receptor discharge was related mainly to the v wave. This suggests that the receptors were activated principally by distortion of the atria.

The present studies demonstrate that atrial C fibers can be activated by changes in atrial pressure within values recorded in normal conditions. However, the experiments required thoracotomy, which has been shown to cause a decrease in cardiac volume and also in the activity of atrial receptors subserved by medullated vagal afferents. If the same was true for atrial C fibers, these would have a higher spontaneous activity when the thorax is intact and respiration spontaneous.

Certain evidence suggests that nonmedullated cardiac vagal afferents are involved in cardiovascular control. Selective electrical stimulation of these fibers in cats causes bradycardia and systemic vasodilation, especially in the renal vascular bed; in contrast, selective activation of the medullated cardiac afferents causes tachycardia and systemic vasoconstriction. It also has been shown recently that atrial receptors with vagal afferents exert a tonic vasomotor inhibition in the dog. Thus it is possible that atrial C fibers are involved in cardiovascular control. The further observation that changes in blood volume within a physiological range in atrial pressure cause an increase in activity of these atrial C fibers might indicate a role in the control of blood volume.

Electrogenesis of Increased Norepinephrine Sensitivity of Arterial Vascular Muscle in Hypertension

KENT HERMSMEYER, PH.D.

SUMMARY The possibility that the vascular muscle cell might contribute to the development of essential hypertension by being more responsive to norepinephrine because of an inherently lower membrane potential ($E_m$) was investigated. Experiments were designed to test the hypothesis that $E_m$ of arterial vascular muscle cells from spontaneously hypertensive rats (SHR) are less negative than those from matched Kyoto normotensive rats (KNR). The caudal artery, a muscular, densely innervated regulating artery, was greater for vascular muscle of SHR than KNR. The caudal artery undergoes a large depolarization when driven slightly into the physiological range of $K^+$ concentrations from 2.7 mM to 50 mM. From the relationship between $E_m$ and $K^+$ concentration, intracellular $K^+$ concentration ([K+]$_i$) was estimated to be 150 mM for SHR and 170 mM for KNR. The caudal artery undergoes a large depolarization when $K^+$ is removed from the superfusing solution and a transient hyperpolarization that exceeds the calculated $E_K$ (potassium equilibrium potential) when $K^+$ is replaced. The magnitude of the hyperpolarization on returning to 30 mM or 50 mM $K^+$ always was greater for vascular muscle of SHR than KNR. The apparently lower [K+]$_i$ and more active (compensating) electrogenic ion transport in the SHR vascular muscle cells thus result in an unaltered $E_m$ at body temperature in the physiological range of $K^+$ concentrations. However, depolarization by norepinephrine was greater over the middle of the dose-response curve, and this greater depolarization caused the contractions of SHR arteries to be greater. The altered electrogensis of the SHR vascular muscle cells is postulated to provide a mechanism for the increased reactivity of arteries to norepinephrine in hypertension.

Acknowledgments

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ALTERED BASIS OF MEMBRANE POTENTIAL

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hypertension, an alteration in properties of the vascular muscle cell is a likely candidate. A difference in cell function at the membrane level has been found by Jones et al in studies of ion flux and regulation in an inbred (the Okamoto) strain of genetically hypertensive rats. There was an increase in turnover of K+ and Cl− and an excess accumulation of intracellular Na+ in arteries of the hypertensive rats, as compared to normotensive rats. These findings suggest an increased permeability to all three ions. On the basis of the ion fluxes, Jones calculated that if increases in the permeability to each ion were about equal, the membrane potential (Em) would be approximately 10 mV less negative in vascular muscle cells from spontaneously (genetically) hypertensive rats (SHR) than in cells from normotensive rats. The present study was carried out to provide a direct test of the hypothesis that Em is less negative in SHR vascular muscle cells. The results show that Em is not lower at physiological temperature. However, when electrogenic ion transport is suppressed by low temperature, the SHR cells have a less negative Em than cells from normotensive animals. The altered Em electrogensis is manifest as a greater depolarization by norepinephrine (NE) and appears therefore to contribute to the increased constrictor response in hypertension.

Methods

Experiments were carried out on caudal arteries from 31 matched pairs of the Okamoto-Aoki strain of Kyoto Wistar hypertensive rats (SHR) and their Kyoto Wistar normotensive controls (KNR). The rats were obtained from colonies maintained at the University of Iowa. The SHR were from the F4 generation, corresponding to the F28 generation from the parental strain as the SHR. The experimental pairs consisted of one from the hypertensive colony and one from the normotensive colony, and were matched on the basis of weight and sex. The rats were 6-10 weeks old; over this age range the mean systolic blood pressure of rats in the SHR colony averaged 152 ± 8 (mean ± SD) mm Hg and in the KNR colony, 128 ± 9 mm Hg. The solutions used for superfusion of the isolated arteries were gassed with 95% O2 and 5% CO2 and had the following composition (mM): 145.3 Na+, 4.7 K+, 1.8 Ca2+, 0.8 Mg2+, 142.9 Cl−, 11.9 HCO3−, 0.4 H2PO4−, 7.8 dextrose, and 0.027 Ca2+ ethylenediaminetetraacetic acid (EDTA). To change K+ concentration, equivalent alterations in the molarity of Na+ were made to maintain constant osmolarity, except for the 150 mm KCl solution, which was 50 mm hypertonic. After exposure to each alteration of the electrolyte composition of the solution, the arteries were returned to control solution and full recovery was verified before the pair was exposed to the next solution.

To record Em, vascular muscle cells were impaled from the adventitial side by KCl-filled glass micropipette electrodes. Caudal arteries, 350 ± 40 (mean ± SD) μm in outside diameter were pinned in silicone rubber chambers with glass pins without being cut open and were carefully protected from stretching at all times. Use of vessels in cylindrical form and avoidance of stretch consistently resulted in larger initial values for Em and greater longevity of the preparation. Caudal arteries usually maintained full responsiveness to NE for at least 5 hours and as much as 10 hours when handled with the precautions noted. Measurements reported here were made during the first 4 hours. The superfusion rate was 3 ml/minute and chamber volume was 1 ml. The intracellular recording electrode and the superfusing solution were connected to a preamplifier (W-P Instruments M-701) by Ag:AgCl half cells, and the preamplifier output was displayed on a storage oscilloscope, from which the data were taken. Cell impalements were accepted only if the reference potential (baseline) and electrode resistance were stable and had the same value before and after an impalement. Cell impalement was signaled by a sharp voltage drop, and cell input resistance (measured with a single microelectrode) was between 4 and 20 MΩ. Sections of caudal arteries from SHR and KNR were mounted side by side in the same chamber, and an equal number of cells of each were impaled with the same electrode to eliminate variability introduced by different micropipette electrodes. All measurements were made 5-30 minutes after a solution change.

Tension was measured by cutting the arteries helically, mounting them in a muscle chamber with a volume of 1.5 ml, attaching them to Grass tension transducers (FT-03) and displaying the record on a Grass polygraph. Superfusion rate was 5 ml/minute. Four strips were mounted simultaneously to provide two SHR and two KNR arteries for immediate comparison. Initial tensions were adjusted to give maximum active tension for each strip. The optimum initial tension was determined by electrical field stimulation as the length of the strip was varied. Dose-response curves were calculated as geometrical means. Cross-sectional area was calculated from strip length and weight to provide an absolute value for tension.

Norepinephrine (r-arterenol HCl, Sigma) (NE) was diluted in an aspirator bottle, which served as the superfusing reservoir, immediately before being introduced into the tissue chamber. Effect of release of endogenous NE was eliminated for all the experiments involving a change in [K+]o by denervation in vitro with 6-hydroxydopamine (6-OHDA), using the method of Aprigliano and Hermesmeyer. This method, which involves exposure for 10 minutes to 300 μg of 6-OHDA/ml in a glutathione antioxidant buffer, causes rapid, specific destruction of adrenergic nerve endings. Phentolamine (1 μM) was added to the 6-OHDA solution to prevent depolarization of the cells by the norepinephrine release that is an initial consequence of 6-OHDA treatment. After 6-OHDA treatment, recovery of the vascular muscle cells was verified by measurements of transmembrane potential which showed pretreatment values of Em.

Results

RESTING Em AS A FUNCTION OF K+ CONCENTRATION

At body temperature resting Em did not differ between caudal arteries from SHR and KNR for extracellular K+ concentrations ([K+]o) below 50 mm. At the normal [K+]o of 4.7 mm, Em was about −55 mV for both SHR and KNR vascular muscle cells (Fig. 1). However, at higher [K+]o...
concentrations of 50, 100, and 150 mM, $E_m$ was significantly less negative in SHR than in KNR ($P < 0.05$ for paired $t$-test comparison). The maximum slope of the line drawn through the data points was 54 and 52 mV per 10-fold change in [$K^*$]$_o$ for SHR and KNR vascular muscle cells, respectively, as compared to the 61 mV per decade calculated on the basis of the electrochemical gradient for $K^+$, $E_K = RT/ZF \ln [K^*]_o/[K^+]$, ($R$ = the gas constant, $T$ = temperature, $Z$ = valence, $F$ = the Faraday constant, and [K$^+$], = intracellular $K^+$ concentration).

The $K^+$ concentrations used in this equation should be corrected for the degree of ionization in solution by the activity coefficients. However, in the present experiments the objective was a comparison of SHR and KNR cells in the same solution. Therefore, the absolute values of $K^+$ activity need not be determined and data were plotted simply as a function of total $K$ concentration. The point at which potential became 0 was at a [$K^*$]$_o$ of 151 mM for SHR and 171 mM for KNR. Standard errors were less than 1.5 mV and are not shown. Numbers in parentheses indicate number of impalements and number of rats. Lines between 50 and 150 mM [$K^*$]$_o$ were determined by linear regression, with $r$ values of 0.9033 and 0.9359 for KNR and SHR, respectively. All $E_m$ values shown are negative with reference to superfusing solution.

There always was a transient hyperpolarization of caudal artery vascular muscle when $K^+$-free solution was changed to one containing $K^+$. Figure 3 compares the depolarizations which occurred in 0 $K^+$ and the hyperpolarizations on returning to 30 mM $K^+$ for SHR and KNR. The transient hyperpolarization was greater by about 7 mV for vascular muscle cells from SHR than from cells from KNR, and the

**FIGURE 1** Membrane potential ($E_m$) of arterial vascular muscle cells as a function of extracellular $K^+$ concentration ([K$^*$]$_o$) in Kyoto Wistar normotensive rats (KNR) and spontaneously hypertensive rats (SHR) at 36°C. At [K$^+$]$_o$ above 50 mM, values for KNR are significantly higher than for SHR. The 0 potential intercept indicates intracellular $K^+$ activities equivalent to extracellular concentrations of 151 mM for SHR and 173 mM for KNR. Standard errors were less than 1.5 mV and are not shown. Numbers in parentheses indicate number of impalements and number of rats. Lines between 50 and 150 mM [K$^+$]$_o$ were determined by linear regression, with $r$ values of 0.9033 and 0.9359 for KNR and SHR, respectively. All $E_m$ values shown are negative with reference to superfusing solution.

**FIGURE 2** Membrane potential ($E_m$) of arterial vascular muscle cells as a function of [K$^*$]$_o$ in KNR and SHR at 16°C. With the energy-dependent portion of $E_m$ greatly suppressed, the ion gradient contribution to $E_m$ can be evaluated. $E_m$ of SHR vascular muscle cells was significantly less negative than for KNR cells at all [K$^+$]$_o$ by paired $t$ test ($P < 0.05$ confidence level). The 0 potential intercepts are practically the same as in Figure 1 at 153 mV for SHR and 171 mV for KNR. Abbreviations, standard errors, and numbers in parentheses are as in Figure 1. Lines between 30 and 150 mM [K$^+$]$_o$ were determined by linear regression, with $r$ values of 0.9999 and 0.9996 for KNR and SHR, respectively. All $E_m$ values shown are negative with reference to superfusing solution.

**FIGURE 3** Membrane potential ($E_m$) of caudal arterial vascular muscle cells from spontaneously hypertensive rats (SHR) and Kyoto Wistar normotensive rats (KNR) when [K$^*$]$_o$ was changed from 4.7 mM to 0 mM and then to 30 mM. Both the depolarization in 0 $K^+$ and the hyperpolarization on return to 30 mM $K^+$ were greater for SHR than KNR. The data shown are from one pair of arteries and are typical of the time courses observed; in several experiments there was a more prolonged hyperpolarization in the SHR cells and less hyperpolarization of the KNR cells, producing an even greater difference. All $E_m$ values shown are negative with reference to superfusing solution.

**EVIDENCE FOR ELECTROGENIC ION TRANSPORT**

There always was a transient hyperpolarization of caudal artery vascular muscle when $K^+$-free solution was changed to one containing $K^+$. Figure 3 compares the depolarizations which occurred in 0 $K^+$ and the hyperpolarizations on returning to 30 mM $K^+$ for SHR and KNR. The transient hyperpolarization was greater by about 7 mV for vascular muscle cells from SHR than for cells from KNR, and the...
plots of $E_m$ cross over during the 1st minute in high K+ solution. The hyperpolarization was eliminated for both SHR and KNR by reducing the temperature by 20° or by exposure to 1 mM ouabain (Table 1). The extent of hyperpolarization of vascular muscle cells of both SHR and KNR thus parallels the portion of the $E_m$ contributed by a temperature-sensitive process (cf. Figs. 1 and 2 for values of $E_m$ at 4.7 mM [K+]o). After action of ouabain or cooling by 20°C, depolarization always was observed when 30 mM [K+] was introduced. Hyperpolarizations to values of $E_m$ more negative than the calculated $E_K$ indicate the presence of electrogenic ion transport in both SHR and KNR vascular muscle, with a greater activity in SHR than in KNR cells. Furthermore, the greater magnitude of the electrogenic element in SHR cells can account for the lack of a difference in $E_m$ at physiological [K+]e (Fig. 1) despite a lower [K+] in SHR cells.

**DEPOLARIZATION BY NOREPINEPHRINE**

The magnitude of depolarization caused by equal concentrations of NE was greater for SHR and KNR arteries at concentrations of 30 ng/ml or higher. Figure 4 shows the difference between $E_m$ of SHR and KNR cells in solutions containing NE and illustrates that progressively greater concentrations of NE caused graded depolarizations of increasing magnitude in the caudal artery vascular muscle cell. Depolarization occurred within 1 minute after exposure of the artery segment to solution containing NE, and the $E_m$ then remained constant during superfusion with that solution. The highest concentrations shown here produced maximal contractions of the arteries, with maximal depolarization to a level of about −25 mV for KNR and −20 mV for SHR. The action of NE on arterial vascular muscle cells thus was limited to depolarization to some intermediate value of $E_m$ (rather than complete depolarization) even at concentrations producing maximal contractile activation.

**TABLE 1 Elimination of the Transient Hyperpolarization to beyond $E_K$ Replacement by Ouabain or Low Temperature**

<table>
<thead>
<tr>
<th>Change in potential</th>
<th>Measured</th>
<th>Calculated</th>
</tr>
</thead>
<tbody>
<tr>
<td>$36°C$ (1)</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>1 mM ouabain (36°C)</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>$16°C$</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

SHR = spontaneously hypertensive rats; KNR = Kyoto Wistar normotensive rats; n = number of impalements and number of rats, respectively; $E_K$ = potassium equilibrium potential. Hyperpolarization (depolarization) in millivolts on switching from 0 mM K+ to 30 mM K+. Hyperpolarizations shown are maxima. Note that hyperpolarizations beyond calculated levels were not observed in ouabain or 16°C solutions. Measurements were made after 1 hour in ouabain or 16°C solutions. Absolute values of membrane potential ($E_m$) in 0 mM K+ solutions without ouabain are given in Figures 1 and 2. In ouabain at 4.7 mM [K+]e, $E_m$ averaged −34.0 mV for SHR and −44.2 mV for KNR vascular muscle cells in 0 mM [K+]e, $E_m$ averaged −27.7 mV for SHR and −29.3 mV for KNR. Calculated values represent the difference between $E_m$ measured in 0 K+ and the $E_K$ based on intracellular K+ concentrations [K+]i, from Figures 1 and 2.

**FIGURE 5** Contraction of caudal artery strips from spontaneously hypertensive rats (SHR) and Kyoto Wistar normotensive rats (KNR) in response to norepinephrine. The responses of SHR vascular muscle are greater in midrange concentrations of NE were greater for SHR than KNR, as shown in Figure 5. The concentration for a half-maximum response (EC_{50}) was shifted to the left by a factor of 2.2 in SHR (22.3 vs. 50.1 ng/ml). The maximum contraction was slightly greater for SHR (770 ± 50 megadynes/cm²) than KNR (650 ± 65 megadynes/cm²) (means ± SE). At sea level, 980 megadynes of force are produced by 1 kg of mass.) There were no detectable differences in threshold concentrations. The increase in sensitivity of vascular muscle of SHR over that of KNR was

**FIGURE 4** Depolarization of vascular muscle cells of spontaneously hypertensive rat (SHR) and Kyoto Wistar normotensive rat (KNR) caudal arteries by norepinephrine. Depolarization of SHR was greater at 30 ng/ml and higher concentrations by the paired t-test (P < 0.05 confidence level). Standard errors all are less than 1.5 mV and are not shown. Numbers in parentheses indicate the number of cells impaled and number of rats, respectively. All values for $E_m$ shown are negative with reference to superfusing solution.
determined for a range of initial muscle lengths including \( L_a \), which provided the data shown above for active tension.

**Discussion**

The three main conclusions from these experiments are that (1) arterial vascular muscle cells of SHR show a lower \( [K^+]_i \) than those of KNR, that in cells of SHR the electrogenic ion transport component of \( E_m \) is larger than for KNR cells, and that depolarization and contractile activation are greater at midrange NE concentrations in SHR than KNR. The experiments thus appear to have uncovered a cellular mechanism which could be a fundamental factor in initiating the series of changes the cardiovascular system undergoes in essential hypertension. Furthermore, the present data provide a connection between the report of Jones\(^4\) that ion transport and regulation are altered in vascular muscle cells of genetically hypertensive rats and the increased sensitivity of the circulatory system of intact SHR to injected NE.\(^9\)\(^10\)

The cause of the increased sensitivity of SHR caudal artery appears to be the increased depolarization at each concentration of NE, which results from the two fundamental alterations in \( E_m \) electrogenesis, that is, a lower ionized \([K^+]_i\) (decreased \( E_m \)) which is offset by a compensatory electrogenic ion transport. The evidence for the lower ionized \([K^+]_i\) is from the \( E_m-\log[K^+]_i \) relationship, which becomes linear at higher \([K^+]_i\) (Figs. 1 and 2). Such measurements allow reliable estimates of ionized \([K^+]_i\) (which is important for cell excitability) and are not subject to interference from bound \( K^+ \), which is included in chemical determinations. The present results show a difference of approximately 20 mV in ionized, unbound \([K^+]_i\), which appears in two independent sets of data (Figs. 1 and 2). The difference in \([K^+]_i\) causes \( E_m \) to be approximately 3 mV less at each value of \([K^+]_i\) (with the electrogenic mechanism eliminated, as in Fig. 2) and thereby contributes to the greater depolarization of SHR than KNR cells by NE. A difference of a few mV in \( E_m \) is quite significant because the progressive depolarization of gradedly responsive vascular muscle by increasing concentrations of vasoconstrictor agents to produce graded contractile activation covers a relatively small range of values of \( E_m \); the entire dose-response curve may be governed by a change of less than 30 mV in \( E_m \) (Fig. 4).\(^11\)\(^12\)

Evidence for electrogenic ion transport is most directly provided by the hyperpolarization found on switching from \( K^+\)-free solution to one containing 30 mm K; this hyperpolarization is abolished by ouabain or by reducing the temperature by 20°C. Thus the values of \( E_m \) of vascular muscle cells are maintained inappropriately negative in relation to \([K^+]_i/[K^+]_o\) only by a temperature-dependent, ouabain-sensitive mechanism. Such an electrogenic ion transport has been reported for arterial vascular muscle by Somlyo et al.\(^14\)\(^15\) and by Hendrickx and Casteels.\(^16\) During neurotransmitter-induced increases in membrane conductance, depolarization would be exaggerated in cells with a larger electrogenic transport component of \( E_m \) because the electrogenic ion current would be short-circuited by the low membrane resistance of the activated cells. Furthermore, due to the decreased \([K^+]_i\) in SHR vascular muscle cells, an exaggerated depolarization would result from an increase in ionic conductance for a depolarizing ion because \( E_m \), which is the only hyperpolarizing influence, would be less negative. Thus a larger dependence of \( E_m \) on an electrogenic ion transport mechanism would be expected to cause increased reactivity of the myovascular cells to NE.

The evidence for increased electrogenic ion transport and low \([K^+]_i\) in SHR vascular muscle at first seems paradoxical. Increased active ion transport would tend to maintain a high \([K^+]_i\) and a low \([Na^+]_i\). However, the electrogenic ion transport may be a minor determinant of the intracellular composition, with exchange mechanisms or separate non-electrogenic ion transport of \( Na^+ \) being the major determinants. In fact, the electrogenic ion transport may be stimulated to greater activity in SHR vascular muscle cells by an elevated \([Na^+]_i\), which in turn results from lower activity of other mechanisms. Alternatively, the electrogenic ion transport could be associated with ions other than \( Na^+ \).

To study directly the electrogenesis of \( E_m \) in vascular muscle cells, it was necessary to eliminate the influence of catecholamine release from nerve endings in caudal artery because we have shown that the innervation is very dense.\(^17\) Furthermore, we have found that a change in \([K^+]_i\) can produce maximal contractions of caudal artery by release of endogenous NE from nerve terminals.\(^18\) Thus, elimination of the intrinsic NE release mechanism was needed for meaningful analysis of the muscle cells. A recently developed method for rapid, specific elimination of adrenergic nerve endings by 6-hydroxydopamine treatment in vitro\(^19\) which does not alter the muscle cell \( E_m \) or NE sensitivity greatly facilitated these experiments.

Both medial thickening and intrinsic hyperresponsiveness have been postulated to be important causes of hypertension, and a basis for discrimination between them has been proposed.\(^19\) The basis for a steeper slope and unchanged threshold of the tension-concentration curve could be medial thickening alone. However, the present data show that a different electrogenesis of the membrane potential also can lead to an increased slope and unchanged threshold. The wall thickness is an important parameter to include in hypotheses constructed about hypertension because medial thickening occurs in hypertension. However, as Folkow et al.\(^20\)(1971) have suggested, the wall thickening seems to be a reversible secondary event following a primary event, and this finding also was demonstrated by Hansen et al.\(^21\) The changes in wall thickness may thus magnify and maintain the increased slope of the NE dose-response curve which results from the primary event initiating hypertension. The alterations in membrane control of ions and consequent changes in excitability that form the subject of the present report would seem to be candidates for the initiating event in hypertension.

**References**

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The Relationship between Overdrive Suppression and Overdrive Excitation in Ventricular Pacemakers in Dogs

MARIO VASSALLE, M.D., MICHAEL CUMMINS, M.D., CARLOS CASTRO, M.D., AND JACKSON H. STUCKEY, M.D.

SUMMARY We studied the excitatory and inhibitory effects of overdrive on idioventricular pacemakers in anesthetized dogs with recently induced complete atrioventricular block. The following results were obtained: (1) a slow driving rate may induce a temporary rhythm which may be reinitiated with additional stimuli; (2) the induced rhythm may appear as coupled extrasystoles which, on interruption of the drive, are found to be self-sustaining; (3) during continued slow driving, extrasystoles may appear and disappear in a cyclical manner; (4) a short period of fast driving may be followed by a fast new rhythm, the rate and duration of which are a function of the rate and duration of drive; (5) fast driving may induce a new rhythm at a rate below predrive control; (6) after a long period fast driving, only suppression follows; and (7) intermittent periods of fast driving lead to a summation of inhibition with each successive period. These results suggest the following conclusions: (1) under certain conditions, electrical driving instead of inducing suppression may induce a rhythm ("overdrive excitation") at a rate similar to, faster than, or slower ("inhibited excitation") than control; (2) the duration of diastole and the number of driven beats are major factors in the induction of new rhythms; and (3) overdrive excitation is counteracted by overdrive inhibition, with development of the former requiring fewer beats than the latter.

IT HAS BEEN SHOWN repeatedly that stimulating the heart at a rate faster than that of its spontaneous pacemaker is followed by a temporary suppression of pacemaker activity.3-10 This phenomenon ("overdrive suppression") has been demonstrated both in vivo4, 6, 7, 8 and in vitro.9, 10 In Purkinje fibers superfused in vitro and exposed to norepinephrine, overdrive may not be followed by suppres-
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