Effects of Angiotensin II on the Blood Flow and Its Distribution in Fetal Lambs

HARRIET S. IWAMOTO AND ABRAHAM M. RUDOLPH

SUMMARY We studied the effects of intravenous infusion of angiotensin II on the circulation of the fetus in lambs in utero through chronically maintained intravascular catheters. Angiotensin II infused in doses of 29-280 ng/min per kg fetal weight resulted in an increase in plasma angiotensin II from a control value of 87 ± 17 to 341 ± 129 (mean ± SE) pg/ml; these levels are similar to those observed following hemorrhage in fetal lambs. Fetal mean arterial blood pressure increased from 46 ± 2.0 to 56 ± 2.7 torr and fetal heart rate increased from 172 ± 6 to 189 ± 6 beats/min, an effect which was not altered by β-adrenergic or cholinergic blockade. Fetal cardiac output and its distribution were measured before and during infusion of angiotensin II by the radionuclide-labeled microsphere technique. Combined ventricular output increased significantly from 526 ± 32 to 616 ± 24 ml/min per kg fetal body weight. Angiotensin constricted the umbilical-placental circulation as well as the gastrointestinal, renal, and thyroidal vascular beds. Angiotensin increased blood flow to the myocardium and markedly increased blood flow to the pulmonary circulation. These studies indicate that angiotensin II, at the plasma levels achieved with moderate hemorrhage, has marked influences on the circulation. The renin-angiotensin system may be important in the fetal response to stress.


ANGIOTENSIN II may play an important role in the fetal response to various stimuli through its actions on the fetal circulation. The activity of the renin-angiotensin system is increased in response to hypovolemia, hypotension, administration of furosemide, and hypoxemia (Smith et al., 1974; Brougherton, Pipkin et al., 1974a; Drummond and Lindheimer, 1979; Lumbers and Lewes, 1979). Previous investigations have shown that injection of angiotensin II into fetal sheep increases arterial pressure, alters heart rate, and alters blood flow through various arteries (Adams et al., 1961; Assali et al., 1962; Tulenko and Millard, 1977; Berman et al., 1978; Lumbers and Reid, 1978). However, it is not known which vascular beds respond to angiotensin II to produce these changes. This present investigation examines the response of chronically instrumented fetal sheep to angiotensin II. Angiotensin II was infused at a rate that increased plasma angiotensin II concentrations to values comparable to those observed in response to hemorrhage (Broughton-Pipkin et al., 1974b). Blood pressure, heart rate, combined ventricular output and its distribution were monitored before and during infusion of angiotensin II.

Methods

Animal Preparation

We used 15 pregnant Western ewes with gestational ages of 120-131 days based on known breeding dates. Under low spinal or epidural anesthesia (Pontocaine HCl, Winthrop Laboratories), polyvinyl catheters (i.d., 1.3 mm; o.d., 2.3 mm) were inserted in the left dorsalis pedis artery and vein and advanced to the distal inferior vena cava and descending aorta of the ewe.

Using aseptic procedures, we inserted polyvinyl catheters (i.d., 0.8 mm; o.d., 1.2 mm) into a vein and artery in each fetal hindlimb and advanced them to the inferior vena cava and descending aorta. Catheters were inserted into a carotid artery and an external jugular vein and advanced to the brachiocephalic trunk and superior vena cava. In two fetuses an additional catheter was inserted into a cotyledonal vein in the uterine horn and advanced to a main umbilical vein 4-5 cm from the umbilicus. A catheter also was placed in the amniotic fluid cavity. Antibiotics (800 mg kanamycin sulfate and 1 million units penicillin G) were administered at the time of surgery and each day after surgery to the ewe and into the amniotic cavity.

Seventeen studies were performed on the 15 fetal sheep 2-3 days after surgery. Ten sheep were used once for the determination of the effect of angiotensin II on the fetal circulation. Five sheep were used for the determination of the effect of β-adrenergic or cholinergic blockade on the fetal response to angiotensin II.

Effect of Angiotensin II on the Fetal Circulation

Fetal arterial and venous and amniotic cavity pressures were measured with Statham P23Db strain gauge transducers (Statham Instruments) positioned at the ewe's midabdomen. The fetal heart rate was recorded continuously by means of a cardiotachometer which was triggered by the pressure signal from the aortic catheter. All vari-
sample's also were obtained for the determination of fetal and maternal arterial blood samples were obtained for the determination of plasma angiotensin concentration and plasma renin activity. Blood samples also were obtained for the determination of blood gases, pH, and hematocrit. Fifteen-μm radionuclide-labeled microspheres (125I, 14C, 51Cr, 85Sr, or 59Nb; Minnesota, Manufacturing and Mining Co.) were injected into the inferior and superior vena cavae while reference blood samples were withdrawn at a rate of 7.75 ml/min from the descending aorta and carotid arteri for the determination of combined ventricular output and blood flow distribution during the control period. The volume of blood removed for plasma samples and reference samples was replaced with an equal volume of maternal blood.

Angiotensin II-amide (Hypertensin, Ciba-Geigy) dissolved in 0.9% NaCl was infused intravenously into the fetal inferior vena caval catheter with a continuous infusion pump. The angiotensin II was infused at a flow rate of 0.097 to 0.388 ml/min in amounts of 169 ± 52 ng/min per kg (mean ± SEM) with a range of 29-280 ng/min per kg. This rate of infusion produced a 10-15% increase in mean arterial blood pressure which was the endpoint used to determine the rate of infusion. In some fetuses it was necessary to increase the rate of infusion to maintain an elevated arterial pressure, and this accounts for the wide range in infusion rates. In studies of adult humans (Chinn and Disterdieck, 1972), there was a variable pressor response to a given rate of infusion that possibly was related to different rates of angiotensin metabolism. Different rates of metabolism and some other unknown factors could account for the wide variation in infusion rates required in these studies. After fetal blood pressure and heart rate had remained stable for at least 10 minutes, a second set of blood samples was obtained. Microspheres again were injected for the determination of combined ventricular output and its distribution during infusion of angiotensin II.

Effect of β-Adrenergic or Cholinergic Blockade on the Response to Angiotensin II

The results from the first series of experiments demonstrated that infusion of angiotensin II into fetal sheep increased heart rate. It is possible that angiotensin II directly increased heart rate, but it also is possible that the increase in heart rate resulted from an increase in sympathetic action or from a decrease in parasympathetic action on the heart. To attempt to determine the possible cause of the increase in heart rate in response to angiotensin II, the following experiments were performed. (1) To test the effect of β-adrenergic blockade on the response to angiotensin II, one of two protocols was followed. The first protocol consisted of comparing the response of the fetuses to an injection of propranolol before infusion of angiotensin II with the response to an injection of propranolol during infusion of angiotensin II. Two studies were performed in two fetuses. After a control period of 30 minutes during which fetal pressures and heart rate were monitored, propranolol HCl, 1 mg (Inderal, Ayerst Laboratories, Inc.), was injected intravenously. Angiotensin II was infused intravenously as described above. After approximately 15-25 minutes, when the heart rate had increased above control levels, an additional 1 mg of propranolol was injected. The second protocol consisted of monitoring the response of the fetus to angiotensin II infusion during an infusion of propranolol. Three studies were performed in three fetuses. Propranolol was infused intravenously at a rate of 0.075 mg/min. This dose has been shown to inhibit the tachycardia in response to an injection of isoproterenol (Vapaavouri et al., 1973). After heart rate and blood pressure had become stable, angiotensin was infused intravenously as before, and both infusions continued for at least 30 minutes. (2) To test the effect of cholinergic blockade on the response to angiotensin II, atropine sulfate (1-2 mg, Invenex) was injected into two fetuses before and during an infusion of angiotensin II.

Measurement and Analysis of the Data

At the end of the studies, the ewes were anesthetized with 1000 mg of sodium pentobarbital injected intravenously and then killed. The fetuses that received microspheres were removed from the uterus and dissected. The distribution of the microspheres and the blood flow to the fetal organs were measured as described previously (Iwamoto and Rudolph, 1979; Buckberg et al, 1971; Heymann et al, 1977; Rudolph and Heymann, 1967).

Blood PO2, PCO2, and pH were determined on a Radiometer blood gas analyzer (HMT3, London Co.). Blood hemoglobin and percent O2 saturation of the hemoglobin were determined on a Radiometer hemoximeter (model OSM2, Copenhagen).

Plasma concentrations of angiotensin II and plasma renin activity were measured by radioimmunoassay. Blood samples (2 ml) for the determination of plasma renin activity were collected in sterile syringes and transferred to tubes containing 7.2 mg EDTA (Vacutainer Tubes, Becton, Dickinson, and Co.). The samples were centrifuged for 20 minutes at 2000 g and 4°C, and the plasma was decanted and stored at −20°C until assay. Plasma renin activity was assayed with the GammaCoat (125I) Plasma Renin Activity Kit (Clinical Assays, Travenol Laboratories).

Blood samples (6 ml) for the determination of angiotensin II concentration were collected and stored as described above for the determination of plasma renin activity. Plasma samples (3 ml) were...
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extracted in Fuller’s earth and eluted with ammonia in methanol and assayed by radioimmunoassay. Aliquots of angiotensin II standards and extracted plasma were incubated with [125I] angiotensin II (1.5 × 10^4 counts/min) and antiserum to angiotensin II (final dilution 1:40,000) in 0.1 M Tris-HCl, pH 8.0, containing 5 g/liter bovine serum albumin. The mixture was incubated at 4°C for 24 hours, then the free [125I] angiotensin II was measured. Standard curves were constructed using 0.0025-0.2 pmole synthetic [Ala7,Leu8]angiotensin II (Schwarz/Mann).

The blood pressure and heart rate responses of the fetuses were analyzed in two different manners. The steady state response compared the blood pressure and heart rate during the control period with the blood pressure and heart rate during the experimental period. Five values for blood pressure and heart rate obtained at 5-minute intervals just prior to the end of the control period were compared with the same number of values obtained at 5-minute intervals just prior to the end of the experimental period. The dynamic response of blood pressure and heart rate was analyzed by recording the values of blood pressure and heart rate at 5-minute intervals continuously during the control period through the experimental period.

The changes in the constituents of the blood, the steady state responses of blood pressure and heart rate, combined ventricular output and its distribution caused by angiotensin II were analyzed by the paired t-test or by the nonparametric Wilcoxon signed rank test (Winer, 1971). The dynamic responses of blood pressure and heart rate were analyzed by one-way analysis of variance for repeated measures. The Newman-Keuls test (Winer, 1971) then was used to determine which means, at the 0.05 level of significance, were statistically different from the means of the control values.

**Results**

During the control period, the blood Po2, PCO2, pH, and hematocrit were within the normal range of values expected for fetal sheep in this range of gestational ages (Table 1). Angiotensin II did not change these values significantly. Angiotensin II concentration in the fetal arterial plasma increased significantly. Although fetal arterial plasma renin activity decreased in every instance (n = 5, paired t-test), this change was not statistically significant.

There was no change in the plasma renin activity or plasma angiotensin II concentration in the maternal plasma during infusion into the fetus.

Angiotensin II increased mean arterial blood pressure (Table 2). Systolic pressure increased more than diastolic pressure so that there was a significant increase in the pulse pressure. Mean arterial blood pressure increased significantly over control values by 5 minutes and remained significantly elevated throughout the duration of the infusion (Fig. 1). Fetal heart rate fell slightly at the beginning of the infusion and then gradually increased to values significantly greater than control values by 30 minutes.

![Angiotensin Infusion](image)

**Table 1 Effect of Angiotensin II on Constituents of the Blood in Sheep**

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Control</th>
<th>Angiotensin II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Po2 (torr)</td>
<td>21 ± 1</td>
<td>21 ± 2</td>
</tr>
<tr>
<td>PCO2 (torr)</td>
<td>45 ± 2</td>
<td>46 ± 1</td>
</tr>
<tr>
<td>pH</td>
<td>7.39 ± 0.01</td>
<td>7.39 ± 0.01</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>29 ± 2</td>
<td>31 ± 2</td>
</tr>
<tr>
<td>Fetal plasma renin activity*</td>
<td>13.7 ± 2.7</td>
<td>8.9 ± 1.9</td>
</tr>
<tr>
<td>(ng/ml per hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal plasma angiotensin II</td>
<td>87 ± 17</td>
<td>341 ± 129†</td>
</tr>
<tr>
<td>(pg/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal plasma renin activity</td>
<td>0.98 ± 0.14</td>
<td>0.94 ± 0.11</td>
</tr>
<tr>
<td>(ng/ml per hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal plasma angiotensin II</td>
<td>33 ± 6.3</td>
<td>35 ± 5.9</td>
</tr>
</tbody>
</table>

*Values are expressed as mean ± SEM; analyzed by paired t-test. n = 10.

* P < 0.01; † P < 0.05; † P < 0.02.

**Table 2 Effect of Angiotensin II on the Steady State Responses of Blood Pressure and Heart Rate in Fetal Sheep**

<table>
<thead>
<tr>
<th>Response</th>
<th>Control</th>
<th>Angiotensin II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (torr)</td>
<td>46 ± 2</td>
<td>56 ± 2.7*</td>
</tr>
<tr>
<td>Systolic pressure (torr)</td>
<td>64 ± 3.0</td>
<td>76 ± 3.6*</td>
</tr>
<tr>
<td>Diastolic pressure (torr)</td>
<td>34 ± 1.2</td>
<td>42 ± 1.8*</td>
</tr>
<tr>
<td>Pulse pressure (torr)</td>
<td>30 ± 2.1</td>
<td>34 ± 2.2†</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>172 ± 6</td>
<td>189 ± 6.6†</td>
</tr>
</tbody>
</table>

*Values are expressed as mean ± SEM; analyzed by paired t-test. n = 10.

* P < 0.01; † P < 0.05; † P < 0.02.

**Figure 1** Infusion of angiotensin II increases mean arterial pressure (MAP) and heart rate (HR) in fetal sheep. Data are means ± SEM from 10 experiments on 10 fetal sheep. Time is in minutes relative to onset of infusion of angiotensin II at time zero. * = significantly different from values during the control period; P less than 0.01.
Propranolol injection or infusion had no effect on the heart rate response to infusion of angiotensin II. In two fetuses, injection of propranolol decreased heart rate from 165 to 120 beats/min in one and from 157 to 145 beats/min in another. Subsequent infusion of angiotensin II increased heart rate to 145 and 185 beats/min, respectively. A second injection of propranolol during infusion of angiotensin II had no effect on heart rate. On two occasions, when angiotensin II was administered during an infusion of propranolol, heart rate still increased at 25–30 minutes after the onset of infusion. Atropine injection alone increased heart rate from 165 to 185 beats/min in one fetus and from 162 to 222 beats/min in the other. After atropine, angiotensin II caused a marked vasodilation in the pulmonary vascular bed since there was a greater than 3-fold decrease in the percent combined ventricular output distributed to the gastrointestinal circulations. The percent of the combined ventricular output it received and an increase in the calculated resistance. These data indicate that angiotensin II constricted the umbilical-placental circulation.

Angiotensin II caused a redistribution of blood flow within the fetal body (Table 4). Angiotensin II decreased the actual blood flow and the percent of the combined ventricular output to the kidneys and thyroid and also increased the calculated vascular resistances in these circulations. This indicates that angiotensin II constricted the renal and thyroidal circulations. The percent of the combined ventricular output distributed to the gastrointestinal circulation decreased and its vascular resistance increased, also indicating that angiotensin II constricted this vascular bed. In the myocardial circulation, the percent combined ventricular output increased and the vascular resistance decreased. Angiotensin II caused a marked vasodilation in the pulmonary vascular bed since there was a greater than 3-fold increase in actual blood flow and a nearly 3-fold increase in the percent combined ventricular output.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Effect of Angiotensin II on Combined Ventricular Output, Blood Flow, and Vascular Resistance in Fetal Sheep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ</td>
<td>Control</td>
</tr>
<tr>
<td>--------</td>
<td>---------</td>
</tr>
<tr>
<td>Heart</td>
<td>210 ± 14</td>
</tr>
<tr>
<td>Fetal body + placental resistance</td>
<td>40.3 ± 2.0</td>
</tr>
<tr>
<td>Umbilical-placental blood flow (ml/min per kg)</td>
<td>316 ± 24</td>
</tr>
<tr>
<td>Umbilical-placental %CVO</td>
<td>59.7 ± 2.0</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM; analyzed by paired t-test. n = 10.

* P < 0.01; † P < 0.005; ‡ P < 0.001; § P < 0.05; ¶ P < 0.02; || P < 0.005.

---

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Effect of Angiotensin II on Distribution of Combined Ventricular Output, Blood Flow, and Vascular Resistance in Fetal Sheep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ</td>
<td>Blood flow (ml/min per 100 g)</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Adrenal</td>
<td>284 ± 62</td>
</tr>
<tr>
<td>Gut</td>
<td>66 ± 8</td>
</tr>
<tr>
<td>Spleen</td>
<td>310 ± 67</td>
</tr>
<tr>
<td>Kidneys</td>
<td>200 ± 15</td>
</tr>
<tr>
<td>Brain</td>
<td>141 ± 17</td>
</tr>
<tr>
<td>Thyroid</td>
<td>147 ± 20</td>
</tr>
<tr>
<td>Heart</td>
<td>250 ± 70</td>
</tr>
<tr>
<td>Lungs</td>
<td>95 ± 19</td>
</tr>
<tr>
<td>Periphery</td>
<td>24 ± 2.5</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM; analyzed by paired t-test. n = 10.

* P < 0.005; † P < 0.05; ‡ P < 0.01; § P < 0.02; ¶ P < 0.005; || P < 0.005.
and a decrease in the calculated resistance.

Discussion

Previous investigators have demonstrated that angiotensin II increases arterial blood pressure (Assali et al., 1962; Berman et al., 1978; Lumbers and Reid, 1978), either decreases (Berman et al., 1978) or increases (Lumbers and Reid, 1978) heart rate, and alters blood flow through various arteries (Adams et al., 1961; Assali et al., 1962; Tulenko and Millard, 1977; Berman et al., 1978). However, previous studies designed to examine the effects of angiotensin II during fetal life have employed acute preparations, large doses of angiotensin II and injections of angiotensin II, rather than infusions. There are several disadvantages to these methods. Animals studied acutely may respond differently to vasoactive agents than do animals studied chronically, largely because the anesthetic agents used in the acute studies may alter physiological responses (Assali et al., 1974). When large doses of angiotensin II are administered as a bolus injection, the response observed may not be representative of a physiological response.

In the present investigation, angiotensin II was infused at a rate that increased plasma angiotensin II concentration to levels comparable to those observed in response to hemorrhage (Broughton-Pipkin et al., 1974b; Iwamoto and Rudolph, unpublished observations). Plasma renin activity decreased slightly but not significantly. Plasma renin activity was measured in only five fetuses, but in all five, it fell by at least 25%. These data are suggestive, but by no means conclusive, that angiotensin II has a negative feedback effect on the secretion of renin from the fetal kidney.

Angiotensin II had profound effects on the hemodynamics of the fetal lamb. With the onset of infusion, blood pressure increased abruptly, causing a bradycardia which was presumably reflex in origin. This response is similar to the response of the fetus to a bolus injection of angiotensin II (Berman et al., 1978). However, as the infusion continued, the heart rate increased until it was significantly greater than control values. This positive chronotropic response has also been observed in adult animals (Heyndrickx et al., 1976) and has been attributed to an increase in the release of neurotransmitter from sympathetic nerve terminals (Krasney et al., 1967) or a stimulation of sympathetic ganglia (Farr and Grupp, 1971). Angiotensin II also can increase heart rate through a centrally mediated action which results in either an increase in sympathetic tone or a decrease in parasympathetic tone (Peach, 1977; Severs and Daniel-Severs, 1973). Any of these mechanisms may be functional in the fetal lamb, which possesses sympathetic innervation and catecholamines in the heart during the stage of development in which these fetuses were studied (Lebowitz et al., 1972).

However, our findings indicate that the effect of angiotensin II on heart rate was not mediated through a change in the tonic neural control of heart rate. Injection or infusion of propranolol had no effect on the increase in heart rate in response to angiotensin II. Injection of atropine alone increased heart rate, but injection of atropine during infusion of angiotensin II decreased rather than increased heart rate. These results are in contrast to those of Ismay et al. (1979), who found that after treatment with atropine and propranolol, angiotensin II did not affect heart rate. The discrepancy between the two sets of results may be explained by the differences in the method of administering angiotensin II. Ismay et al. injected angiotensin II into the fetuses and examined the immediate response. In the present studies, angiotensin was infused, and it should be emphasized that the increase in heart rate was evident only after 20–30 minutes of angiotensin II infusion. From the present studies, one must conclude that angiotensin II increased heart rate directly or that the pharmacological blockade was incomplete. The mechanism responsible for the positive chronotropic action of angiotensin II in fetal sheep is not clear.

Angiotensin II increased combined ventricular output but had no effect on the total peripheral resistance. Part of the increase in the combined ventricular output could have been due to a direct positive inotropic action on the myocardium as indicated by the significant increase in pulse pressure (Dempsey et al., 1971). Part of this increase could have been due to an increase in circulating blood volume as a result of sodium and fluid retention; however, this possibility is not likely since hematocrit did not change significantly. Most of this increase probably was due to the increase in heart rate since the heart of the fetal lamb has limited capacity to increase contractility (Rudolph and Heymann, 1973).

Angiotensin II markedly constricted the umbilical-placental circulation, as has been reported by other investigators who studied the response of fetal sheep to an injection of angiotensin II (Assali et al., 1962; Dyer, 1970; Tulenko and Millard, 1977; Berman et al., 1978). We were not able to discern whether the vasoconstriction occurred in the large umbilical vessels or in the placental circulation. Tulenko (1979) demonstrated that angiotensin II causes a larger vasoconstriction of the small villous arteries of the placental circulation than of the larger arteries.

Angiotensin II had various effects on the distribution of blood flow within the fetal body. The largest and most striking change was the 3.5-fold increase in blood flow to the pulmonary circulation. Since angiotensin II is not known to cause vasodilation directly, this effect possibly was mediated through some other mechanism such as increasing the production of local prostaglandins (McGiff et al., 1970; Needleman et al., 1973; Grimbone and Alexander, 1975; Blumberg et al., 1977). It is possi-
able that angiotensin II increased the production of prostaglandins in the fetal lung and that the prostaglandins mediated a vasodilation that increased pulmonary blood flow (Cassin et al., 1978; Tripp et al., 1978). The increase in myocardial blood flow could have been due to an increase in cardiac work. Both heart rate and peak systolic pressure increased significantly, and the product of the two variables could have been due to an increase in cardiac work.

Both heart rate and peak systolic pressure increased significantly, and the product of the two variables could have been due to an increase in cardiac work. From these results, it could be concluded that angiotensin II may be important for maintenance of blood pressure during the acute response to hemorrhage.

**Acknowledgments**

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**References**


Drummond WH, Lindheimer CA (1979) Plasma renin response to acute hypoxia in the ewe and fetal lamb (abstr). Physiologist 22: 31


Rudolph AM, Heymann MA (1970) Circulatory changes during
Characteristics of Sarcomere Shortening in Single Frog Atrial Cardiac Cells during Lightly Loaded Contractions

MERRILL TARR, JOHN W. TRANK, AND PAUL LEIFFER

SUMMARY We studied sarcomere performance in single isolated intact cardiac cells using techniques that allow direct measurement of sarcomere length and force. This investigation dealt primarily with sarcomere performance during twitch contractions under lightly loaded conditions. In such contractions, there was a significant portion of the contraction in which sarcomere shortening occurred at constant velocity over a significant range of sarcomere lengths. The constant velocity phase of shortening was followed by a phase of shortening in which sarcomere velocity decreased markedly. Both the velocity and extent of sarcomere shortening depended on the stimulus parameters used to excite the cell. With threshold stimulation, sarcomere velocities during the constant velocity phase of shortening ranged from 1 to 5.5 μm/sec in different cells and significant slowing did not occur until a sarcomere length of about 1.6 μm was reached. The threshold stimulus strength-stimulus duration relationship was determined on the single cell, and it was found to be of the type expected for a cell having an intact excitable membrane capable of generating an action potential when depolarized to a fixed voltage threshold. The data presented in this paper give direct evidence that the lightly loaded cardiac sarcomere has a velocity of shortening which depends on the level of contractile activation but is independent of sarcomere length at sarcomere lengths greater than about 1.6 μm. Circ Res 48: 189-200, 1981

THERE have been few direct determinations of the relationships between sarcomere length and developed force in cardiac muscle. Elegant experiments have been performed to determine these relationships in single cardiac cells in which the cell membrane has been removed, and these experiments on skinned cardiac cells have given information about the relationships between sarcomere length and developed force at various levels of contractile activation (Fabiato and Fabiato, 1976, 1978). However, it is difficult to make an extrapolation from these data to predict quantitatively sarcomere performance during a twitch contraction in the intact tissue. Attempts to measure sarcomere performance directly during twitch contractions in intact tissue have been limited due to the general difficulty of directly measuring sarcomere lengths in intact living cardiac tissue. Recently, the laser diffraction technique has been applied to very thin bundles of intact cardiac tissue and it has been possible with this technique to measure directly the performance of a large group of sarcomeres during twitch contractions (Nassar et al., 1974; Krueger and Pollack, 1975). However, interpretation of data derived from
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