Mechanistic Insights Into Very Slow Conduction in Branching Cardiac Tissue
A Model Study

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Abstract—It is known that branching strands of cardiac tissue can form a substrate for very slow conduction. The branches slow conduction by acting as current loads drawing depolarizing current from the main strand (“pull” effect). It has been suggested that, upon depolarization of the branches, they become current sources reinjecting current back into the strand, thus enhancing propagation safety (“push” effect). It was the aim of this study to verify this hypothesis and to assess the contribution of the push effect to propagation velocity and safety. Conduction was investigated in strands of Luo-Rudy dynamic model cells that branch from either a single branch point or from multiple successive branch points. In single-branching strands, blocking the push effect by not allowing current to flow retrogradely from the branches into the strand did not significantly increase the branching-induced local propagation delay. However, in multiple branching strands, blocking the push effect resulted in a significant slowing of overall conduction velocity or even in conduction failure. Furthermore, for certain slow velocities, the safety factor for propagation was higher when slow conduction was caused by branching tissue geometry than by reduced excitability without branching. Therefore, these results confirm the proposed “pull and push” mechanism of slow, but nevertheless robust, conduction in branching structures. Slow conduction based on this mechanism could occur in the atrioventricular node, where multiple branching is structurally present. It could also support reentrant excitation in diseased myocardium where the substrate is structurally complex.

Key Words: slow conduction ■ discontinuous conduction ■ source-to-load mismatch ■ atrioventricular node ■ mathematical model

It is well-known that slow conduction of the cardiac action potential (AP) is essential for the function of the atrioventricular (AV) node.1 However, when slow conduction occurs in the working myocardium under pathological conditions, it can precipitate life-threatening reentrant arrhythmias.2

Conduction velocity (v) is determined primarily by membrane excitability (ie, the magnitude and kinetics of depolarizing currents) and by the degree of intercellular gap-junctional coupling.1,3–6 In the AV node, both reduced excitability (conduction is based predominantly on the L-type Ca2+ current, ICa,L) and reduced coupling are the major mechanisms of very slow conduction.1 During acute ischemia, slow conduction in the myocardium is mostly due to hyperkalemia-induced membrane depolarization, which acts to inactivate sodium channels,7,8 and reduced intercellular coupling.9 In aging and fibrotic myocardium, and probably in the AV node as well, nonuniform anisotropy contributes to discontinuous slow conduction in the direction transverse to myocardial fibers.10,11

Conduction is also influenced by the presence of structural inhomogeneities within cardiac tissue. Such inhomogeneities can create an electrical source-to-load mismatch, eg, a misbalance between the current provided by a smaller mass of tissue (source) and the current necessary to bring to threshold a larger mass of tissue downstream (load). As shown previously, source-to-load mismatch can induce a local slowing of conduction or conduction block.12–15 It is hypothesized that, in addition to reduced excitability and reduced intercellular coupling, structurally-based source-to-load mismatch can also contribute to slow conduction in the AV node and in structurally complex myocardium. In the AV node, so-called “dead-end” pathways could play this role by shunting a fraction of electrotonic current.16,17 Furthermore, in parts of the AV node consisting of myocardial fascicles interspersed with collagen,18,19 branchings of these fascicles could form sites of source-to-load mismatch. In the myocardium, structural complexities can develop during chronic infarction: the infarct border zone consists of interconnected islands and strands of surviving myocytes intermingled with scar tissue and is known to support very slow conduction.20

The effects of branching on conduction were investigated recently in patterned cultures of neonatal rat ventricular...
myocytes.21 In preparations consisting of multiple successive strands branching from a main strand, slow conduction resulted from the repetition of source-to-load mismatch at the successive branching points. The main hypothesis suggested by these experiments was that branches would have a dual effect: (1) by acting as a current sink, they slow conduction ("pull" effect); (2) once depolarized, they would act as a current source, reinjecting current back into the main strand ("push" effect), stabilizing conduction. The pull effect is in accordance with the classical source-to-load mismatch concept. The push effect challenges the notion that a current load cannot switch to become a current source for the upstream tissue that caused its excitation. However, the existence of the push effect and its contribution to conduction could not be demonstrated and evaluated specifically in the experiments.

Motivated by the experimental observations, the aim of the present study was to gain deeper insight into the mechanism of slow conduction in branching structures. Specifically, the experimental observations were reproduced in networks of Luo-Rudy dynamic (LRd) ventricular model cells in order to (1) demonstrate the existence of the push effect, (2) quantify the current flowing retrogradely from the branches into the main strand (push current), (3) assess the contribution of the push effect/push current to the velocity and stability of conduction, and (4) characterize the conduction of premature APs in branching structures.

Materials and Methods

The LRd cell model,22 with its updates published in detail previously,23 was used to construct branching networks of cardiac cells reproducing the geometry of the cultures used in the experiments.21 Whereas the original LRd cell has a long cylindrical shape (100 μm length, 22 μm diameter), cultured rat heart cells are shorter (~60 μm) and flattened against the growth surface.24 In order to use the LRd cell with dimensions closer to those of the cultured cells, the LRd cell was reshaped into a prism (58.8×58.8×11 μm) with identical surface-to-volume ratio and intracellular compartmentalization. Basic characteristics of conduction were assessed in an unbranched strand of 121 cells. The effects of a single branching on conduction were studied in this strand by connecting a pair of sealed-end branches of a predefined length (L) to its middle cell. The effects of multiple successive branchings were studied in strands of at least 121 cells, with the sealed-end branches of each defines a predefined length and at predefined distances between branchings along the entire main strand. Previous work3 showed that spatial discretization into elements equal to the cell length (cell considered isopotential) leads to <0.5% error in computed θ compared with high-resolution subcellular discretization. Therefore, a discretization length equal to the cell length (58.8 μm) was used. The myoplasmic resistance (150 Ω·cm) was therefore lumped with the gap-junctional resistance (1.5 Ω·cm2) and the extracellular resistance was considered negligible.5,21 Membrane potential (Vm) was computed using the Crank-Nicholson algorithm25 at time-steps of 0.005 ms. Ion current components were recomputed at every time-step and integrated using the Euler method.

Conduction was examined in normal and elevated extracellular potassium ([K+]o = 4.5 and 14.8 mmol/L, respectively). Elevated [K+]o, which was the same as that used experimentally,6,21 mimicked hyperkalemia during acute ischemia6,8 and created excitability conditions similar to those of the AV node (IcaL-based conduction).1 Initial conditions were obtained from a single cell, which was paced for 10 seconds at 2 Hz. In order to reproduce θ, dVm/dtmax, and the space constant measured experimentally in the cell cultures for similar [K+]o,5,21 the sodium current (INa) was reduced by 50% and IcaL was increased by 100%. In the unbranched model strand for normal [K+]o, θ was 38.7 cm/s, dVm/dtmax was 121.4 V/s, and the space constant was 446 μm. In elevated [K+]o, these values were 14.5 cm/s, 16.0 V/s, and 314 μm, respectively.

If not specified otherwise, the results correspond to the first elicited AP (control, S1). Propagation of premature APs (S2), elicited at predefined S1S2 intervals, was studied in specific simulations. In further simulations, the specific contribution of the push current to conduction was investigated by not allowing retrograde current flow from the branches into the main strand. At every time step and for every branch, if Vm at the branch point was less than in the first cell of the branch, the corresponding intercellular conductance was set to 0; otherwise, it was kept at its nominal value.

The safety (stability) of propagation was quantified with the safety factor (SF).5 The SF is defined for every cell as the ratio of the charge generated by the cell to the charge required for its excitation. The fraction of SF above 1 represents the excess of charge generated over the charge required and quantifies the margin of safety. A recently generalized definition of the SF was used.22 The minimal SF in a given network was considered the determinant of the overall safety of propagation.

Results

Propagation in Networks With Single Branching

Figure 1 illustrates the effects of single branching on propagation in the situation of short branches (L=2 cells, Figure 1A) and long branches (L=10 cells, Figure 1B). In both situations, the source-to-load mismatch resulted in local slowing of propagation proximal to the branch point (Figure 1, panel I), and thus in a conduction delay across the branching site (Figure 1, panel IV). Because the magnitude of the source-to-load mismatch depended on L, this delay was, as expected, longer for L=10 cells.

The activation pattern of short branches was very different from that of long branches. Short branches were activated virtually simultaneously (Figure 1A, panel II) and earlier than the distal portion of the strand. Furthermore, because of the reflection of electrotonic current from the sealed ends, Vm in the branches was greater than Vm at the branch point (main strand), and the gradient of Vm between the main strand and the branches was reversed. On the contrary, activation of long branches was gradual (Figure 1B, panel II), in a manner similar to the distal segment of the main strand, and accelerated only in close vicinity to the sealed branch ends. In networks with short branches, the reversal of the Vm gradient resulted in a push current (Figure 1, panel III), i.e., in a retrograde electrotonic current flowing from the branches into the strand. In networks with long branches, the reflection of current at the sealed ends occurred too far from the branch point and no push current was observed.

Figure 2 shows the behavior of the peak push current as a function of L. In both normal and elevated [K+]o, this current first increased with increasing L, reached a maximum, and decreased toward 0. In normal [K+]o, the push current had a significant magnitude for L ranging from 1 to 7 cells (~60 to 400 μm). The maximum push current was observed for L=2 cells and its peak amplitude (185 μA/μF) was comparable to that of peak IS (234 μA/μF). In elevated [K+]o, IS was 99.8% inactivated and propagation was supported by IcaL. The push current was important over a broad range of L and its maximum (57 μA/μF), obtained at L=5 cells, was even larger than IcaL itself (21.6 μA/μF).
The large magnitude of the push current suggests that this current can provide a major contribution to impulse propagation in the main strand. To assess this contribution, the push current was specifically blocked. This is illustrated in Figure 3 for L = 2 and normal [K\textsuperscript{+}]. Surprisingly, this intervention resulted in only a very small prolongation of the overall conduction delay. This almost negligible effect is explained by the fact that, at the time of the onset of the push current, Vm at the branch point and immediately distal to it in the main strand had already undergone almost complete depolarization (Vm > 0). Therefore, although the push current was large, it occurred too late to contribute to the activation of downstream cells within the main strand.

Figure 1. Characteristics of propagation across a single branching site under normal [K\textsuperscript{+}]., for branch lengths (L) of 2 cells (118 μm, A) and 10 cells (588 μm, B). Top, Schematic representation of the single branching networks. Cells for which data are presented in other panels are shaded. The arrows denote the direction of propagation. I and II, Membrane potential (Vm) in main strand and in branches, respectively. AP upstrokes are shown. The thick dashed traces correspond to the branch point. III, Pull-Push current. Electrotonic current (scaled to the capacitance of the cell at the branch point) flowing from the branch point into (positive, pull) and retrogradely out of (negative, push) the branches. IV, Activation profiles (activation time as a function of distance) of the main strand (filled symbols) and the branches (open symbols). Distance 0 corresponds to the branching site. In each profile, the thin line corresponds to the activation profile in the absence of branching. The interval between this line and the distal profile of the main strand corresponds to the overall branching-induced delay.

Figure 2. Peak push current in single branching networks as a function of branch length. A, Normal [K\textsuperscript{+}]. B, Elevated [K\textsuperscript{+}].

Figure 3. Effects of blocking the push current on propagation across a single branch point for L = 2 cells in normal [K\textsuperscript{+}]. In the scheme of the network, the arrow indicates the direction of propagation. The shaded cells indicate the cells for which Vm is shown in A (the thick traces correspond to the branch point), before (solid traces), and after (dashed traces) blocking the push current. This intervention only minimally prolonged the branching-induced delay (rightmost solid and dashed traces are practically superimposed). B, I\textsubscript{Na}, I\textsubscript{Ca,L}, pull current (I\textsubscript{pull}), and push current (I\textsubscript{push}, before block) at the branch point. The block of I\textsubscript{push} resulted in only a minimal modification of I\textsubscript{Na} and I\textsubscript{Ca,L} (dashed traces).
The dependence of the conduction delay on L is shown by the solid curves in Figure 4A. In close agreement with experimental results, the delay increased with increasing branch length and reached a plateau at \( \approx 1 \) ms in normal \([K^+]\), and at \( \approx 6 \) ms in elevated \([K^+]\), respectively. Block of the push current induced only a negligible prolongation of the delay (dotted curves indicated by arrows, almost superimposed on the solid curves). This minimal effect was only present for shorter L, consistent with the observation that the push current is smaller for longer branches (see Figure 2).

The finding that the contribution of the push effect is small seems in disagreement with the experimental study. In the experiments, the push effect was suppressed by a pharmacological block of \( I_{Na} \) and \( I_{Ca,L} \) confined to the branches. This intervention resulted in a significant prolongation of the delay in normal \([K^+]\), and conduction block in elevated \([K^+]\), for \( L=960 \) \( \mu \)m. To address this discrepancy, the same protocol was reproduced computationally by setting \( I_{Na} \) and \( I_{Ca,L} \) to 0 inside the branches (Figure 4A, dashed curves). Consistent with the experiments, this led to a significant prolongation of the delay in normal \([K^+]\), and to conduction block for \( L>700 \) \( \mu \)m in elevated \([K^+]\). Detailed analysis (not shown) revealed that blocking the depolarizing membrane currents in the branches indeed suppressed the push current. However, slowing or block of conduction was caused mainly by an increase of the pull effect. Because the branches could not generate inward transmembrane currents for local depolarization, they constituted an increased electrotonic load drawing a larger pull current during a prolonged period of time.

Figure 4B shows the dependence of the conduction delay on L for premature APs elicited during the relative refractory period of the control AP. Reduced excitability during that period (incomplete recovery from inactivation of \( I_{Na} \) and \( I_{Ca,L} \)) led to prolongation of the delay for all L. For moderate prematurity, no conduction blocks occurred. For more premature impulses, conduction failed at the branch point when L exceeded a critical length. With increasing prematurity, this critical length became progressively shorter.

**Figure 4.** Propagation delay induced by single branching as a function of branch length, L, for control (A) and premature APs (B). A. Solid curves: in the presence of the push current. Dotted curves: during specific block of the push current; note the minimal prolongation of the delay that occurs only for short L (arrows). Dashed curves: when branches were rendered inexitable \( I_{Na} \) and \( I_{Ca,L} \) set to 0; note the significant increase of the delay; in elevated \([K^+]\), conduction block occurred when L was \( >12 \) cells \((\approx 700 \mu \)m). B. All curves: in the presence of the push current and excitable branches. Curve labels indicate the coupling interval of the premature beat (S1S2 interval). With increasing prematurity, the delay became progressively longer until conduction block occurred at progressively shorter critical L.

**Propagation in Networks With Multiple Branching**

In consistency with the experimental observations, the succession of source-to-load mismatches in the model with multiple branching resulted in an overall slow conduction. We defined \( \theta \) as the average velocity in the main strand. Figure 5A depicts the behavior of \( \theta \) as a function of L and of the distance between successive branch points (D). In both normal and elevated \([K^+]\), for a given D, \( \theta \) decreased with increasing L and reached a steady value. For a given L, \( \theta \) decreased with decreasing D (ie, with increasing spatial frequency of branching). In elevated \([K^+]\), very slow conduction in the range of a few cm/s was observed for the \( I_{Ca,L} \)-based AP. The slowest \( \theta \) was \( \approx 2 \) cm/s (\( \approx 14\% \) of \( \theta \) in unbranched strands).

Figure 5B compares conduction patterns of control and premature APs in a network with \( L=15 \) cells and \( D=10 \) cells in normal \([K^+]\). Conduction of the control AP was characterized by equal delays at successive branch points. The premature AP elicited at a S1S2 interval of 210 ms was blocked at the first branch point. When elicited at 220 ms, it underwent a very long delay at the first branch point; therefore, conduction resumed in less refractory tissue beyond this point. Because of the dependence of the conduction delays on refractoriness (see Figure 4B), the delays at the next branch points were progressively shorter as the AP propagated in progressively less refractory tissue. Conduction was thus characterized by major initial slowing, which partially compensated for the prematurity. Distally in the network, conduction was similar to that of a premature AP elicited later, eg, at 240 ms. This phenomenon was observed for networks with D and L over the entire range studied.

The contribution of the push effect to conduction was further investigated by blocking the push current. Figure 6 illustrates the behavior of \( \theta \) as a function of L and D when the push current was blocked at all branch points. \( \theta \) in the absence of the push effect was normalized relative to \( \theta \) in its presence. In normal \([K^+]\), (Figure 6A), for \( D=2 \) cells, the block of the push effect resulted in a reduction of \( \theta \) by up to \( \approx 50\% \) (for \( L=7 \) or 8 cells). For \( L>8 \) cells, propagation could...
not be supported when the push effect was suppressed. For D=4, 6, 8, and 10 cells, the reduction of $\theta$ was smaller (up to $\approx 10\%$) and only for short L. In elevated [K$^+$], (Figure 6B), the effects of suppressing the push current were very prominent; the reduction of $\theta$ ranged up to $\approx 50\%$, and for D=2, 4, and 6 cells propagation could not be supported in networks with relatively long branches.

The finding that the push effect provides such a large contribution to conduction is in sharp contrast to the observation that its contribution is insignificant in the strand with single branching. The data presented in Figure 7 explain why this contribution becomes important in the setting of multiple branching. Conduction along a network with L=4 cells and D=4 cells was simulated under conditions of elevated [K$^+$], (solid traces). In contrast to the single branching situation, the onset and the peak of the push current at a given branching site occurred at a time when downstream cells, located within a distance of electrotonic influence, were still undergoing depolarization. This delayed depolarization was due to the slowed conduction in the presence of multiple branches that acted to increase the electrical load. When the push current was blocked at the branching site under consideration (dashed traces), $V_m$ at the corresponding branch point was significantly depressed by $\approx 10$ mV during the late phase of its upstroke. This depression resulted in a decreased driving force for current to the distal cells and, consequently, to further delay of their activation. Therefore, because the push current was occurring at the time of distal depolarization, it contributed to propagation by maintaining the late phase of the upstroke at the branch point and consequently the driving force for current to the depolarizing distal cells.

**Safety Factor Considerations**

Whereas the action of branches as current loads leads to slow conduction, it was hypothesized that the action of branches as current sources would contribute to the safety of propagation. Consequently, conduction in multiple branching structures would be slow but nevertheless stable. In branching networks, SF also decreased with $\theta$. However, beyond a certain degree of conduction slowing, SF became higher when slow conduction was due to branching than when slow conduction was due to reduced excitability. This indicates that at these slow velocities, branching is a more robust mechanism for supporting slow conduction than reduced excitability.
Local Delays

Conductivity delays

By maintaining the plateau in proximal tissue, the push current was blocked. The shaded cells indicate the cells for which Vm is shown in A (the thick traces correspond to the branch point), before (solid traces), and after (dashed traces) blocking the push current. Blocking the push current resulted in a depressed Vm during the late phase of the upstroke of the corresponding branch point (arrow). This depression occurred at a time when distal cells were still undergoing depolarization and, consequently, resulted in their delayed activation. B, I_{Na}, I_{Ca,L} pull current (I_{pull}), and push current (I_{push} before block) at the branch point. Note that in elevated [K+]o, I_{Na} is inactivated and that the amplitude of I_{push} is large relative to I_{Ca,L}. The block of I_{push} resulted in only a small modification of I_{Ca,L} (dashed trace).

Discussion

By reproducing the characteristics of conduction in patterned cardiac cell cultures, this study provided mechanistic insight into the proposed “pull and push” mechanism of slow conduction. In essence, it demonstrated that a structurally-based current load can convert to a source, and that, if properly timed, this conversion can enhance conduction and make it more robust.

The Push Current Plays a Similar Role to I_{Ca,L} During Propagation That Involves Long Local Delays

In situations where I_{Na}-based conduction involves long propagation delays (several milliseconds), the role of I_{Ca,L} becomes critical by providing a crucial contribution to sustain AP propagation. During these delays, I_{Na} inactivates within ~1 ms, but I_{Ca,L} progressively increases to its peak amplitude. By maintaining the plateau in proximal tissue, I_{Ca,L} maintains the driving force for depolarizing current to distal tissue. Similarly, in multiple branching tissue, conduction is sufficiently slowed so that the push current contributes to propagation by maintaining the plateau in proximal tissue at a time when distal tissue is not yet fully depolarized. Therefore, in the presence of sufficiently long local conduction delays, any delayed current that supports the plateau of the AP will provide a significant contribution to propagation. This principle is independent of whether this current is a transmembrane inward current or an electrotonic current flowing from neighboring tissue.

The Safety of Slow Conduction

A previous modeling study compared the effects of reduced I_{Na} with those of reduced gap-junctional coupling on SF in one-dimensional cell strands. Progressive reduction of I_{Na} resulted in progressive conduction slowing from 54 down to ~17 cm/s (69% slowing) with a concomitant reduction of the SF until propagation failed. In contrast, during reduction of gap-junctional coupling, conduction slowing was first accompanied by a seemingly paradoxical increase of the SF. With further reduction of coupling, SF dropped abruptly when \( \theta \) was <2 cm/s (97% slowing), until block occurred at <1 cm/s (>99% slowing). The SF increase was explained by the fact that with reduced coupling, a larger fraction of the depolarizing charge provided by transmembrane currents during the activation of a given cell accumulated in the cell because less charge was leaking downstream. Similarly, it could be hypothesized that in branching structures, charge would accumulate in the cells of a given branch, and that SF would increase as branching becomes more extensive. However, SF actually decreased with increased branching. This is explained by the fact that the large load imposed by distal...
branches increased in parallel with charge accumulation. In contrast, in the poorly coupled strand, the large junctional resistance decreased the downstream load. Nevertheless, the push current returned a fraction of this accumulated charge to the main strand. When L was long enough to provide a substantial push current, SF was higher in branching structures than in unbranched structures where an equal degree of conduction slowing was obtained by reducing excitability.

**Frequency-Dependence of Propagation in Branching Structures**

Two essential functions of the AV node are to protect the ventricles from atrial tachyarrhythmias and to regulate the delay between atrial and ventricular excitations. In the present study, propagation of premature APs across single branchings was characterized by long delays or even conduction failure. In multiple branching structures, propagation of premature APs was either blocked or markedly delayed. These impairments were caused by an increased source-to-load mismatch (less source current during the relative refractory period). In multiple branching structures, the push effect contributed to the conduction of premature impulses as well (block of the push current resulted in further conduction slowing or in the precipitation of conduction block, data not shown). Although the long-term behavior during rapid pacing was not assessed, these observations suggest that source-to-load mismatch in single or multiple branching structures might be involved in blocking or delaying the conduction of premature atrial impulses through the AV node and, possibly, in the establishment of characteristic beat-to-beat patterns (eg, intermittent block, Wenckebach periodicities). Furthermore, these phenomena might determine cycle length variations and spontaneous termination of reentrant arrhythmias involving strong head-tail interactions in discontinuous myocardium.

**The Push Effect In Vivo: Limitations of the Present Study**

In extrapolating the above findings and considerations to conduction in vivo, the present study suffers from the following limitations: (1) this study assumes that the branches have a sealed end; (2) both the AV node and structurally complex myocardium present a much more elaborate and irregular topology than the prototypical networks studied here; and (3) no histological information is available concerning the detailed branching patterns and their spatial scales and distribution in such structures. In vivo, it is likely that emanating branches merge with adjacent tissue (eg, in nonuniform anisotropic bundles where branches form side-to-side connections between myocardial fascicles). The pull and push effects will obviously be modulated by the activation of parallel fascicles or adjacent tissue. This modulation will further depend on the global activation pattern, ie, on the manner in which the waveform enters into and spreads through the complex tissue and on the geometry of the excitation wave. Although the present study considers propagation in relatively simple structures, it shows that the push effect contributes to propagation over a wide range of L and D in structures with multiple branching. The documented presence of such structures in cardiac tissue supports the hypothesis that the pull and push effects are fundamental mechanisms in the establishment of slow conduction in vivo. However, elucidation of the detailed effects of more complex structures on conduction will necessitate further investigation.

Another limitation is that the cell model used is of a ventricular cell, and a similar study should be conducted with an AV-nodal cell model to support conclusions regarding the AV node. Nevertheless, at sufficiently elevated [K+]o, the ventricular cell AP upstroke is supported by ICa,L and mimics this aspect of AV-nodal cells. It is therefore likely that using an AV-nodal cell model would lead to observations similar to those reported in this study.

**Physiological and Clinical Implications**

The pull and push effects can act to increase the robustness of slow conduction in cardiac tissue that contains complex structures and structural heterogeneities. Such substrates exist in the AV node and in the healed infarct. It is likely that this mechanism plays an important role in the slow conduction through the AV node (a desired property essential to normal function) and in slow conduction in the infarct border zone that can lead to reentrant arrhythmias.

**Acknowledgments**

This work was supported by fellowships from the Swiss National Science Foundation and the Swiss Foundation for Stipends in Biology and Medicine (to J.P.K.), and by grants ROI-HL49054 and R37-HL33343 from the National Institutes of Health, National Heart, Lung and Blood Institute (to Y.R.).

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_Circ Res._ 2001;89:799-806; originally published online September 13, 2001;
doi: 10.1161/hh2101.098442
_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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