Pathophysiological Basis for Monitoring of Whole Heart Conductance by 2-Lead System

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Background The defibrillation threshold (DFT) is elevated during myocardial ischemia, but the underlying mechanism remains to be elucidated. The hypothesis tested by the present study was that whole heart conductance (WHC) is a determinant of DFT.

Methods and Results WHC was monitored across the longest diameter of the isolated perfused rat heart, using a 2-electrode instrument under various conditions including ischemia–reperfusion (IR). In the control study, WHC was influenced by the conductivity and flow rate of the solution. In IR, WHC decreased immediately after the onset of perfusion arrest in a single exponential manner, then declined again gradually. The second decrease was augmented and accelerated by pretreatment with 1.0 mmol/L heptanol (p<0.005) or high-[Ca2+]e (p<0.001), and was attenuated and delayed by pretreatment with 1.0 μmol/L verapamil (p<0.01). WHC after reperfusion was greater than the pre ischemic level. The postischemic change in WHC was proportional to the ischemic interval and tissue water content as assessed by desiccation method.

Conclusion Although time-dependent alterations in DFT in ischemic hearts may be attributable at least in part to dynamic changes in WHC, WHC should be interpreted carefully because it reflects many physiological factors such as coronary perfusion, electrical coupling of cardiac myocytes and tissue edema. (Circ J 2006; 70: 495–501)

Key Words: Ischemia; Myocardial edema; Reperfusion; Whole heart conductance

Implantable cardioverter defibrillator (ICD) is widely used as an effective prevention of sudden cardiac death from ventricular fibrillation. The defibrillation threshold (DFT), which influences the safety and the efficacy of ICD, is reportedly increased by transient myocardial ischemia and time-dependently after the onset of ventricular fibrillation. DFT is usually estimated by electrical induction of ventricular fibrillation lasting several seconds under nonischemic conditions, and dynamic alteration of DFT in response to transient ischemia is not taken into account in the programming of the ICD.

We hypothesized that whole heart conductance (WHC) would be one of the determinants of DFT. Because it is the current density that influences successful defibrillation by the ICD (ie, the larger the WHC, the greater the current delivered, leading to the better defibrillation efficacy (low DFT) of the ICD). If our hypothesis was correct, elevation of the DFT in ischemic hearts would be based on a time-dependent fall in WHC during progression of the ischemia. Therefore, in the present study, we analyzed the dynamic changes of WHC in Langendorff-perfused rat hearts using a 2-lead system under a variety of experimental conditions, including ischemia–reperfusion (IR).

Methods

Heart Preparations

Experimental designs and procedures used in this study complied strictly with the ‘Guiding Principles for the Care and Use of Laboratory Animals’ approved by the Japanese Physiological Society. The procedures used in this perfusion study have been described elsewhere in detail. Male Wister rats (n=60) weighing 300–350 g (Kyudo Co Ltd, Yoshitomi, Japan) were anticoagulated and anesthetized with intraperitoneal injections of heparin (500 IU) and sodium pentobarbital (40 mg/kg; Abbott Laboratory, Chicago, IL, USA), respectively. The beating hearts were excised immediately after thoracotomy under conditions of artificial respiration (KN-55, Nazme, Tokyo, Japan), rinsed and weighed in ice-cold Krebs-Henseleit (K-H) solution. The wet weight of the preparations prior to the perfusion study ranged from 1.2 to 1.6 g (1.4±0.1 g, n=54). Within 30 s of thoracotomy, the ascending aorta was cannulated for modified Langendorff perfusion and secured with a braided silk suture. The heart was perfused retrogradely with nonrecirculating oxygenated K-H solution.

The pulmonary artery (PA) was cut near its origin and a small cannula was inserted via the cut end into the right ventricle for coronary sinus and thebesian venous drainage. The epicardial surface was moisturized by humidity arising from a warmed reservoir. A latex balloon was inserted into left ventricle (LV) through a left atrial incision and was connected to a digital manometer (Tsukasa-Sokken, Tokyo, Japan). LV end-diastolic pressure (LVEDP) was adjusted to 5 mmHg by inflating the balloon at the beginning of the perfusion study. Perfusion pressure was monitored continuously at the site of aortic cannulation. Flow rate was estimated by sampling effluent at designated times. Perfusion...
with a volume-regulated peristaltic pump (model 7553-20, Cole Parmer, Chicago, IL, USA) was carefully controlled to maintain a constant flow rate (10 ml·min⁻¹·g ww⁻¹) to yield a physiological perfusion pressure (=100 mmHg) during the equilibration period. K-H solution was of the following composition: NaCl, 140.0; KCl, 5.4; CaCl₂, 1.8; MgCl₂, 0.5; NaH₂PO₄, 0.33; glucose, 5.5 (mmol/L). The external sodium concentration ([Na⁺]ₑ) was reduced or depleted depending on the experimental protocol by replacing NaCl with equimolar N-methyl-D-glucamine (Sigma, St Louis, MO, USA). Similarly, the external calcium concentration ([Ca²⁺]ₑ) was increased to 3.6 mmol/L, by substituting CaCl₂ to keep the total ionic strength of the solution constant. The solution was oxygenated with 100% O₂ and the temperature was maintained at 37±1°C. The pH was adjusted to 7.4 using 10.0 mmol/L N-2-hydroxyethylpiperazine-N'-2-ethanesulphonic acid (HEPES; Sigma) with NaOH titration. Partial oxygen pressure of the solution was estimated by a blood gas analyzer (ABL 620; Radiometer, Copenhagen, Denmark) and was approximately 850 mmHg. Osmotic pressure was estimated by a vapor pressure osmometer (Model 5520, Wescor Co Ltd, Logan, UT, USA) and was approximately 290±4 mOsm/L. Effluent temperature estimated by thermister was 36±1°C.

WHC was evaluated by a commercially available DC conductance meter (M&S Instruments Inc, CD-35MII, Tokyo, Japan), which was calibrated using known resistors in the range of 10 kΩ to 100 mΩ and connected to a pair of Ag-AgCl clip electrodes. Preliminary conductance measurement of solutions with differing [Na⁺]ₑ confirmed that this device was capable of real-time measurement of solution conductance, depending on [Na⁺]ₑ and interelectrode distance. A pair of clip electrodes was arranged on the surface of the heart in such a way that the interelectrode distance corresponded to the longest diameter of the preparation. Care was taken to minimize possible errors from electrode polarization by Ag-AgCl treatment, and effluent-induced short-circuiting of the electrodes by PA drainage. WHC and perfusion pressure were monitored continuously by a pen-writing recticorder (Nihon-Kohden, Tokyo, Japan), and stored on digital audiotapes using a data recorder (RD-101T PCM, TEAC, Tokyo) for off-line analyses (Fig 1A). After each preparation was subjected to equilibration, perfusion protocols were commenced. Preparations showing sustained arrhythmias were excluded from data analyses (n=6).

Perfusion Protocols
A control perfusion study without any interventions (n=4) was continued for 4 h because long-term Langendorff perfusion without erythrocytes and albumin is prone to cause tissue edema. As a test perfusion study, isolated hearts (n=50) were randomly assigned to one of 4 protocols. The first protocol was designed to assess the effects of heart rate on perfusion pressure and WHC (n=5). Preparations were paced at the desired rate by a pair of platinum clip electrodes attached to right atrial (RA) appendage and upper end of the RA free wall. After determining the RA pacing threshold, fixed rate pacing was conducted with 2 ms duration and twice the diastolic threshold intensity. RA pacing was undertaken over a wide range of pacing rate with 25 beats/min increments, depending on the initial spontaneous beating rate (275–400 beats/min). Then the effects of flow rate on perfusion pressure and WHC were investigated (n=5). The flow rate was altered carefully by regulating the peristaltic pump (3.0–13.0 ml·min⁻¹·g ww⁻¹), after which [Na⁺]ₑ was altered to assess the effects of solution conductance on perfusion pressure and WHC (n=5) (ie, [Na⁺]ₑ was gradually reduced, depleted and then normalized to 140 mmol/L). The flow rate was altered in some preparations under the [Na⁺]ₑ alteration (n=3). Finally, an IR insult was introduced by ceasing the Langendorff perfusion for an appropriate period (20, 40 or 60 min) and then restoring the perfusion to exactly the preischemic flow rate (n=7). Hearts were either untreated (control, n=7) or pretreated for 10 min before the 60 min insult with either high-[Ca²⁺]ₑ (3.6 mmol/L; n=7), verapamil (Sigma, 1.0 μmol/L; n=7) or heptanol (Wako Chemical Co Ltd, Tokyo, Japan, 1.0 mmol/L; n=7). The second to fourth protocols were conducted without RA pacing.

Estimation of Tissue Water Content
Tissue water content was estimated by a desiccation technique (ie, all preparations weighed immediately after the perfusion study were placed in an oven to evaporate tissue water over a 48 h period under a constant temperature of 80°C). Relative tissue water content was calculated:

\[ \text{water content} = \frac{[\text{WW} - \text{DW}]/\text{WW}] \times 100 \% \]

where WW is the wet weight at the end of perfusion study, and DW is the dry weight after desiccation.

Data Analysis
Data are presented as mean±SD. Comparisons of vari-
ous parameters among the different perfusion protocols were done by unpaired Student’s t-test. Linear regression analysis was performed with the least-square method. Practical computation was done by commercially available statistical software (Microsoft Excel 2003, Microsoft, Tokyo, Japan). Results were considered to be statistically significant at p<0.05.

Results

Initial WHC values ranged from 2.1 to 3.0 (2.58±0.22)mS in the control perfusion study (n=4) and the 4 perfusion protocols (n=50). In the control perfusion at a flow rate of 10 ml·min⁻¹·g ww⁻¹, neither WHC nor perfusion pressure showed significant alterations for 4h. LVEDP at the end of control perfusion was 7.3±0.8 mmHg and the relative tissue water content was 54.8±4.7%, which was close to our previous perfusion study using isolated guinea pig hearts (51.1±2.9%). This observation indicated that there was not any time-dependent deterioration of the preparations with 4h of perfusion.

Effects of RA Pacing

All excised hearts (n=5) were captured by fixed RA pacing at rates up to 400 beats/min. As shown in Fig 2A, perfusion pressure and WHC remained unchanged during spontaneous beating and fixed RA pacing at 300 or 350 beats/min. The other 4 preparations also showed constant perfusion pressure and stable WHC under RA pacing ranging from 275 to 400 beats/min in the well perfusion (10 ml·min⁻¹·g ww⁻¹).
Effects of Flow Rate

As in Fig 2B, both the perfusion pressure and WHC changed in response to the stepwise alteration of the flow rate (3.0–12.5 ml·min⁻¹·g ww⁻¹). Fig 2C shows the changes in perfusion pressure and WHC as a function of flow rate. The steady state relationship between the perfusion pressure and flow rate in these preparations (n=5) was linear (r=0.979, p<0.005), and the slope theoretically indicates the total coronary resistance of the preparation. Steady-state WHC showed a small increase as the flow rate increased (r=0.997, p<0.001).

Fig 4. (A) Relationship between the average whole heart conductance (WHC %) and [Na⁺]ₑ, (n=5). (B) Pressure vs flow rate relationship of the total experiments under [Na⁺]ₑ reduction (●140 mmol/L, ■100 mmol/L, ▲60 mmol/L, n=3). Note that the slope of linearity (ie, total coronary resistance) increases as [Na⁺]ₑ decreases. Columns, symbols and bars indicate mean±SD.

Fig 5. (A) Changes in perfusion pressure (Upper) and whole heart conductance (WHC; Lower) at the onset of no-flow ischemia. (B) Semilogarithmic plot of the fall in WHC observed in (A), showing single exponential decay with a time constant (τ) of 108 s.

Fig 6. Representative experiments of the 3 different preparations subjected to 60 min of no-flow ischemia (A) without any pretreatments or with pretreatment with (B) verapamil or (C) heptanol. Perfusion pressure (Upper most) and whole heart conductance (WHC) were monitored during the entire period of ischemia. (---) Quasi-steady state level of WHC during ischemia. Calibration was inserted at the end of ischemia (arrows).
Effects of \([Na^+]\) Reduction

Fig 3 shows representative data from the experiments investigating the effects of \([Na^+]\)-reduction, depletion and normalization on the perfusion pressure and WHC under a constant flow rate of 10 ml·min\(^{-1}·g\) ww\(^{-1}\). The perfusion pressure gradually increased from 100 to 140 mmHg as \([Na^+]\) was reduced from 140 to 40 mmol/L. The perfusion pressure increased further to 180 mmHg with \([Na^+]\) depletion. As \([Na^+]\) was normalized, the perfusion pressure decreased to approximately 120 mmHg, but did not return completely to the baseline value. WHC was lowered by \([Na^+]\)-reduction and restored by \([Na^+]\)-normalization with a time lag for equilibration. Calibration was inserted at each step of \([Na^+]\)-alteration by disconnecting and short-circuiting the electrodes (arrows). Fig 4A summarizes the results from five preparations subjected to this protocol, which indicate that WHC is strongly dependent on \([Na^+]\). In 3 of 5 preparations, the flow rate gradually altered (from 3.0 to 13.0 ml·min\(^{-1}·g\) ww\(^{-1}\)) for each step of \([Na^+]\)-reduction. As shown in Fig 4B, a linear relationship between perfusion pressure and flow rate was obtained for each level of \([Na^+]\)-reduction. The lower the \([Na^+]\), the steeper the slope, indicating an increase in the total coronary resistance in response to the \([Na^+]\)-reduction.

Effects of IR

Global no-flow ischemia was achieved by abruptly ceasing perfusion while monitoring the perfusion pressure and WHC. At the beginning of ischemia of 20, 40 or 60 min in duration (n=7), the perfusion pressure decreased abruptly toward zero in a stepwise manner, but the reduction of WHC was delayed (Fig 5A), corresponding to a semilogarithmic regression. The time constant (\(\tau\)) of WHC decay was 108 s in this preparation (Fig 5B), and for the other preparations ranged from 91 to 119 s (104±8 s). WHC monitoring during 60 min of no-flow ischemia is shown in Fig 6. Control ischemia caused an initial sharp reduction in WHC, which was followed by a quasi-steady state at approximately 0.9 mS for the first 20 min. Thereafter, WHC showed a further gradual decline for approximately 25 min after the onset of ischemia, and reached a final value of 0.4 mS. Pretreatment with verapamil (1.0 \(\mu\)mol/L) had no influence on the initial decay, but attenuated the magnitude of the second gradual decline (ie, the difference between the quasi-steady state (0.9 mS) and minimum WHC (0.6 mS) was less than for the control ischemia). Moreover, verapamil delayed the onset of the second gradual decline (35 min after the onset of ischemia). In contrast, pretreatment with heptanol (1.0 mmol/L) augmented the magnitude of the

### Table 1 Effects of Verapamil, Heptanol and High-[Ca\(^{2+}\)]\(_e\) on WHC During Ischemia-Reperfusion Insult

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Verapamil</th>
<th>Heptanol</th>
<th>High-[Ca(^{2+})](_e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Preischemic value (mS)</td>
<td>2.47±0.35</td>
<td>2.59±0.27</td>
<td>2.53±0.33</td>
<td>2.61±0.24</td>
</tr>
<tr>
<td>Initial rapid decline time constant (min)</td>
<td>10±7</td>
<td>10±7</td>
<td>10±7</td>
<td>10±7</td>
</tr>
<tr>
<td>Second gradual decline magnitude (%)</td>
<td>20.6±2.6</td>
<td>15.1±2.1</td>
<td>29.4±2.2</td>
<td>32.0±3.1</td>
</tr>
<tr>
<td>Second gradual decline onset (min)</td>
<td>24.9±2.9</td>
<td>30.7±1.9</td>
<td>20.0±2.1</td>
<td>18.9±2.0</td>
</tr>
<tr>
<td>Minimum value (mS)</td>
<td>0.41±0.07</td>
<td>0.57±0.10</td>
<td>0.36±0.05</td>
<td>0.33±0.05</td>
</tr>
<tr>
<td>Postischemic increase (%)</td>
<td>10.0±0.5</td>
<td>9.4±0.4</td>
<td>10.8±0.9</td>
<td>11.8±1.1</td>
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All data are given as mean±SD. The magnitude of the second decline in whole heart conductance (WHC; %) is expressed as the difference between the quasi-steady state and the minimum WHC relative to that between the preischemic and the minimum WHC (c.f. Fig 6). The postischemic increase in WHC means the percent increase at the end of reperfusion relative to the preischemic level. *p<0.05, †p<0.01, ‡p<0.005 and §p<0.001 vs control.

Fig 7. (A) Alteration of whole heart conductance (WHC) with the ischemia-reperfusion insult. (B) Postischemic increase in WHC (%) is greater as the ischemic interval is prolonged (n=7). (C) The increase in WHC (%) is dependent on the tissue water content (%), as assessed by the desiccation method (r=0.861). Columns and bars indicate mean±SD.
second WHC decline (from 1.5 to 0.4 mS) and accelerated its onset (<20 min from the onset of ischemia) without any changes in the initial WHC decay. Pretreatment with high-[Ca\textsuperscript{2+}]\textsubscript{e} (3.6 mmol/L) caused similar changes in WHC to those observed with heptanol (data not shown).

Table 1 summarizes the effects of the pretreatments with verapamil, heptanol and high-[Ca\textsuperscript{2+}]\textsubscript{e} on the dynamic changes of WHC in response to IR (ie, τ of the initial decay, relative magnitude and onset of the second gradual decline, and the minimum WHC). These pretreatments had no significant influence on the preischemic value of WHC and τ of its initial decay. The relative magnitude of the second decline (%) is expressed as the difference between the quasi-steady state and minimum WHC relative to that between the preischemic and minimum WHC values. This magnitude was significantly greater with the heptanol (n=7) and high-[Ca\textsuperscript{2+}]\textsubscript{e} (n=7) pretreatments (p<0.001) and less with verapamil (n=7) pretreatment (p<0.005) compared with the control ischemia (n=7). The onset of the second decline was significantly delayed by verapamil (p<0.01) and accelerated by heptanol (p<0.005) and high-[Ca\textsuperscript{2+}]\textsubscript{e} (p<0.001) pretreatments. The minimum WHC at the end of ischemia was significantly enhanced by verapamil (p<0.005), but significantly attenuated by high-[Ca\textsuperscript{2+}]\textsubscript{e} (p<0.05).

Fig 7 shows the effects of reperfusion on the perfusion pressure and WHC at the preischemic flow rate (10 ml·min\textsuperscript{−1}·g ww\textsuperscript{−1}) (n=7). The duration of control ischemia was set at 20, 40 or 60 min. After the reperfusion, the perfusion pressure returned exactly to the preischemic level, but the WHC was greater than the preischemic level (n=7). The onset of the second decline was significantly delayed by verapamil (p<0.01) and accelerated by heptanol (p<0.005) and high-[Ca\textsuperscript{2+}]\textsubscript{e} (p<0.001) pretreatments. The minimum WHC at the end of ischemia was significantly enhanced by verapamil (p<0.005), but significantly attenuated by high-[Ca\textsuperscript{2+}]\textsubscript{e} (p<0.05).

The main findings of this study are that (1) WHC in the well-perfused hearts decreases in response to a reduction of [Na\textsuperscript{+}]\textsubscript{e}, (2) WHC declines initially in a single exponential manner, and the subsequent quasi-steady state is followed by a second gradual decline during no-flow ischemia, (3) this gradual decline is augmented by both heptanol and high-[Ca\textsuperscript{2+}]\textsubscript{e} and attenuated by verapamil, and (4) the postischemic WHC is greater than the preischemic level and this difference is proportional to the ischemic interval and tissue water content.

**WHC Under Physiological Perfusion**

No prior studies have investigated the determinants of WHC comprehensively and in addition the interpretation of WHC is complicated because beating whole hearts contain inhomogeneous compartments (ie, vascular network containing solution, complex interstitial space and compact myocardium with variable extent of cellular coupling). In the present study the WHC remained constant under altered electrode positioning that kept the interelectrode distance to the longest preparation diameter, suggesting that epicardial fiber orientation and motion artifacts have no substantial impact on global WHC monitoring. Our perfusion study showed [Na\textsuperscript{+}]\textsubscript{e}-dependent coronary resistance (Figs 3,4), which is in good agreement with the literature. WHC in the well-perfused heart is also greatly influenced by [Na\textsuperscript{+}]\textsubscript{e}. This [Na\textsuperscript{+}]\textsubscript{e}-dependence is not only related to the altered solution conductivity, but is also ascribed to the [Na\textsuperscript{+}]\textsubscript{e}-dependent tissue excitability or cellular coupling mediated by the internal Ca\textsuperscript{2+} concentration ([Ca\textsuperscript{2+}]\textsubscript{i}), which is regulated by the Na\textsuperscript{+}/Ca\textsuperscript{2+} exchanger. Thus, WHC is considered to be governed by both coronary circulation and myocardial characteristics.

**WHC During IR**

As shown in Fig 1B, the gross equivalent circuit of our experiment is a parallel combination of (1) extracellular resistance (r\textsubscript{e}) and (2) a series combination of intracellular resistance (r\textsubscript{i}) and membrane capacitance (C\textsubscript{m})\textsuperscript{10} The contribution of coronary perfusion to cardiac impedance (or conductance as the inverse condition) depends greatly on the experimental setting and electrode design (ie, impedance rise during ischemia is controversial in large animal studies)\textsuperscript{10–12} Kléber et al\textsuperscript{13} used arterially perfused rabbit papillary muscle to evaluate r\textsubscript{e} and r\textsubscript{i} and they reported an initial rise in r\textsubscript{e}, which coincided with a fall in perfusion pressure at the onset of ischemia. In the present study, the WHC value halved within several minutes of control ischemia (Fig 6). The single exponential decay of WHC in this phase was not influenced by any of the pretreatments (Table 1), suggesting that vascular collapse (elevation of r\textsubscript{e}) per se is involved (Fig 5). Comparing our data with that from the literature, the relative contribution of r\textsubscript{e} to tissue impedance in our study was greater than in other studies\textsuperscript{10–12}

The second gradual decline of WHC is important because it relates to cellular uncoupling, which is one of the determinants of DFT\textsuperscript{14} The time course of this decline during control ischemia (Fig 6) was in good accordance with that of an increase in r\textsubscript{i} in papillary muscle subjected to ischemia\textsuperscript{13,15} Myocardial ischemia induces intracellular acidosis, [Ca\textsuperscript{2+}]\textsubscript{i} overload, and a fall in ATP content, leading to cellular uncoupling\textsuperscript{16} Changes in the second WHC decline observed after the various pretreatments (Fig 6) are readily explained by cellular uncoupling during ischemia (ie, high-[Ca\textsuperscript{2+}]\textsubscript{e} may have accelerated [Ca\textsuperscript{2+}]\textsubscript{i} accumulation and heptanol pretreatment may have evoked earlier cellular uncoupling, whereas verapamil may have attenuated [Ca\textsuperscript{2+}]\textsubscript{i} overload and delayed cellular uncoupling)\textsuperscript{15}

The preischemic WHC showed no significant changes with any of the pretreatments (Table 1) partly because of low r\textsubscript{i}. The postischemic increase in WHC was proportional to the ischemic interval and tissue water content (Fig 7) and was modified by the various pretreatments (Table 1), suggesting that postischemic WHC reflects tissue edema based on [Ca\textsuperscript{2+}]\textsubscript{i}-mediated IR injury\textsuperscript{17} Ischemic catabolite accumulation raises tissue osmolarity, and the transmembrane...
osmotic gradient causes time-dependent tissue swelling\textsuperscript{18–20} This is supported by significant (p<0.001) differences in LVEDP at the end of reperfusion in the verapamil and high-
[Ca\textsuperscript{2+}]e groups relative to the control group in this study.

**Clinical Implications**

Our results suggest some clinical implications with respect to DFT. Coronary circulation collapses and [Ca\textsuperscript{2+}]e homeostasis is impaired by prolonged ventricular fibrillation\textsuperscript{21} In such circumstances, WHC declines (Figs 5, 6), while DFT is reportedly elevated.\textsuperscript{1,2} On the other hand, ECG parameters. Second, the electrode-tissue interface us from monitoring arrhythmias or correlating WHC with

**Study Limitations**

The effects of Ca antagonists on DFT are also controver-
tional studies.

**Conclusion**

DFT depends on the density of current traversing the whole heart at the moment of defibrillation. Although time-
dependent alterations in DFT in ischemic hearts may be attributable at least in part to dynamic changes in WHC, WHC data should be interpreted carefully because the monitoring reflects many physiological factors, such as coronary circulation, electrical coupling of contiguous cardiac myocytes, and myocardial tissue edema.

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