycardias in AICD patients can be pace terminated. Sustained ventricular fibrillation requires shocks and episodes of torsade de pointes initiate shocks if of sufficient duration.

As noted above, some lethal arrhythmias occur as a result of mutant ion channels being present on a hereditary basis. These

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disorders may occur in the absence of heart failure, and the victims are frequently young, in contrast to most heart failure patients, who are elderly. In appropriately selected patients, implantation of an AICD can be lifesaving for these patients as well. However the decision to implant must take into account the specific defect that the patient has, the likelihood that drug therapy (especially beta blockade) would suffice, and the presence or absence of sudden cardiac death, or cardiac arrest in the patient, or a close family member. Finally, AICD devices with pacing capacity often perform biventricular pacing in patients with a wide QRS complex and low ejection fraction. This can lead to a decrease in ejection fraction.

What about in-born protective mechanisms?

Given the overwhelming evidence for Darwin's theory of evolution, one could ask why inborn mechanisms that eventually harm the organism aren't eliminated by natural selection. There are many constructive ways to answer this question, but one of them is that a protective mechanism may evolve in parallel with a harmful trait, and counteract it. In the case of calcium-activated arrhythmogenic currents, this appears to be the case.

Calcium activated outward currents, carried by potassium selective channels were first recognized in 1974 – now forty years ago [12,13]. Such channels were found to be widespread in the nervous system (including muscle cells and sensory receptor cells), and to mediate essential processes such as accommodation and repetitive firing. But they are not ubiquitous in cardiac tissue, where their effects were overlooked for many years.

In 1975, Gerrit Isenberg showed that intracellular injection of calcium through a glass microelectrode in sheep Purkinje fibers produced transient shortening of the action potential [14]. In a subsequent study, injection of the calcium chelating agent, EGTA, into the fiber produced transient lengthening of the action potential [15]. In the absence of knowledge to the contrary, Isenberg [15] proposed that repolarization of the cardiac action potential was, in general, due to calcium activated potassium current.

Isenberg's work was not widely acknowledged, because it soon became clear that the principal repolarizing currents, IK_r and IK_s are purely voltage dependent and are not turned on by $[Ca]_i$. However in the past few years, well-designed studies have shown that calcium regulated potassium currents do contribute to repolarization in certain cardiac tissues, and that their importance increases during heart failure [16].

There are two principal types of calcium-activated potassium channels, large conductance channels, known as BK channels, and small conductance channels, known as SK channels. The latter have three distinguishable variants, attributed to separate genes. These are SK1, SK2 and SK3. Activation of BK channels is brought about by membrane depolarization and by a rise in intracellular calcium (or either alone); whereas SK channels, especially SK2, are only activated by $[Ca^{2+}]_i$ and are insensitive to membrane potential. SK2 channels are inhibited by apamin, a biological toxin (from bee venom) which is selective for SK channels and can produce a modest lengthening of the action potential when applied to cardiac tissue that contains these channels [7]. The question of whether calcium activated potassium channels exist in the heart was decisively answered once the amino acid sequence of these channels had been determined, and it became possible to identify them through molecular techniques such as cloning and polymerase chain reaction. Such techniques have become less labor intensive than single channel recording, particularly in cardiac cells that contain many different varieties of ion channels.* In 2003-4 Dr. N. Chiamvimonvat's laboratory used these techniques to identify small conductance calcium activated potassium channels in both human and mouse hearts for the first time [16-18].

With respect to the distribution of SK channels in the mammalian heart, studies such as those above showed that in normal hearts, SK channels tend to be more prominent in the atria than in the ventricles, and they are also more prominent in conduction tissues of the heart than in working muscle [17]. The latter finding accounts for the somewhat misleading impression given by Isenberg's experiments in Purkinje fibers which suggest that intracellular Ca^{2+} might be the principal factor controlling repolarization of the entire heart. Qi et al [19] found that SK currents play a role in atrial repolarization in dogs, and are largest in the pulmonary veins. These currents are enhanced by atrial tachycardia remodeling and appear to play a role in the maintenance of atrial fibrillation.

*Patch clamp recordings often involves "ripped off" patches, where the high resistance seal (gigaseal) survives excision of the membrane patch. The cyto-plasmic surface of the membrane is then exposed to solutions of varying $[Ca^{2+}]_i$.

Perhaps the most important development in the present decade regarding SK channels in the heart has been the finding that they become up regulated in the ventricle during heart failure, both in animal models and in human tissue [7,20-23].

Studies of the mechanisms of heart failure in human tissues often involve enzymatic dissociation of surgically obtained left ventricular tissue to produce single cardiac myocytes, which are then compared in failing and non-failing ventricles. Action potentials can be recorded from such cells and whole cell voltage clamp studies can be performed as well as biochemical studies of ion channel protein. Chang et al [7] showed that apamin produced significant prolongation of the action potential in heart failure myocytes but not in non-heart failure myocytes. Moreover the SK2 protein expression was increased three-fold in the heart failure myocytes compared to control. Very similar results have been obtained in animal models of heart failure. Bonilla et al [22] found that in a canine heart failure model involving ventricular pacing, heart failure was associated with a 3-fold increase in SK2 protein, and that apamin produced a large increase in ventricular cell action potential duration, not observed in control hearts. In a companion study, marked effects on repolarization were found in chronic heart failure (4 mo.) but not short term heart failure (1 mo) [23]. These were due to a 4-fold increase in SK3. The increase in SK channels during heart failure should be reversible with alleviation of the heart failure, although this has not been shown clinically. One clinical situation where this might be tested is the use of a bi-ventricular pacemaker to improve LV performance in heart failure patients with a wide QRS complex (see above).

Based on the above information, it is clear that calcium-activated inward current, mediated by sodium calcium exchange, and SK channels, which carry outward current during the action potential,

must coexist in certain cardiac tissues and have countervailing effects on the total membrane current. These tissues include the atria and conduction system in normal hearts. SK channels (especially SK2 and SK3) may be expressed at a low level in the left ventricle of normal hearts but are increased in heart failure. Then, under appropriate conditions, even a large calcium increase event during diastole might produce no change in membrane potential in the heart failure cells. Since heart failure is a very lethal condition, a clear implication of this discussion is that there would be no ambulatory patients with heart failure and perhaps no humans if calcium-activated potassium channels had not evolved in the heart.

Quantitative measurement of calcium-activated inward currents, including cells over expressing SK_2

Early descriptions of calcium activated inward currents in cardiac tissue did not include experiments with apamin. A possible contribution of SK channels to these experiments was therefore not recognized, and the magnitude of the calcium activated inward current may have been underestimated at most clamp potentials, especially in Purkinje fibers [24]. A particularly good way to study calcium-activated inward current due to electrogenic sodium-calcium exchange cardiac cells is abrupt superfusion with 20 mM caffeine, which produces a Transient Inward current (TI) due to release of sequestered calcium from the Sarcoplasmic Reticulum (SR). This method was first demonstrated in clusters of coupled embryonic cells from the chick [25]. Use of caffeine superfusion to measure the total calcium content of the SR in adult ventricular myocytes [26,27] is probably valid due to the very low level of SK channels in these cells. However, the accuracy of this method needs to be reassessed in situations where SK channels might be up regulated. SK channels would distort the net caffeine-induced current, so that the time integral would no longer equal the amount of calcium released from the SR [26]. This has recently been confirmed in a study involving rat cardiac myocytes that over express SK2 due to up regulation of the channel with an adenovirus. In these cells, rapid superfusion with 10 mM caffeine produces an outward current through SK2 channels rather than a net inward current through sodium calcium exchange [28].

Very early embryonic ventricular cells beat spontaneously and have action potentials similar to adult sinoatrial node cells. During maturation, the action potential acquires the characteristics of adult myocardium where action potentials have a rapid upstroke, a high resting potential, and no pacemaker potential. An attractive and as yet untested explanation for this that the early embryonic cells have abundant SK channels which diminish with maturation.

A Word about Acute Ischemia and Infarction: Why does the Action Potential Shorten in Acute MI?

Acute myocardial infarction leads to shortening of the action potential in the infarct zone, as well as reduction of the resting potential. The latter is partly due to accumulation of extracellular potassium. These changes cause "in jury" currents to flow between the infracted and non-infracted tissue, which are the basis for S-T segment elevation on the electrocardiogram. The basis for shortening of the action potential is not entirely certain, but a number of investigators dating back to Isenberg [14] in 1975 have suggested that a rise in cytosolic calcium during acute ischemia initiates calcium activated potassium current that shortens the plateau. Acute ischemia has been shown by fluorescent calcium indicators to increase both the systolic and diastolic levels of $[Ca^{2+}]_I$ [29], and there are a number of other conditions that increase $[Ca^{2+}]_i$ (e.g. hypercalcemia and digitalis toxicity) which also shorten the action potential.

Recent experiments by Gui et al in the rat [30] have provided additional support for the above hypothesis and have implicated involvement of the SK channels. Myocardial infarction was produced by ligation of the left anterior descending coronary, and monophasic action potentials were measured in the infarct and non-infarct zone along with Ventricular Fibrillation (VF) thresholds. Apamin was administered prior to the infarct at several doses. There were multiple control groups including several sham operated groups and two vehicle treated groups. An additional group was given UCL 1684, an investigational compound which also blocks SK channels. Measurements were made between 20 min. and 3 hours. Biochemical measurements showed that the levels of mRNA and protein for SK1, SK2 and SK3 were identical in the sham operated and infarct hearts, meaning that there was no net synthesis or degradation of the SK proteins as a result of experimental maneuvers.

Among the findings were that infarction produced significant shortening of the action potential (APD_{90}) in the infarct zone, which was largely (and significantly) prevented by apamin and UCL1684. Importantly, apamin and UCL1684 had no significant effects on APD_{90} in the non-infarct zone or in sham operated rats. This suggests that ischemia causes activation of SK channels that do not normally contribute to ventricular repolarization, even though the three SK channels are all present and measureable, and there is no net increase in SK channel protein during the infarct. These results are consistent with the studies cited above, which state that SK channels do not contribute to ventricular repolarization in normal hearts. The VF threshold measurements showed that the ischemia-induced reduction in VF threshold was largely and significantly ameliorated by apamin and UC1684, except at the lowest apamin dose. These results are consistent with the hypothesis that Action Potential Duration (APD) shortening as a result of calcium activated SK channel current is a cause of acute ischemic ventricular fibrillation. A similar conclusion involving calcium-activated currents was reached in earlier experiments involving the ability of pretreatment with calcium channel blockers (verapamil and diltiazem) to reduce, prevent or delay the development of action potential changes and ventricular fibrillation during coronary artery occlusion in dogs [31,32]. The work of Gui et al [30] presents a more refined version of the calcium hypothesis, insofar as a specific calcium-activated channel – a potassium channel with known structure and cellular distribution-- is implicated. Ischemia also causes beat to beat fluctuations in the amplitude of cytosolic calcium transient which are associated with APD alternans [2]. APD alternans is another important arrhythmogenic mechanism that contributes to dispersion of ventricular refractoriness. The phenomenon of APD alternans has not been specifically related to SK channel activity and is thought to be caused by fluctuations in electrogenic sodium calcium exchange [33-35].

It should be noted that if the conclusions of Gui et al [30] are correct, then the effect of the SK channels in acute infarction is

harmful (i.e. proarrhythmic, making apamin an antiarrhythmic) whereas in heart failure, the effect of the SK channels seems to be beneficial (antiarrhythmic). Further work is needed to determine why or how SK channels could be functionally "up-regulated" during ischemia with no increase in channel protein synthesis. This emerging information about SK channels reminds one of the early days of clinical research with calcium channel blockers. Calcium channel blockers were once viewed as drugs that might reduce mortality in coronary patients based on their anti-fibrillatory action in experimental coronary occlusion [32]. Appropriate clinical studies showed that these drugs could reduce mortality and reinfarction in patients without pulmonary congestion, but increased these adverse outcomes in patients with pulmonary congestion. A similar pattern was observed with respect to ejection fraction [36]. There was no net survival benefit [36,37]. It would now be equally premature to conclude that large numbers of people would benefit from having more SK channels in their heart, and that methods to achieve this should be developed.

Conclusion

It has now been forty years since the hypothesis was put forward that potassium ion channels activated by cytosolic free calcium play a role in repolarization of the cardiac action potential, as they do in the nervous system. Molecular biological research, together with use of the patch clamp technique and an appropriate toxin (apamin) have shown that small conductance calcium activated potassium channels (SK channels) normally contribute to repolarization in mammalian atria and the conduction system. These channels may also contribute to and alter ventricular repolarization in the important widespread disease states of heart failure and acute myocardial infarction. They also appear to be involved in the maintenance of atrial fibrillation. Activation of SK channels counteracts the arrhythmogenic effects of abnormal calcium release, which produces depolarizing inward current via the sodium calcium exchange. This could have beneficial effects in heart failure, where the SK channels become up-regulated due to increased synthesis. In contrast, early studies suggest that a functional up-regulation of SK channels during myocardial infarction may be responsible for the shortening of the ventricular action potential, which is one of the mechanisms responsible for dispersion of refractoriness and vulnerability to ventricular fibrillation. It is too early to decide whether a molecular or stem cell approach that caused patients to synthesize more SK channels in their cardiac ventricles would have a net positive effect on survival.

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References

1. Beuckelmann, DJ, Nabauer M, Erdmann E. Alterations of K+ currents in isolated human ventricular myocytes from patients with terminal heart failure. Circ. Res. 1993; 73: 379-385.
2. Clusin WT. Calcium and cardiac arrhythmias: DADs, EADs, and alternans. Crit Rev Clin Lab Sci. 2003; 40: 337-375.
3. Middlekauff HR, Stevenson WG, Saxon LA, Stevenson LW. Amiodarone and torsades de pointes in patients with advanced heart failure. Am J Cardiol. 1995; 76: 499-502.
4. Milberg P, Pott C, Frommeyer G, Fink M, Ruhe M, Matsuda T, et al. Acute inhibition of the Na(+)/Ca(2+) exchanger reduces proarrhythmia in an experimental model of chronic heart failure. Heart Rhythm. 2012; 9: 570-578.
5. Clusin WT. Role of sodium/calcium exchange in heart failure-induced arrhythmias: a potential therapeutic target. Heart Rhythm. 2012; 9: 579-580.
6. Chopra N, Kannankeril PJ, Yang T, Hlaing T, Holinstat I, Ettensohn K, et al. Modest reductions of cardiac calsequestrin increase sarcoplasmic reticulum Ca2+ leak independent of luminal Ca2+ and trigger ventricular arrhythmias in mice. Circ Res. 2007; 101: 617-626.
7. Chang PC, Turker I, Lopshire JC, Masroor S, Nguyen BL, Tao W, et al. Heterogeneous upregulation of apamin-sensitive potassium currents in failing human ventricles. J Am Heart Assoc. 2013; 2: e004713.
8. Gwathmey JK, Copelas L, MacKinnon R, Schoen FJ, Feldman MD, Grossman W, et al. Abnormal intracellular calcium handling in myocardium from patients with end-stage heart failure. Circ Res. 1987; 61: 70-76.
9. Gwathmey JK, Bentivegna LA, Ransil BJ, Grossman W, Morgan JP. Relationship of abnormal intracellular calcium mobilisation to myocyte hypertrophy in human ventricular myocardium. Cardiovasc Res. 1993; 27: 199-203.
10. Tracy CM, Epstein AE, Darbar D, Dimarco JP, Dunbar SB, Estes NA 3rd, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2012; 60: 1297-1313.
11. Clusin W, Spray DC, Bennett MV. Activation of a voltage-insensitive conductance by inward calcium current. Nature. 1975; 256: 425-427.
12. Meech RW. Calcium-dependent potassium activation in nervous tissues. Annu Rev Biophys Bioeng. 1978; 7: 1-18.
13. Berkefeld H, Fakler B, Schulte U. Ca2+-activated K+ channels: from protein complexes to function. Physiol Rev. 2010; 90: 1437-1459.
14. Isnberg G. Is potassium conductance of cardiac Purkinje fibres controlled by (Ca2+)? Nature. 1975; 253: 273-274.
15. Isenberg G. Cardiac Purkinje fibres: [Ca2+]i controls steady state potassium conductance. Pflugers Arch. 1977; 371: 71-76.
16. Xu Y, Tuteja D, Zhang Z, Xu D, Zhang Y, Rodriguez J, et al. Molecular identification and functional roles of a Ca(2+)-activated K+ channel in human and mouse hearts. J Biol Chem. 2003; 278: 49085-49094.
17. Tuteja D, Xu D, Timofeyev V, Lu L, Sharma D, Zhang Z, et al. Differential expression of small-conductance Ca2+-activated K+ channels SK, SK2, and SK3 in mouse atrial and ventricular myocytes. Am J Physiol Heart Circ Physiol. 2005; 289: H2714-2723.
18. Zhang Q, Timofeyev V, Lu L, Li N, Singapuri A, Long MK, et al. Functional roles of a Ca2+-activated K+ channel in atrioventricular nodes. Circ Res. 2008; 102: 465-471.
19. Qi XY, Diness JG, Brundel BJ, Zhou XB, Naud P, Wu CT, et al. Role of small-conductance calcium-activated potassium channels in atrial electrophysiology and fibrillation in the dog. Circulation. 2014; 129: 430-440.
20. Chang PC, Hsieh YC, Hsueh CH, Weiss JN, Lin SF, Chen PS. Apamin induces early afterde-polarizations and torsades de pointes ventriculary arrhythmia from failing rabbit ventricles exhibiting secondary rises in intracellular calcium. Heart Rhythm. 2013; 10: 1516-1524.
21. Hsieh YC, Chang PC, Hsueh CH, Lee YS, Shen C, Weiss JN, et al. Apamin-sensitive potassium current modulates action potential duration restitution and arrhythmogenesis of failing rabbit ventricles. Circ Arrhythm Electrophysiol. 2013; 6: 410-418.
22. Bonilla IM, Long VL, Vargas-Pinto P, Green J, Yoo J, Allen D, et al.

Calcium-activated potassium current modulates ventricular (but not atrial) repolarization in chronic heart failure. Circulation AHA Meeting Abstracts: Ion channels and cell function. 2013; 126: A16846.

23. Bonilla IM, Long VP, Wright P, Mowrey K, Green J, Vargas-Pinto AP, et al. IKca current contributes to ventricular repolarization during chronic, not short term, heart failure. Circulation AHA Meeting Abstacts: Ion channels and cell function. 2013; A16746.

24. Kass RS, Lederer WJ, Tsien RW, Weingart R. Role of calcium ions in transient inward currents and aftercontractions induced by strophanthidin in cardiac Purkinje fibres. J Physiol. 1978; 281: 187-208.

25. Clusin WT. Caffeine induces a transient inward current in cultured cardiac cells. Nature. 1983; 301: 248-250.

26. Venetucci L, Trafford AW, Eisner DA. Illuminating sarcoplasmic reticulum calcium. Circ Res. 2003; 93: 4-5.

27. Schlotthauer K, Bers DM. Sarcoplasmic reticulum Ca(2+) release causes myocyte depolarization. Underlying mechanism and threshold for triggered action potentials. Circ Res. 2000; 87: 774-780.

28. Terentyev D, Rochira JA, Terentyeva R, Roder K, Koren G, Li W. Sarcoplasmic reticulum Ca^{2+} release is both necessary and sufficient for SK channel activation in ventricular myocytes. Am J Physiol Heart Circ Physiol. 2014; 306: H738-746.

29. Lee HC, Mohabir R, Smith N, Franz MR, Clusin WT. Effect of ischemia on calcium-dependent fluorescence transients in rabbit hearts containing indo 1. Correlation with monophasic action potentials and contraction. Circulation. 1988; 78: 1047-1059.

30. Gui L, Bao Z, Jia Y, Qin X, Cheng ZJ, Zhu J, et al. Ventricular tachyarrhythmias in rats with acute myocardial infarction involves activation of small-conductance Ca2+-activated K+ channels. Am J Physiol Heart Circ Physiol. 2013; 304: H118-130.

31. Muller CA, Opie LH, McCarthy J, Hofmann D, Pineda CA, Peisach M. Effects of mibefradil, a novel calcium channel blocking agent with T-type activity, in acute myocardial ischemia: Maintenance of ventricular fibrillation threshold without ionotropic compromise. J Am Coll Cardiol. 1998; 32: 268-274.

32. Clusin WT, Anderson ME. Calcium channel blockers: current controversies and basic mechanisms of action. Adv Pharmacol. 1999; 46: 253-296.

33. Qian YW, Clusin WT, Lin SF, Han J, Sung RJ. Spatial heterogeneity of calcium transient alternans during the early phase of myocardial ischemia in the blood-perfused rabbit heart. Circulation. 2001; 104: 2082-2087.

34. Qian YW, Sung RJ, Lin SF, Province R, Clusin WT. Spatial heterogeneity of action potential alternans during global ischemia in the rabbit heart. Am J Physiol Heart Circ Physiol. 2003; 285: H2722-2733.

35. Goldhaber JI, Xie LH, Duong T, Motter C, Khuu K, Weiss JN. Action potential duration restitution and alternans in rabbit ventricular myocytes: the key role of intracellular calcium cycling. Circ Res. 2005; 96: 459-466.

36. The effect of diltiazem on mortality and reinfarction after myocardial infarction. The Multicenter Diltiazem Postinfarction Trial Research Group. N Engl J Med. 1988; 319: 385-392.

37. The Danish study group on verapamil in myocardial infarction. Effect of verapamil on mortality and major events after acute myocardial infarction (The Danish Verapamil Infarction Trial II – DAVIT II).Am. J. Cardiol. 1990; 66: 779-785.

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