Correlation of ventricular mechanosensory neurite activity with myocardial sensory field deformation

R. D. Foreman, R. W. Blair, H. R. Holmes, and J. A. Armour

Correlation of ventricular mechanosensory neurite activity with myocardial sensory field deformation. Am. J. Physiol. 276 (Regulatory Integrative Comp. Physiol. 45): R979–R989, 1999.—The mechanosensory activity generated by ventricular epicardial sensory neurites associated with afferent axons in thoracic sympathetic nerves was correlated with sensory field deformation (long axis, short axis, and transmural dimension changes), regional intramyocardial pressure, and ventricular chamber pressure in anesthetized dogs. Ventricular mechanosensory neurites generated activity that correlated best with strain developed along either the long or short axis of their epicardial sensory fields in most instances. Activity did not correlate normally to local wall thickness or to regional wall or chamber pressure development in most cases. During premature ventricular contractions, the activity generated by these sensory neurites correlated best with maximum strain developed along at least one sensory field epicardial vector. Identified sensory neurites were also activated by local application of the chemical bradykinin (10 µM) or by local ischemia. These data indicate that the activity generated by most ischemia-sensitive ventricular epicardial sensory neurites associated with afferent axons in sympathetic nerves is dependent on not only their local chemical milieu but on local mechanical deformation along at least one epicardial vector of their sensory fields.

ANATOMIC AND FUNCTIONAL DATA indicate that axons associated with some mammalian ventricular sensory neurites (sensory nerve endings) course centrally in the cranial thoracic sympathetic rami (4, 7, 17, 19, 21) to somata in dorsal root ganglia (12). Most ventricular sensory neurites associated with dorsal root ganglion afferent neurons (14) or afferent axons in sympathetic nerves respond to chemicals such as bradykinin (4, 6, 10, 14, 17, 21, 22) as well as local mechanical deformation (14, 17). Few ventricular sensory neurites associated with axons in sympathetic nerves (20) or dorsal root ganglion neurons (14) respond to either mechanical or chemical stimuli. Ischemia-induced alterations in the activity generated by left ventricular sensory neurites associated with axons in sympathetic nerves have been ascribed to local bulging as well as alterations in their chemical milieu (17, 19, 21, 22). Although chemicals like bradykinin and nitroglycerin act to reduce left ventricular systolic pressure when they enter the circulation in sufficient quantities to affect systemic vascular resistance (11), some of the effects that pharmacological agents exert on ventricular sensory neurites may be secondary to regional mechanical alterations (8, 14).

Atrial mechanosensory neurites respond to changing strain in one vector of their sensory fields (3, 9). Whether ventricular sensory neurites respond to the mechanical deformation along one or more vectors of their sensory fields during normal cardiac cycles remains unknown. Nor is it known how ventricular epicardial sensory neurites sense abnormal ventricular mechanical events such as occur during ventricular ectopic beats.

The present series of experiments was performed to determine the response characteristics of ischemia-sensitive ventricular epicardial sensory neurites associated with axons in sympathetic nerves to regional deformation and local pressure development during normal cardiac cycles. We also sought to determine the response characteristics of such sensory neurites during abnormal ventricular contractile states such as occur during ventricular premature contractions. The characteristics of such sensory neurites in response to an exogenously applied chemical, bradykinin, were also studied to determine whether and how identified ischemia-sensitive neurites responded to chemical stimuli. In this manner we sought to characterize the mechanosensory properties of ischemia-sensitive ventricular sensory neurites associated with dorsal root ganglion afferent neurons.

METHODS

Adult mongrel dogs (n = 22) of either sex, weighing between 18 and 22 kg, were studied. All experiments were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of the University of Oklahoma Health Sciences Center.

General methods. Animals were sedated with ketamine hydrochloride (10 mg/kg im) and anesthetized with α-chloralose (100 mg/kg iv). Supplemental doses of α-chloralose (25–35 mg/kg iv) were administered every hour or less, as required. Noxious stimuli were applied to a paw throughout the experiments to ascertain the adequacy of the anesthesia. After intubation, the lungs were inflated with a Harvard Respirator pump to an end-tidal CO₂ of 3–4%. Rectal temperature was maintained at 37.5 ± 2°C with the use of a heating pad. A constant infusion of Tyrode solution was administered via a femoral vein at a rate of ~150 ml/h. After a bilateral

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
Thoracotomy was performed, PE-50 catheters were placed in the left atrial cavity via an incision in its appendage and the right ventricular cavity via an incision in the right atrial appendage. A Cordis no. 7 catheter was led into the aortic arch via a femoral artery to record aortic pressure. These catheters were attached to Statham pressure transducers. A Millar PC-360 Mikro-tip pressure transducer was inserted via the apex of the left ventricle into the left ventricular cavity to measure left ventricular cavity pressure. Separate lengths of umbilical tape were placed around the descending thoracic aorta and the pulmonary artery to allow us to partially occlude each of these vessels individually later in the experiments. A lead II electrocardiogram, along with the various pressures described above, was monitored continuously on paper using a Gould eight-channel rectilinear recorder. All data were also stored on tape via an Ampex SR1300 tape recorder for later analysis.

Recording activity generated by sympathetic afferent axons. The left T2 to T4 rami communicantes or the left sympathetic chain caudal to the left stellate ganglion was sectioned. The peripheral (cardiac) end of each sectioned nerve was placed in a mineral oil bath. A dissecting microscope was used to desheath each nerve and isolate groups of axons. Each isolated nerve was then placed in a tissue saline solution and the axons were superfused with fresh saline. A second platinum electrode was then placed in the tissue saline solution, and the axons were stimulated with a rectangular pulse delivered directly onto the axons. The three pairs of ultrasonic crystals used to assess sensory field dimensions interfered with the recording of action potentials generated by axons identified by means of an oscilloscope. Thus a window discriminator was employed to identify afferent axonal activity when the various interventions (described in Interventions) were introduced. A Mentor N-750 window discriminator permitted the identification and isolation of activity generated by individual axons in the presence of this electrical interference. The threshold of the window discriminator was set above the ultrasonic crystal signals registered on the oscilloscope, thereby permitting overriding afferent axonal activity signals to be quantified. The output of the window discriminator and measured cardiovascular indexes were recorded on paper using a Gould eight-channel pen rectilinear recorder. Data were also stored for later analysis on tape using an Ampex 5R 1300 tape recorder. Interventions were carried out before and after placement of the ultrasonic crystals and the Konigsberg Instruments pressure transducer to ensure that the placement of these devices in the myocardium did not alter the responsiveness of local mechanical stimuli in a detectable fashion.

At the termination of each experiment, epicardial loci containing each identified sensory field were stimulated electrically (0.1 Hz, 4 V, 1 ms) using one electrode while the ultrasonic length recorder was turned off; the other electrode was attached to the mediastinum. This was done so that the latency of activation of action potentials generated by functionally identified axons could be determined. A silk thread was then placed from each identified sensory field along the course of the nerves to the site where axonal activity was recorded so that the distance from sensory neurites to the axonal recording site could be estimated (20–27.5 cm). An overdose of Euthanol Forte (20 ml iv) was then administered to the animals, and baseline sensory field dimensions were determined. Each identified sensory field was undercut with a sharp scalpel to confirm that it was superficial in nature (i.e., when mechanically distorted it still generates action potentials after undercutting). Tissues around each investigated sensory field were then trimmed away, starting from its apical region, to confirm the epicardial extent of studied sensory fields.

Interventions. Bipolar electrodes were placed on the right atrial appendage and connected to a Grass model SD9 stimulator. The frequency with which these electrodes were activated was regulated with a DEC PDP 11/10 computer. This permitted the delivery of electrical stimuli (0.1 ms, 1 V) to the atria at 15 beats/min above resting heart rates by means of the computer. The data obtained during such epochs were stored and analyzed later by shifting afferent axonal activity back in time during each cardiac cycle to account for the calculated conduction delay that occurred due to the distance between each investigated sensory neurite and the axon site where its activity was recorded. Data obtained during atrial pacing were summed using the computer's capabilities to generate average activity histograms during
cardiac cycles of fixed duration. The computer-driven stimulator was then employed to pace the ventricles at a rate 15 beats/min above the intrinsic heart rate for 25 epochs, each epoch consisting of 15 cardiac cycles (total of 375 cardiac cycles/run). Ventricular pacing electrodes were attached to the epicardium of the ventricle that did not contain the identified sensory field. In the one animal in which the investigated afferent axon was associated with two separate sensory fields, one located on each ventricle (DRM 30; Fig. 1), the ventricular pacing electrodes were placed on the left lateral wall of the left ventricle away from the left ventricular sensory field. Once cardiac pacing was discontinued, premature ventricular beats were elicited. This was done by introducing an electrical stimulus to a distant ventricular epicardial site during diastole, thereby producing a premature ventricular contraction in lieu of every 7th normal beat in a sequence of 15 successive atrial paced beats of fixed duration. Data generated during these 15 cardiac cycles, which comprised normal, ectopic, and postectopic beats, were collected for 25 successive epochs to study the cumulative effects of ventricular premature contractions produced in a reproducible manner on afferent axonal activity.

After discontinuing cardiac pacing, the descending aorta and then the pulmonary artery were occluded individually for ~10 s. Afterward, bolus injections of normal saline (35 ml) were introduced into the cavity of the ventricle that contained studied sensory fields. Bradykinin (10 µM dissolved in 0.1 ml of room temperature normal saline, Sigma, St. Louis, MO) was then applied to each identified sensory field for 30–60 s via 1 cm × 1 cm gauze squares soaked with this chemical. After removing the bradykinin-soaked pledgets, the sensory field(s) were flushed with normal saline (~2 ml/s for at least 20 s) to wash away the chemical. The excess fluid was removed from the thoracic cavity. Gauze squares soaked with normal saline at room temperature were also applied to identified epicardial sensory fields to test vehicle effects. A sufficient amount of time was allowed between each intervention (~5 min) for the preparation to return to a steady state. Bradykinin (10 µM dissolved in 1 ml of physiological saline) was then administered as a bolus into the left atrial cavity. Thereafter, the left anterior descending and circumflex coronary arteries were occluded individually for 1 min with snare made of 3-0 silk thread that had been previously placed around these vessels ~1 cm from their origins. Care was taken during the placement of these snare to avoid damaging the axons that course adjacent to these arteries. At least 5 min elapsed between each coronary artery occlusion for the preparation to return to steady-state conditions.

Fig. 1. Defined borders of ventricular epicardial neurite fields associated with 1 sympathetic axon in each of 8 dogs are illustrated. Note that 2 separate sensory fields were identified in 1 animal (DRM 30). Locations of examined axons (sympathetic chain, left T2, T3, and T4 rami), as well as their conduction velocities, are listed at right of each schematized view of ventral surface of heart.
Strain experiments. In 8 of the 22 animals, the extent of each investigated sensory field was identified with certitude by means of touch. This permitted accurate placement of the ultrasonic crystals at the edges of sensory fields so that computational analysis could be performed in which activity was compared with sensory field deformation. Using the DEC PDP 11/10 computer, epicardial sensory field dimensions determined at end-systole and end-diastole were compiled using the length (L) data from the pairs of ultrasonic crystals so that changes in sensory field deformation (ΔL and dL/dt) could be computed. Estimates of the surface area (long axis × short axis) and relative volume (multiplication of all 3 recorded axis lengths) changes along each of the three identified vectors. Strain development along each epicardial sensory field axis was estimated in each of these eight dogs using the formula (L − L₀)/L₀, where L₀ was the length measured when the heart was fibrillated and emptied of blood at the end of each experiment, an index of basal regional diastolic length. Sensory field strain was calculated at the time in the cardiac cycle when afferent axonal activity was greatest, taking into account the conduction velocity of the axons involved.

Data analysis. The activity generated by afferent axons, expressed as impulses per cardiac cycle, along with recorded cardiac variables, were averaged over 15 consecutive cardiac cycles during steady-state conditions as well as during peak responses induced by each intervention. Data obtained before and during each intervention, presented as means ± SE, were compared using a two-way ANOVA with repeated measures followed by Fisher’s protected least significant difference test (P ≤ 0.05 utilized).

The computational capabilities described above permitted comparing recorded activity with cardiodynamics at the appropriate time in each cardiac cycle, taking into account the delay identified at the termination of each experiment due to the estimated conduction time along individual afferent axons (cf. Figs. 2 and 3). This computational analysis also permitted comparisons of afferent axonal activity vs. sensory field deformation, local pressure development, and ventricular chamber pressure development. This was done during successive cardiac cycles of fixed duration (presented as segments of 25 successive epochs) as well as during the induction of ventricular premature beats at a consistent time in one cardiac cycle during one of 15 consecutive cardiac cycles for 25 epochs. Analysis of the data performed offline.
activity patterns were identified before and after length-sensing crystals and the intramyocardial pressure sensors were placed near identified sensory fields. The intramyocardial pressure sensors were placed in a superficial location adjacent to identified sensory fields. Thus in most instances intramyocardial peak systolic pressures of 25–50 mmHg were recorded (see Figs. 2, 3, and 8), as has been found in the past when the ventricular epicardium is so monitored (2). In a few instances, recorded left ventricular regional systolic pressure was greater (see Fig. 5), reflecting the fact that the sensor was placed at a greater depth within the myocardium.

Activity patterns generated by axons associated with each sensory field bore no relation to that generated by the others, inasmuch as each displayed unique patterns in control states. Application of von Frey hairs to the various identified sensory fields demonstrated that the threshold for their activation ranged between 1.67 and 2.46 g. Mechanical deformation of identified epicardial sensory fields with graded von Frey hairs induced graded enhancement of activity to a point. Identified mechanical thresholds of individual sensory fields did not correlate with estimated conduction velocities associated with studied axons, nor did their activity patterns. Afferent axonal activity increased from $0.51 \pm 0.10$ impulses/cardiac cycle (range $0.21–0.92$ impulses/cardiac cycle), or 0.99 impulses/s, to $1.24 \pm 0.41$ impulses/cardiac cycle (range $0.72–3.01$ impulses/cardiac cycle), or 2.41 impulses/s, during local mechanical deformation of the sensory fields (Table 1). During control states, heart rate was $117 \pm 5$ beats/min and left ventricular chamber systolic pressure was $115 \pm 7$ mmHg. Cardiac indexes did not change significantly during epicardial application of mechanical or chemical stimuli. Greater enhancement of axonal activity occurred when bradykinin was applied to identified epicardial sensory fields ($+287\%$) than when local mechanical stimuli ($+143\%$) were applied (Table 1). The levels of enhanced activity generated by sensory neurites when exposed to bradykinin increased even more when local mechanical stimuli were applied to them in the presence of bradykinin.

Cardiac cycles of fixed duration. During atrial pacing the activity generated by ventricular sensory neurites increased in 18 of the 22 animals. Despite the fact that

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Afferent Axonal Activity, impulses/cardiac cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>$0.44 \pm 0.07$</td>
</tr>
<tr>
<td>Epicardial touch</td>
<td>$0.51 \pm 0.10$</td>
</tr>
<tr>
<td>Ventricular pacing</td>
<td>$0.47 \pm 0.07$</td>
</tr>
<tr>
<td>Premature ventricular beats</td>
<td>$0.41 \pm 0.09$</td>
</tr>
<tr>
<td>Epicardial bradykinin</td>
<td>$0.69 \pm 0.11$</td>
</tr>
<tr>
<td>Coronary artery occlusion</td>
<td>$0.59 \pm 0.14$</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SE; n = 22 dogs. Activity was generated by afferent axons in sympathetic nerves of dogs. $^*P < 0.05$ compared with data obtained before intervention.
atrial pacing induced cardiac cycles of fixed duration, maximum activity occurred at different times in the diastolic phase of the cardiac cycle when comparing data obtained from one animal with that derived from other animals. Maximum activity occurred most frequently at a time in the cardiac cycle when the greatest change in sensory field deformation occurred (Figs. 2 and 3). Thus maximal activity was generated by most identified sensory neurites during diastole at a time when sensory field muscle fascicle length (sensory field epicardial longitudinal axis) was undergoing maximal shortening and circumferential length (sensory field epicardial short axis) was increasing (Figs. 2 and 3).

Of the 22 dogs studied, the borders of the identified epicardial sensory fields were clearly demarcated in 8 animals. This permitted the placement of ultrasonic crystals on the borders of these sensory fields with exactitude so that mechanosensory field deformation could be quantified. The average conduction velocity of the axons associated with the ventricular mechanosensory fields in these 8 dogs was 7.5 m/s. Maximal activity varied in time during different cardiac cycles in each animal. This occurred even when the duration of the cardiac cycle was held constant by atrial pacing (Fig. 4). As the association of activity with strain development usually related to dimension change along only one vector of identified sensory fields, afferent axonal activity did not correlate with estimated sensory field area or volume change (Table 2). With respect to DRM 30, afferent axonal activity occurred when the epicardial sensory field axes were undergoing maximal dimensional change. No correlation of activity to sensory field strain was identified in the remaining dog. The activity generated by ventricular sensory neurites during each cardiac cycle increased when heart rate was increased by atrial or ventricular (Fig. 5; Table 1) pacing.

With the exception of one animal, afferent axonal activity did not correlate with regional intramyocardial pressure or rate of pressure development (\(+dP/dt\)). That ventricular pacing induced greater afferent axonal activity even though there was a reduction in adjacent intramyocardial systolic pressure or, for that matter, chamber systolic pressure presumably occurred because of a concomitant increase in sensory field deformation (Fig. 5).

Ventricular ectopic beats. When ventricular ectopic beats were induced at regular intervals every 15 cardiac cycles, the activity generated by afferent axons increased overall (Fig. 6; Table 1). Afferent axonal activity enhancement occurred even during ventricular premature contractions in which regional ventricular wall and chamber systolic pressures were less than normal (Fig. 6, beats A, E, and F). In those beats, sensory field dimension changes were equal to or greater than those found in control states.

Epicardial application of bradykinin or ventricular outflow obstruction. When bradykinin was applied topically to identified sensory fields, small and insignificant changes occurred in sensory field dimensions. Regional

Fig. 4. Example of variability of sensory field dimension at end systole. Sensory field end-diastolic vertical (A) and circumferential (C) lengths and end-systolic vertical (B) and circumferential (D) lengths were measured in DRM 34 over 20 consecutive cardiac cycles. Degree of scatter of end-diastolic lengths (left) was less than that encountered during end systole (right).
and chamber systolic pressures were also unaffected (Fig. 7). That intervention increased afferent axonal activity significantly (Table 1). Afferent axonal activity and recorded cardiac indexes did not change when saline-soaked pledgets were applied to identified sensory fields. The activity generated by identified afferent axons increased when the outflow artery of the ventricle that contained investigated sensory neurites (pulmonary artery for right ventricular sensory fields and aorta for left ventricular sensory fields) was occluded partially. Activity changes induced in such instances were associated with increasing deformation in at least one sensory field epicardial vector. When 35 ml of saline was injected rapidly into the cavity of the ventricle that contained an investigated sensory neurite, activity and sensory field dimensions did not change significantly.

Myocardial ischemia. Activity generated by ventricular sensory neurites increased by 224% (0.59 ± 0.14 to 1.91 ± 0.58 impulses/cardiac cycle or 1.15 ± 0.27 to 3.72 ± 1.13 impulses/s) in the 22 dogs studied when the major coronary artery that perfused tissues in which each sensory field was located was occluded in a transient fashion (Table 1). Sensory neurite activity increased gradually after the induction of ischemia, returning to baseline values slowly after their regional

Table 2. Coefficient of determination of activity compared with cardiac indexes

<table>
<thead>
<tr>
<th>Dog (DRM)</th>
<th>LVCP, mmHg</th>
<th>LVIMP, mmHg</th>
<th>Strain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systole</td>
<td>Diastole</td>
<td>Long axis</td>
</tr>
<tr>
<td>26</td>
<td>0.31</td>
<td>0.4</td>
<td>0.54*</td>
</tr>
<tr>
<td>27</td>
<td>0.19</td>
<td>0.16</td>
<td>0</td>
</tr>
<tr>
<td>28</td>
<td>0.06</td>
<td>0</td>
<td>0.11</td>
</tr>
<tr>
<td>29</td>
<td>−0.94*</td>
<td>−0.16</td>
<td>0.96*</td>
</tr>
<tr>
<td>30a (LV)</td>
<td>0.2</td>
<td>0.17</td>
<td>−0.42</td>
</tr>
<tr>
<td>30b (RV)</td>
<td>0.29</td>
<td>0.03</td>
<td>0.25</td>
</tr>
<tr>
<td>31</td>
<td>0.3</td>
<td>0.04</td>
<td>0.26</td>
</tr>
<tr>
<td>33</td>
<td>−0.39</td>
<td>0.44</td>
<td>−0.08</td>
</tr>
<tr>
<td>34</td>
<td>0.23</td>
<td>−0.29</td>
<td>0.67*</td>
</tr>
</tbody>
</table>

Values are coefficients of determination ($r^2$) derived when afferent axonal activity was compared with pressure development and computed sensory field length, area, and volume strains. Asterisk indicates correlation with afferent axonal activity. Afferent axonal activity correlated to the strain that developed in at least 1 sensory field vector in all animals except DRM 28. In DRM 29 it also correlated to ventricular systolic pressure. LV, left ventricle; RV, right ventricle; LVCP, cavity pressure; LVIMP, LV intramyocardial systolic pressure.

![Fig. 5. Activity generated by an afferent axon in the left sympathetic chain associated with left ventricular epicardial sensory neurites in DRM 31 before and during ventricular pacing. Afferent axonal activity increased from 1.21 to 2.23 impulses/cardiac cycle when the right ventricle was paced at 15 bpm above control heart rates. This occurred despite the fact that regional left ventricular intramyocardial and left ventricular chamber systolic pressures fell. Diastolic lengths in short and long axes of this sensory field increased concurrently. Minor changes in systolic lengths occurred, indicating that total excursion of epicardial sensory field dimensions increased in these 2 vectors. Estimated conduction velocity of axon associated with this sensory field was 1.2 m/s (inset).](http://ajpregu.physiology.org/cgi/content/full/R985/2/10.220.336/10.220.336)
arterial blood supply was restored (Fig. 8). Investigated sensory neurites received their blood supply from the left anterior descending coronary artery in nine dogs. When the left anterior descending coronary artery was occluded, the activity generated by these sensory neurites increased (0.63 ± 0.16 to 2.14 ± 0.9 impulses/cardiac cycle; P < 0.01). The sensory neurites associated with identified afferent axons in the other 13 dogs lay in tissues perfused by the circumflex coronary artery. Transient occlusion of that coronary artery enhanced the activity generated by their sensory neurites (0.51 ± 0.13 to 1.06 ± 0.33 impulses/cardiac cycle; P < 0.01). Occlusion of a coronary artery that did not perfuse tissues containing studied sensory fields did not alter the activity they generated or the dimensions of their sensory fields. Monitored epicardial diastolic lengths (circumferential and cranial-caudal) increased during ischemia (Fig. 8). Because systolic and diastolic lengths increased concomitantly, minor changes in the total excursion of epicardial sensory fields occurred overall. Identified sensory fields thickened a little too.

Sensory field deformation induced by focal left ventricular ischemia was of magnitude similar to that induced by occlusion of the outflow artery.

DISCUSSION

In agreement with previous reports (5, 7, 8, 13, 17, 19–22), the ongoing activity generated by ventricular epicardial sensory neurites associated with afferent axons in thoracic sympathetic nerves of anesthetized dogs identified in this report was sporadic in nature and of relatively low frequency. The majority of the ventricular epicardial sensory neurites that are associated with axons in intrathoracic sympathetic nerves of anesthetized dogs identified in this report was sporadic in nature and of relatively low frequency. The majority of the ventricular epicardial sensory neurites that are associated with axons in intrathoracic sympathetic nerves of anesthetized dogs identified in this report was sporadic in nature and of relatively low frequency. The majority of the ventricular epicardial sensory neurites that are associated with axons in intrathoracic sympathetic nerves of anesthetized dogs identified in this report was sporadic in nature and of relatively low frequency. The majority of the ventricular epicardial sensory neurites that are associated with axons in intrathoracic sympathetic nerves of anesthetized dogs identified in this report was sporadic in nature and of relatively low frequency. The majority of the ventricular epicardial sensory neurites that are associated with axons in intrathoracic sympathetic nerves of anesthetized dogs identified in this report was sporadic in nature and of relatively low frequency. The majority of the ventricular epicardial sensory neurites that are associated with axons in intrathoracic sympathetic nerves of anesthetized dogs identified in this report was sporadic in nature and of relatively low frequency. The majority of the ventricular epicardial sensory neurites that are associated with axons in intrathoracic sympathetic nerves of anesthetized dogs identified in this report was sporadic in nature and of relatively low frequency. The majority of the ventricular epicardial sensory neurites that are associated with axons in intrathoracic sympathetic nerves of anesthetized dogs identified in this report was sporadic in nature and of relatively low frequency. The majority of the ventricular epicardial sensory neurites that are associated with axons in intrathoracic sympathetic nerves of anesthetized dogs identified in this report was sporadic in nature and of relatively low frequency. The majority of the ventricular epicardial sensory neurites that are associated with axons in intrathoracic sympathetic nerves of anesthetized dogs identified in this report was sporadic in nature and of relatively low frequency. The majority of the ventricular epicardial sensory neurites that are associated with axons in intrathoracic sympathetic nerves of anesthetized dogs identified in this report was sporadic in nature and of relatively low frequency. The majority of the ventricular epicardial sensory neurites that are associated with axons in intrathoracic sympathetic nerves of anesthetized dogs identified in this report was sporadic in nature and of relatively low frequency. The majority of the ventricular epicardial sensory neurites that are associated with axons in intrathoracic sympathetic nerves of anesthetized dogs identified in this report was sporadic in nature and of relatively low frequency. The majority of the ventricular epicardial sensory neurites that are associated with axons in intrathoracic sympathetic nerves of anesthetized dogs identified in this report was sporadic in nature and of relatively low frequency. The majority of the ventricular epicardial sensory neurites that are associated with axons in intrathoracic sympathetic nerves of anesthetized dogs identified in this report was sporadic in nature and of relatively low frequency.
epicardial vector of their sensory fields. These data suggest that most ventricular epicardial sensory neurites may be uniquely oriented in a functional sense. As mentioned above, it is known that atrial mechanosensory neurites respond primarily to changing strain in one vector of their sensory fields (3, 9). In the present series of experiments, strain development along at least one epicardial vector of the identified ventricular epicardial sensory fields correlated best to the generation of maximum activity during cardiac cycles of fixed duration (Table 2). That such was not the case in every instance suggests that sensory field orientation in some instances may have been intermediate between the epicardial vectors studied. Activity did not correlate to deformation in the transmural axis or to regional pressure development overall.

Individual ventricular epicardial sensory neurites generated varied activity patterns when comparing different cardiac cycles generated during control states (Fig. 2). When afferent axonal activity was analyzed over a number of cardiac cycles of fixed duration induced by atrial pacing, maximal activity occurred with greatest frequency in late diastole at the time when epicardial sensory field strain was greatest (Figs. 2–4). Taking into account the time for the impulse to reach the recording electrodes, maximum activity occurred during maximum deformation along the long epicardial axis of the receptor field in five of eight cases and along the short epicardial axis of the receptor field in three cases (Table 2). In one case this occurrence was associated with maximal deformation along both epicardial vectors; no such correlation was found in the other
case examined. Thus it appears that deformation along at least one sensory field epicardial vector accounts for the majority of activity generated by such sensory neurites in control states. That the time during diastole when maximum activity occurred varied between cardiac cycles presumably was due, in part, to the fact that sensory field diastolic dimensions also varied among individual cardiac cycles in each animal during cardiac cycles of fixed duration (Fig. 4). That afferent axonal activity increased during ventricular pacing even though intramyocardial systolic pressure fell presumably occurred because greater sensory field deformation was elicited in that state (Fig. 5).

The activity generated by ventricular sensory neurites increased during some ventricular ectopic beats. Enhancement of activity occurred during many ectopic beats in which peak systolic wall pressure was less than that identified during control states. That sensory field deformation during these ectopic beats was greater than during normal cardiac cycles, even though peak intramyocardial systolic pressure was less than in control states (Fig. 6, beats A, E, and F), supports the contention that sensory field deformation represents an index that correlates with ventricular sensory neurite activity better than local tissue pressure development.

Many ventricular sensory neurites are sensitive to local ischemia (1, 4, 5, 7, 10, 13, 15, 17, 19–22). During myocardial ischemia, the local release of chemicals such as bradykinin into coronary venous blood increases (16). Increasing concentrations of locally released chemicals may account, in part, for the enhancement of activity generated by ventricular sensory neurites in the presence of ischemia (13, 15). On the other hand, ventricular deformation also occurs during myocardial ischemia (Fig. 8), a change that may lead to the enhancement of activity generated by such sensory neurites. As a matter of fact, ischemia-induced increases in activity generated by ventricular sensory neurites with axons in sympathetic nerves have been ascribed to regional mechanical bulging (i.e., local stretch of sensory terminals) (7, 17). That sensory field deformation is important was demonstrated by the finding that sensory field epicardial lengths increased in the presence of regional ischemia (Fig. 8). There was a concomitant reduction in regional systolic pressure, whereas local and chamber diastolic pressures remained relatively unaffected by the short bouts of regional ischemia. Thus, consistent with the fact that afferent axonal activity increased during altered regional deformation induced by ventricular pacing (Fig.
Ventricular epicardial mechanosensory afferent neurites

5), afferent axonal activity increased during sensory field deformation induced by brief periods of local myocardial ischemia.

Application of bradykinin to identified epicardial sensory fields in control states induced greater activity enhancement than did local mechanical stimuli (Table 1). Chemical stimuli enhanced afferent axonal activity to such a degree that, in some instances, activity became entrained to the cardiac cycle, an observation that has been made previously (14). That sensory field deformation with calibrated von Frey hairs enhanced activity by similar amounts in the absence or presence (when activity was greater than in control states) of locally applied bradykinin (Fig. 7) indicates that ventricular epicardial sensory neurites may transduce mechanical deformation relatively independently of their capacity to sense alterations in their chemical milieu (15).

One limitation of the present study is the fact that afferent axons associated with only epicardial sensory fields were studied. This was done so that mechanical stimuli could be applied to sensory neurites while minimizing the effects that such stimuli exert on overall cardiac dynamics. This also permitted placement of length sensors around the periphery of identified sensory fields so that sensory field dynamics could be investigated concomitantly with sensory neurite function. Furthermore, it allowed local application of chemicals to identified sensory fields. Because sensory field dimension changes were monitored along only two of their epicardial vectors, inferences cannot be drawn from these data to account for sensory field orientation in intermediate epicardial directions.

Perspectives

The activity generated by ischemia-sensitive ventricular epicardial neurites associated with afferent axons in sympathetic nerves generally correlates with strain development along at least one epicardial vector of their sensory fields. During ventricular premature contractions alterations in sensory field strain, rather than in the development of regional pressure, account for most of the increased activity encountered. The data obtained from the present experiments indicate the complexity of the interplay of local strain and chemical stimuli that affect ventricular sensory neurites associated with dorsal root ganglion afferent neurons, interactions that together account for their varied activity responses to pathologic states such as ventricular dysrhythmias or focal ventricular ischemia.

This work was supported by the National Institutes of Health, the Medical Research Council of Canada (MT-10122), and the Nova Scotia Heart and Stroke Foundation.

Address for reprint requests and correspondence: J. A. Armour, Dept. of Physiology and Biophysics, Faculty of Medicine, Dalhousie Univ., Halifax, Nova Scotia, Canada B3H 4B7 (E-mail: jarmour@is dal.ca).

Received April 21, 1998; accepted in final form November 24, 1998.

REFERENCES


