A phenomenon that has fostered much experimental investigation and theoretical speculation is “gain” in cardiac E-C coupling. So-called “macroscopic” or “whole-cell” gain may be defined as the ratio of the total flux through the SR Ca²⁺ release channels (RyR) to that through the L-type Ca²⁺ channels (LCC). Experimentally, gain was found early on to be relatively high, and this observation, together with the seemingly incompatible fact that Ca²⁺-induced Ca²⁺ release (CICR) is normally tightly controlled in cardiac muscle, led to the development of the modern understanding of cardiac E-C coupling, the “local control” theory. Gain reflects not only the operation of the fundamental processes that underlie normal E-C coupling, but also those involved in important pathological conditions of the heart, particularly those produced by uncontrolled SR Ca²⁺ release, such as triggered arrhythmias.¹

In the heart, it can be said that “not all Ca²⁺ currents (i_Ca) are created equal”; i_Ca at negative potentials is much more efficacious in triggering SR Ca²⁺ release than is equivalent (peak) i_Ca at positive potentials. Therefore, gain decreases as activating voltage is made more positive. The conventional and widely accepted explanation of this phenomenon is based on the voltage-dependence of the single-channel (unitary) Ca²⁺ current (i_Ca), and was stated succinctly by Stern and his colleagues,² “gain decreases with voltage because the efficacy of the L-type current to trigger release from the RyR depends on the unitary current of the L-type channel, which decreases as the calcium reversal potential is approached”. Indeed this is a cornerstone of the local control theory of cardiac E-C coupling. However, early on it had been recognized³ (also by Stern) that “the discrepancy between these two curves (Ca²⁺ current and SR Ca²⁺ release) is actually a clue to the fact that the number of sarcoplasmic channels activated, on the one hand, and the magnitude of their unitary current, on the other, play fundamentally different roles in controlling calcium release...”. In this issue of Circulation Research, 15 years later, Altamirano and Bers⁴ report real progress in defining experimentally for the first time the different roles of these 2 factors, the number of L-type Ca²⁺ channels activated (N*P_n), and the magnitude of the Ca²⁺ current through each (i_Ca). In the process, they have overturned the conventionally held notion about the origin of macroscopic “gain”, and have shown that E-C coupling, under physiological conditions, is dominated by different rules than just those that are known to govern the isolated interaction of a single L-type Ca²⁺ channel and nearby SR Ca²⁺ release channels. When it comes to macroscopic gain of cardiac E-C coupling, it turns out that having neighbors, at least of the L-type Ca²⁺ channel variety, makes a big difference.

The conceptual framework of cardiac E-C coupling has been well established by numerous studies; Ca²⁺ release through ryanodine receptors (RyR) at individual cardiac dyads (viz a Ca²⁺ “spark”) is triggered locally, via Ca²⁺-induced Ca²⁺ release, specifically by the Ca²⁺ that have entered the cell through a single, coassociated L-type Ca²⁺ channel (LCC).⁵ An unknown number, but several at least, RyR become activated, perhaps in “concerted” fashion. The control of SR Ca²⁺ release is thus exerted in the subspace between LCC and RyR, and in the crystal-lattice array of RyR. The whole cell Ca²⁺ transient that activates contraction arises from the spatial and temporal summation of individual Ca²⁺ sparks that have diffused outward to fill the cytoplasm. The whole cell Ca²⁺ current is given by the well known equation: i_Ca = N*P_n*i_Ca. Until now, experimental examination of the details of Ca²⁺ release triggering by L-type Ca²⁺ channels has almost invariably involved using conditions in which the number of active LCCs (N*P_n) was markedly reduced, through the use of Ca²⁺ channel antagonists (reduce N), or by working at the foot of the channel voltage-activation curve (where P_n is small). This is necessary as a practical expedient, as it vastly reduces the number of Ca²⁺ sparks that are elicited by depolarization, and makes accurate counting of Ca²⁺ sparks possible. Most importantly, it also makes tractable the analysis of the relationship between unitary Ca²⁺ current and Ca²⁺ sparks because it creates a situation in which the total Ca²⁺ current at a given dyad is only i_Ca. These conditions are ideal, and necessary for examining the rules of the intermolecular interaction between a single LCC and the RyR. These conditions preclude observation of any effect that the number of active channels might have on E-C coupling or gain. Under these conditions, several phenomena have been established. First, the probability of triggering a Ca²⁺ spark (designated P_n) has been found to vary proportionally to the square of the amplitude of the unitary Ca²⁺ current (i_Ca).⁷ This is a highly satisfying result that is consonant with the known dynamics of [Ca²⁺] in the subspace near an open channel and the Ca²⁺-dependence of RyR activation⁸ (its likely that 2 Ca²⁺ are required to activate a RyR and initiate Ca²⁺ release). Also under these same conditions, all available studies suggest that

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¹ The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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Theoretical dependence of macroscopic cardiac E-C coupling gain on \( I_{Ca} \) and number (N) of L-type Ca\(^{2+}\) channels in a dyadic junction. The probability of SR Ca\(^{2+}\) release, in the form of a single Ca\(^{2+}\) spark, at a single cardiac dyadic junction as a result of L-type Ca\(^{2+}\) current is calculated. The junction is assumed to consist of a cluster of L-type Ca\(^{2+}\) channels (LCC; of number, \( N \)), and a large number of associated RyR. Ca\(^{2+}\) current \( (I_{Ca}) \) is given by: \( I_{Ca} = N \times P_o \times I_{Ca} \), where \( P_o \) is the open probability of the LCC, and \( I_{Ca} \) is the unitary LCC current. Activation of an individual RyR is assumed to be proportional to subspace \( [Ca^{2+}]_i \) and thus also to \( (I_{Ca})^2 \), similar to experimental results\(^2\) in which spark probability, \( P_s \), was found to be proportional to \( (I_{Ca})^2 \) when \( N \) was reduced to low levels through the use of nifedipine. The range of \( I_{Ca} \) shown is below that at which maximal probability of RyR activation would be achieved, and where deviation from the power function would occur. (A) Probability (P) that a given junction \( (j) \) will be active is calculated as a function of \( I_{Ca} \), in arbitrary units. See text for details. "Active" means that SR Ca\(^{2+}\) release occurs, in the form of one and only Ca\(^{2+}\) spark, in response to current flow through the LCC. Thin solid line gives \( P_j \) as a function of \( I_{Ca} \) for the case in which the cluster contains 1 LCC \((N = 1)\) that is certain to open \((P_o = 1)\). Thick solid line gives \( P_j \) for the case in which the cluster contains 12 LCC, all of which are certain to open. Dashed line is an intermediate case which gives \( P_j \) for the cases in which \( N \) is changed through the use of different holding potentials, before a standard activating pulse. The relationship between magnitude of \( I_{Ca} \) and SR Ca\(^{2+}\) release, as given by the fraction of active dyads, \( P_j \), is always proportional to \( (I_{Ca})^2 \), similar to experimental results\(^7\) and, as shown earlier,\(^7\) and, to conventional expectation. Whether \( I_{Ca} \) was changed through the use of driving force or changed external \([Ca^{2+}]_o\), the macroscopic gain (active junctions/\( I_{Ca} \)), decreased as \( I_{Ca} \) increased.

The question should be asked: How is it possible that the probability of an active junction (ie, one that produces a spark), is in fact proportional to \( (I_{Ca})^2 \), as shown earlier,\(^7\) and, at the same time, that increasing \( I_{Ca} \) actually decreases macroscopic gain? Consideration of the simple statistics of spark production in a dyad provides some insight to this question. Assume the "rules" of the isolated LCC-RyR interaction as given above,
Ca\(^{2+}\) influx through one LCC can trigger a spark after 2 Ca\(^{2+}\) bind to an RyR, and only 1 spark can be triggered at a dyad. Subspace [Ca\(^{2+}\)] is proportional to \(i_{Ca}\). When one LCC is open (\(n=1.0\), \(P_o=1.0\)), the probability of an active junction is proportional to \((i_{Ca})^2\) (thin line, Figure, A), in agreement with experimental data. Note that for RyR activation, and hence spark production rate to be proportional to \((i_{Ca})^2\), the subspace [Ca\(^{2+}\)] (proportional to \(i_{Ca}\)) must be well below the \(K_0\) for the binding of 2 Ca\(^{2+}\). Hence the maximum probability considered is 0.5. Now assume that a dyadic junction contains 12 LCC, and that depolarization to 0 mV opens all of them (\(n=12\), \(P_o=1.0\)). This describes a hypothetical case in which all LCC of the dyadic junction are open at the peak \(I_{Ca}\). The probability of the junction being active (\(P_J\)), or producing a spark, is calculated as: \(P_J=1.0-(1.0-P_o)^{N*P_o}\), (where \(P_o=i_{Ca}\)), as above. The quantity, \((1.0 - P_o)\), is the probability that a spark will not be triggered by the opening of a particular LCC. When raised to the power, \(N*P_o\), it is the probability that no spark will be produced when \(N*P_o\) channels are open. This is then subtracted from 1.0 to obtain the probability that the junction will be active. In the case of more than 1 open LCC at peak \(I_{Ca}\) of a junction, the probability of the junction producing a spark is much higher than when only 1 LCC is open. “Macroscopic” gain (Figure, B) is calculated as \(P_J/I_{Ca}\), where \(I_{Ca}=N*P_o*i_{Ca}\). Gain is linearly related to \(i_{Ca}\) for the single open LCC, as expected (thin line, Figure, B). In qualitative agreement with the new data of Altamirano and Bers, gain at a given \(i_{Ca}\) is reduced when \(N\) is increased, and most significantly, gain can decrease when \(i_{Ca}\) increases (over the appropriate range of \(i_{Ca}\)), even though \(P_o\) is proportional to \((i_{Ca})^2\) for all \(i_{Ca}\) (The decrease in gain is most evident with the larger \(N\), and occurs at a lower \(i_{Ca}\)).

In summary, Altamirano and Bers have certainly disproved any idea that the characteristics of macroscopic gain derive entirely from the voltage-dependence of the the unitary Ca\(^{2+}\) channel current. Macroscopic gain is clearly influenced by the number of active channels in the cluster, in ways not appreciated fully before. Nevertheless, the experimental results are not inconsistent with the previous findings that the probability of triggering a Ca\(^{2+}\) spark is a function of the unitary Ca\(^{2+}\) current. Thus, the “local control” theory of cardiac E-C coupling\(^6\) remains intact, but we do have a new, quite different, explanation for the phenomenon of macroscopic gain.

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References


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