what is currently known of these variables, Monte Verde would imply an arrival in the New World before 20,000 years ago.

This, in turn, raises the question of why traces of the initial migrants have not proven more evident in North America, through which they must have passed en route to South America. There are hints of an early presence, but agreement has not been reached on these sites, and none have been as thoroughly documented as Monte Verde. Importantly, the acceptance of Monte Verde and its demonstration of a deeper antiquity in the Americas is not warrant to accept previously rejected pre-Clovis claims from the Americas. If a site was not old before Monte Verde, it will not become any older because of Monte Verde. Meadowcroft Rockshelter (Pennsylvania), with human occupations apparently from more than 14,250 years ago (9), may prove the exception to that rule (3).

That more traces of early peoples have yet to be found raises the possibility that the initial migrants were so few and widely scattered they were for a considerable time archaeologically invisible (*10*). It also suggests that archaeologists may not have looked in the right places or in the right way for potentially early sites (*11*). But if history is a guide, more early sites will soon emerge, as they did on the heels of the Folsom (New Mexico) discovery in 1927, which first proved humans had arrived in the Pleistocene (*12*). Discoveries such as these yield important leads in the search for other sites, which in turn help fill in the archaeological details of the colonization process. Those details will be of considerable general interest in understanding migration, adaptation, and population dynamics (*13*), as this case is one of the few instances in which fully modern humans radiated into a previously uninhabited continent.

Monte Verde's acceptance will also reverberate beyond American archaeology. Geneticists and linguists have actively sought, through analysis of modern Native American populations, clues to the number, timing, and antiquity of migratory pulses into the Americas (*14*). The Monte Verde evidence may ultimately help refine the currently varied mitochondrial DNA mutation rates used in molecular clocks (*15*). It also raises questions about the number of populations in the New World at the end of the Pleistocene, such as whether the groups at Monte Verde and Clovis represent the same or separate migratory pulses. Resolving these questions will have implications for our understanding of the diversity of the founding population (or populations) and the debate over the phylogenetic history of contemporary Native American populations (*16*).

Some 70 m away from the 12,500-year-old deposits, Dillehay's team recovered traces of a separate occupation that appears to date to >33,000 years before present. Dillehay (*1*) remains noncommittal about those materials. He feels further excavations are required to confirm this occupation. If confirmed, its implications will be even more profound. Until then, however, those interested in the peopling of the Americas have plenty to occupy themselves, in the effort to fully explore the ramifications of the 12,500-year-old occupation at the site.

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MEDICINE

Quenching the Spark in the Heart

David T. Yue

The human heart is a marvel of inspired engineering that faithfully supplies blood to the body by contracting over 3 billion times in a lifetime. Most of us blissfully ignore its smooth functioning until this biological pump begins to fail, with lethal consequences apparent in any intensive-care unit. What goes wrong in heart failure remains unclear, in part because there are so many potential problem spots in heart excitation-contraction (EC) coupling—the complex choreography of Ca^{2+} signaling and chemomechanical transduction that underlies each heart beat. On page 800 of this issue, Gómez *et al.* (*1*) use high-resolution, intracellular Ca^{2+}-imaging techniques to reveal that much of the problem resides at a single step in the EC coupling of hypertrophied and failing hearts. This discovery promises to simplify understanding of heart dysfunction. But the result is all the more satisfying because the nature of the defect would not have been recognized without insight from fundamental studies of EC coupling.

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Our understanding of EC coupling has changed dramatically over the past few years. In older, "common-pool" (*2*) theories, each cardiac contraction was thought to occur as follows (see figure, part A): (i) Electrical excitation sweeps across the surface of a heart. (ii) This depolarization opens voltage-gated, dihydropyridine-sensitive Ca^{2+} channels (DHPRs), allowing an influx of Ca^{2+} that modestly increases a common pool of intracellular Ca^{2+} (Ca_{common}). (iii) This increase in Ca_{common} triggers the opening of ryanodine-sensitive intracellular Ca^{2+} channels (RyRs) (*3*). The resulting efflux of Ca^{2+} from the sarcoplasmic reticulum causes a far larger increase of Ca_{common}. (iv) This increase activates the contractile machinery, causing contraction.

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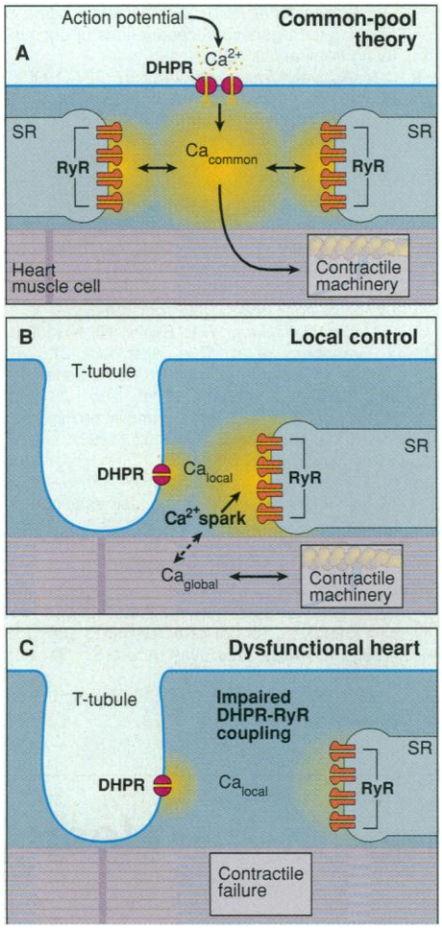
Recently, a growing body of data (*2*, *4*–*6*)



Excitation-contraction coupling in heart, then and now. (**A**) Classic, common-pool theory of EC coupling. (**B**) Current, local-control mechanism of EC coupling. (**C**) Defect in EC coupling during heart dysfunction (*1*).

has proven problematic for the common-pool theory. The most striking evidence for a new "local-control" mechanism of EC coupling comes from confocal microscopic visualization of punctate, transient increases of intracellular Ca^{2+} ("Ca^{2+}sparks") (*7*), thought to arise from the opening of one or a tight cluster of RyRs in close proximity to one (or a few) DHPRs in the t-tubules (part B). In the local-control mechanism, the intimate juxtaposition of a DHPR and a cluster of RyRs (forming a local response element) may enable Ca^{2+} influx through one opening of a single DHPR to increase a local pool of Ca^{2+} (Ca_{local}) sufficiently to open adjacent RyRs, thereby producing a Ca^{2+} spark. All of this can occur locally, without appreciable perturbation of a global pool of Ca^{2+} (Ca_{global}). If enough DHPRs open, multiple Ca^{2+} sparks are recruited and coalesce to increase Ca_{global}, resulting in macroscopic activation of the contractile machinery.

The new results in this issue (*1*) reveal which steps in the local-control mechanism are impaired in two forms of cardiac dysfunction. In hypertension, heart cells compensate for the increased pressure afterload by growing larger (hypertrophy). Despite their enhanced stature, hypertrophied cardiac cells can demonstrate impaired contraction. By relating the magnitude of Ca^{2+} currents flowing through DHPRs to the rate of Ca^{2+}-spark production, the authors cleverly deduce that the ability of DHPR openings to activate adjacent RyRs is markedly suppressed in hypertrophied cells. Surprisingly, additional experiments exclude the involvement of other steps in the local-control mechanism, such as altered DHPR or RyR function, revealing impaired coupling between adjacent DHPR and RyR molecules as the primary defect in the overall contractile failure. If hypertension persists, hypertrophied hearts may progress to a form of congestive heart failure. The investigators find a remarkably similar defect in DHPR-RyR coupling of cells derived from such failing hearts, hinting that a common defect may underlie various forms of cardiac dysfunction. One possible explanation for the impaired coupling is that changes in the microarchitecture of local response elements result in suboptimal spacing between adjacent DHPR and RyR molecules (part C).

Whether this defect in EC coupling generalizes to other forms of heart dysfunction remains to be explored. In addition, in skeletal and smooth-muscle myocytes, as well as neurons, Ca^{2+}-signaling molecules are also juxtaposed to permit rapid, tête-à-tête communication through Ca^{2+} sparks or their analogs (*8*). Coupling defects between adjacent signaling molecules may be the basis for disease in other tissues, as well.

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ORGANIC CHEMISTRY

Catching an Elusive Cation

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One of the major achievements of modern chemistry was the development of methods for the direct spectroscopic characterization of short-lived reaction intermediates. The observation of positively charged carbocation intermediates in the condensed phase under long-lived stable ion conditions in superacidic media was pioneered by Olah in the early sixties (*1*). With superacids as the reaction media, a wide variety of trivalent carbenium ions, hypercoordinated carbonium ions, acylium, carboxonium, halonium, oxonium, sulfonium, azonium, and related systems have been subsequently prepared and characterized by a host of spectroscopic techniques, including single-crystal x-ray diffraction studies (*1*, *2*). The formyl cation (HCO^+) is one of the most significant intermediates invoked in electrophilic formylation reactions of aromatic compounds [the Gatterman-Koch reaction (*3*)], but it has eluded direct observation under long-lived conditions in the condensed phase. As de Rege *et al.* report on page 776 of this issue, the formyl cation has been now characterized (*4*).

The formyl cation has previously been spectroscopically detected as an abundant species in interstellar dust clouds (*5*), and its identification has been confirmed in the gas phase by a variety of methods including microwave, infrared, and mass spectrometry (*6*). It is easily generated in the gas phase by electron-impact ionization of CH_3OH or by direct protonation of CO (which has a high proton affinity of 145.6 kcal/mol). In spite of the stability of the formyl cation in the gas phase, all previous attempts (*7*) to observe it under long-lived superacidic conditions were unsuccessful. Direct protonation of CO in highly acidic media such as FSO_3H-SbF_5 [known as Magic Acid (*1*)] or HF-SbF_5 at atmospheric pressures was inconclusive. Ionization of formyl fluoride in SbF_5 or by cleavage of protonated formic acid in superacid was also futile (*7*). In these experiments, only dissolved CO was observed by ^{13}C nuclear magnetic resonance (NMR) spectroscopy, indicating the difficulty in generating the

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