Ontogeny of Blood Pressure and the Renin-Angiotensin-Aldosterone System
Sequential Studies in the Newborn Lamb

THOMAS A. WILSON, DONALD L. KAISER, EUGENE M. WRIGHT, JR., MICHAEL J. PEACH, AND ROBERT M. CAREY

With the technical assistance of Nancy A. Tisdale and Elizabeth M. Ortt

SUMMARY To test the hypothesis that the rise in arterial pressure occurring with maturation is due to an increase in the vascular responsiveness to angiotensin II, sequential cumulative doses of angiotensin II were infused intravenously into chronically catheterized newborn lambs maintained on a constant, weight-adjusted sodium intake from birth to 8 weeks of age. Basal mean arterial pressure correlated with both age and weight, but age was a stronger determinant of mean arterial pressure than was weight. No change in the mean arterial pressure response to angiotensin II occurred with maturation. Basal plasma renin activity and plasma aldosterone concentrations were low and did not change significantly with age. Therefore, in the newborn lamb in the sodium replete state, age is a better determinant of arterial pressure than is weight. However, an age-related change in vasoconstrictor responsiveness to angiotensin II does not occur and, therefore, cannot account for the rise in arterial pressure that is observed with maturation. Circ Res 49: 416-433, 1981

ARTERIAL pressure rises progressively throughout infancy and childhood (Moss and Adams, 1969; Lauer et al., 1975; Voors et al., 1977). The increase in arterial pressure is greatest in the first year of life (Nadas and Fyler, 1972). However, the mechanisms governing this age-dependent rise in arterial pressure have not been defined.

Whereas arterial pressure is low in early life, numerous studies have documented increased activity of the various components of the renin-angiotensin-aldosterone system in infancy in the human (Siegel et al., 1974; Dillon et al., 1976; Pipkin et al., 1977; Raux-Eurin et al., 1977; Van Acker et al., 1979) and in many experimental animals (Pohlová and Jelinek, 1974; Mott, 1975; Siegel and Fisher, 1980; Wallace et al., 1980). Cross-sectional data in humans suggest that plasma renin activity and plasma aldosterone concentrations decrease progressively throughout infancy and childhood (Sassard et al., 1975; Hiner et al., 1976; Stalker et al., 1976; Dillon et al., 1976; Kowarski and Migeon, 1977; Van Acker et al., 1979). However, the renin-angiotensin-aldosterone system has not been studied systematically or longitudinally under conditions of constant sodium intake during the first few weeks of life in either humans or experimental animals.

Since blood pressure increases while plasma renin activity and angiotensin II concentrations apparently fall, it is possible that the gradual increase in arterial pressure that occurs with maturation may be related to a progressive increase in the vascular responsiveness to angiotensin II. Thus, as arterial pressure and renal perfusion increased, renin release would be inhibited. This mechanism might account for the rise in blood pressure and the gradual diminution in plasma renin activity observed during maturation. Alternatively, an increase in number or affinity of angiotensin II receptors in the juxtaglomerular apparatus might occur with age, thus enhancing the negative feedback inhibition of angiotensin II on renin release and thereby reducing plasma renin activity.

Experimental evidence suggests that angiotensin II receptors do change with maturation. Pernollet et al. (1979) reported that angiotensin II receptors in membranes from the adrenal cortex of the rabbit increased with maturation. Moore (1980) reported that high affinity angiotensin II receptors appeared between 15 and 19 days in the embryonic chicken heart. Several investigators have suggested that vascular responses to angiotensin II also increase with maturation (Boatman et al., 1965; Hébert et al., 1972; Gray, 1976; Pernollet et al., 1979; Moore, 1980). Gray (1978) reported that the sensitivity and maximal response to angiotensin II of carotid artery strips from lambs of different ages increased with maturation. Hébert et al. (1972) concluded that fetal and newborn lambs required larger intra-aortic doses of angiotensin II to achieve a 20 mm Hg pressor response than did adult ewes. Similarly, Boatman et al. (1975) determined that the pressor
response to a fixed dose of angiotensin II in the isolated hindlimb of the puppy increased with age. However, Gray's (1976) in vitro study on carotid artery strips was not performed at a standardized point on the length-tension curve, and, therefore, the responses of individual preparations are not necessarily comparable. Furthermore, none of these studies was longitudinal in design and all used anesthetized animals in which sodium balance was unknown and uncontrolled. Sodium intake must be controlled in any comparative study of vascular responses to angiotensin II, since these responses vary with sodium balance (Stewler et al., 1972; Williams et al., 1976).

To test the hypothesis that the rise in arterial pressure occurring with maturation is due to an increase in vascular responsiveness to angiotensin II, the conscious newborn lamb was chosen as an experimental model. Sodium intake was standardized by weight. Responses of blood pressure, plasma renin activity, and aldosterone concentration to sequential cumulative doses of angiotensin II were measured longitudinally as the lambs matured.

Methods

Newborn female Dorset lambs were obtained from local farms and were weaned from their mothers at 1 or 2 days of age. They were housed at the University of Virginia Vivarium and were exposed to 12 hours of light daily. The lambs were fed a fixed quantity per kilogram per day of a standard lamb formula (Land of Lakes milk replacer Webster City, Iowa) and had free access to water. A 2-4 days of age, the lambs were premedicated with atropine (0.2 mg/kg, im) and anesthetized with ketamine (44 mg/kg, im) (Thurman et al., 1973). Arterial and venous catheters (Tygon i.d. 0.05", o.d. 0.090"; Cadillac Plastic and Chemical) were placed in the carotid artery and jugular vein or in the femoral artery and vein under sterile conditions. Catheter dead space was 1.2 ml. After surgery, the lambs were treated with chloramphenicol (50 mg/kg per day, iv) for 3 days and allowed to stabilize for 24-48 hours prior to study. Catheters were flushed daily with saline and refilled with heparin (100 U/ml) in saline. Catheters were replaced if they became obstructed.

Angiotensin II was dissolved in sterile water at a concentration of 50 μg/ml and stored at 4°C. Immediately prior to each infusion, an aliquot of this stock solution was diluted in sterile 5% dextrose in water to an appropriate concentration based on the lamb's weight. Responses to angiotensin II were studied according to the following protocols.

Experimental Protocol I

A 24-hour urine collection was obtained for sodium analysis. The afternoon after this collection, the lambs were transported to the laboratory, placed in a sling with their feet on the floor, and wrapped snugly with an Ace bandage. Direct arterial pressure was recorded (Gould recorder, 2400, Gould, Inc.) for at least 60 minutes to establish a stable baseline arterial pressure. Following this control period and after the dead space in the venous catheter had been cleared, angiotensin II amide (Asn¹, Val²-angiotensin II; Ciba, M-1229) was infused via a Harvard infusion pump (Harvard infusion/withdrawal pump, #901, Harvard Apparatus Co.) in sequential cumulative doses of 2, 4, 10, 20, and 40 pmol/kg per min. Total volume of fluid infused into each lamb at each study was 60 ml. Each dose was infused for 30 minutes. Arterial pressure was monitored continuously prior to and throughout the infusion period. As nearly as possible, the lambs were studied at the following ages: 1, 2, 4, 6, and 8 weeks.

Experimental Protocol II

On the evening prior to study and again on the morning of study, the lambs were given dexamethasone, 0.25 mg, iv. One hour after the second dose of dexamethasone, 2 ml of blood were drawn into a heparinized syringe. The sample was centrifuged and the plasma removed and frozen for cortisol determination. Beginning between 9:00 and 10:00 a.m., the lambs then again were given an infusion of angiotensin II as in protocol I. However, prior to the infusion and at the end of each dosage period of angiotensin II, a 15 ml sample of blood was withdrawn via the arterial catheter and immediately replaced with an equal volume of warmed sheep blood in citrate-phosphate-dextrose buffer. The lamb blood was drawn into a chilled tube containing Na₂ EDTA (final concentration, 1 mg/ml) and was immediately placed in an ice bath and then centrifuged at 16,000 g, at 4°C for 20 minutes. The plasma was decanted, aliquots obtained for plasma renin activity and aldosterone assays, and the aliquots frozen at —70°C. Because protocol II followed protocol I by one or more days in each lamb, the age groups differ slightly from each other.

Blood Pressure Calculations

Systolic and diastolic blood pressure measurements were obtained from the recorder tracing. A pressure value was calculated for every 10th pulse for the first 40 consecutive pulses of each 5-minute interval throughout the 30 minutes at each angiotensin II dose level. These values were averaged to give the mean systolic or diastolic pressure for that particular 30-minute period. Mean arterial pressure was calculated by the following formula: diastolic pressure + (pulse pressure/3).

Assays

Plasma renin activity was determined in duplicate for each plasma sample by radioimmunoassay of angiotensin I generated according to the method of Sealey and Laragh (1977) using an incubation time of 3 hours. The lowest limit of detection was 0.18 ng/ml per hr. Any values less than 0.18 ng/ml per hr were arbitrarily assigned the value 0.18 ng/ml per hr for statistical purposes and for calculation
of mean values. Interassay variation was less than 10% and intraassay variation was less than 5%. All samples from each lamb were run in the same assay.

Plasma aldosterone concentration was determined in duplicate aliquots by the radioimmunoassay method of Bühler et al. (1974). The lowest limit of detection was 0.1 ng/dl. Samples below the limit of detection were assigned a value of 0.1 ng/dl for statistical purposes and for calculation of the mean values. Interassay variation was less than 10% and intraassay variation was less than 5%.

Plasma cortisol was measured by radioimmunoassay (Gammacoat, Clinical Assay, Travenol Laboratories). Urinary sodium and potassium concentrations were measured by flame photometry; lithium was used as the internal standard.

**Statistics**

The effects of age were examined using hypothesized models (Goodnight, 1978) expressed as linear equations with either age or age group as independent variables (GLM procedure, Statistical Analysis System, SAS System, Inc.; Version 79.3). An initial model was constructed for each dependent variable hypothesizing effects on that variable for (1) baseline value for that particular variable, (2) dose of angiotensin II, (3) sodium excretion, (4) a term representing the interaction of dose of angiotensin II and sodium excretion, (5) age groups, and (6) a term representing the interaction of dose of angiotensin II and age group. The terms were entered in the model in the above order to provide (a) an adjustment of variation from age group to age group in baseline values (1), (b) a test of the main effects of dose of angiotensin II, sodium excretion and age group (2, 3 and 5), and (c) a final test (homogeneity of slopes) of the possible interaction of dose of angiotensin II and sodium excretion (4) or of dose of angiotensin II and age group (6). Levels of significance were accepted when \( P < 0.05 \).

**Results**

Mean 24-hour urinary sodium excretion (± SD) for all lambs at all ages was 7.2 ± 2.6 mEq/kg per day. After dexamethasone suppression for protocol II, plasma cortisol concentration was less than 1 ng/dl in a representative sample of lambs, indicating adequate suppression of ACTH.

**Arterial Pressure and Maturation**

[Figs. 1 and 2]

Basal mean arterial pressure was associated with age in both protocol I (\( r = 0.778; P < 0.0001 \)) and protocol II (\( r = 0.714, P < 0.0001 \)). When basal mean arterial pressures in both protocols were combined, the correlation coefficient with age was 0.746 (Fig. 1). Basal mean arterial pressure was associated also with weight (\( r = 0.672 \); Fig. 2). When the effect of weight was removed, basal mean arterial pressure still was associated with age (\( P = 0.0003 \)). However, when the effect of age was removed, the association between basal mean arterial pressure and weight was no longer significant (\( P = 0.489 \)).

**Arterial Pressure Responses to Angiotension II**

(Fig. 3)

Mean arterial pressure increased in response to angiotensin II in an approximately parallel manner for each age group. When the effects of basal mean arterial pressure, angiotensin II dose, and weight were removed, age did not influence the level of mean arterial pressure at each dose level of angiotensin II. Similar results were observed following dexamethasone suppression in protocol II (data not shown).

**Basal Plasma Renin Activity and Maturation**

(Fig. 4)

Mean basal plasma renin activity for all age groups was 2.75 ± 2.07 ng/ml per hr (mean ± SD). Age did not have a significant effect on basal plasma renin activity (\( r = 0.149; P = 0.413 \)). Likewise, basal plasma renin activity was not influenced by weight (\( r = 0.093; P = 0.613 \)) or sodium excretion (\( r = 0.149; P = 0.413 \)).
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Mean arterial pressure: response to sequential cumulative doses of angiotensin II at different ages in the newborn lamb.

Renin Responses to Angiotensin II (Fig. 5)

When adjusted for basal plasma renin activity, angiotensin II significantly suppressed plasma renin activity in all lambs ($P < 0.0001$). When the data were analyzed by age group and adjusted for basal plasma renin activity and angiotensin II dose, age was found to have a significant effect on the response of plasma renin activity to angiotensin II ($P = 0.027$). The oldest age group (58-66 days) was responsible for this age effect in that this was the only age group that did not show significant suppression of plasma renin activity during the angiotensin II infusion. The other groups demonstrated plasma renin activity suppression curves with similar configurations, and no significant difference could be demonstrated among them. However, when the data were adjusted further for sodium excretion, the effect of age group on renin responses to angiotensin II was no longer significant ($P = 0.121$).

Basal Plasma Aldosterone Concentration and Maturation (Fig. 6)

Mean basal plasma aldosterone concentration for all lambs at all ages was $1.02 \pm 1.24 \text{ ng/100 ml}$ (mean $\pm$ SD). Basal plasma aldosterone concentration tended to decrease with age ($r = -0.316; P = 0.078$) and weight ($r = -0.309; P = 0.085$), but this...
was not statistically significant. Basal plasma aldosterone concentration was not associated with either plasma renin activity ($P = 0.645$) or urinary sodium ($P = 0.547$) or potassium ($P = 0.988$) excretion. Basal plasma aldosterone concentrations were measured also in three lambs both before and after dexamethasone suppression. Although basal plasma aldosterone concentrations were lower after dexamethasone suppression ($0.83 \pm 0.40$ vs $1.73 \pm 1.21$ ng/100 ml), the difference was not significant by Student's paired t-test.

**Aldosterone Responses to Angiotensin II**  
(Fig. 7)

Plasma aldosterone concentrations increased significantly in all age groups in response to angiotensin II. When plasma aldosterone concentrations were adjusted for basal concentrations, lambs that were 28–31 days old had a significantly steeper rise in plasma aldosterone concentration than the other groups combined ($P < 0.0001$). When this group was excluded from the analysis, however, no significant difference in plasma aldosterone responses to angiotensin II could be demonstrated among the younger and older age groups.

**Discussion**

This study demonstrates that the increase in arterial pressure observed with maturation in infants and children (Moss and Adams, 1969; Nadas and Fyler, 1972; Lauer et al., 1975; Voors et al., 1976; Blumenthal et al., 1977) occurs in the lamb as well. The rise in arterial pressure that we observed was progressive throughout the 8 weeks of observation. Our findings differ from those of Woods et al. (1977), who described a stable mean arterial pressure in five conscious lambs studied longitudinally from 1–8 weeks of age. In their study, lambs were maintained on ewe's milk and alfalfa, and thus the sodium intake was probably considerably less than that of the lambs that were maintained on milk replacer in the present study. It is possible that the relatively high sodium intake in our lambs contributed to the rise in arterial pressure. However, sodium intake is unlikely to be the only explanation for the differences in findings in the two studies. The mean arterial pressures (75–80 mm Hg) reported by Woods et al. (1977) in lambs from 1 to 8 weeks of age correspond better with the pressures we observed at 55–60 days of age (79.9 ± 5.8 mm Hg) than with the pressures we observed at 0–5 days of age (58.5 ± 5.9 mm Hg). If sodium intake alone were responsible for the difference in observations in the two studies, we would have expected our newborn lambs to have had pressures comparable to those reported by Woods et al. (1977) and older lambs to have had higher pressures. Since we demonstrated an increase in arterial pressure with age, the lamb model is suitable for studying the mechanisms responsible for the rising arterial pressure that occurs with maturation.

Previous studies have suggested that weight and height are important determinants of blood pressure in children (Lauer et al., 1975; Voors et al., 1976; Pipkin et al., 1977). However, our data indicate that, in the lamb, age is a stronger determinant of arterial pressure than is weight, and suggest that the rise in arterial pressure may be a function of the aging process per se.

Since arterial pressure is a function of cardiac output and total peripheral vascular resistance, changes in either or both factors could be responsible for the age-associated increase in arterial pressure. When related to surface area, cardiac output remains constant with age (Rudolph, 1974). If sodium intake alone were responsible for the difference in observations in the two studies, we would have expected our newborn lambs to have had pressures comparable to those reported by Woods et al. (1977) and older lambs to have had higher pressures. Since we demonstrated an increase in arterial pressure with age, the lamb model is suitable for studying the mechanisms responsible for the rising arterial pressure that occurs with maturation.

The rise in cardiac output is due to an increase in stroke volume, since heart rate declines with maturation (Rudolph, 1974). The increase in cardiac output alone may be responsible for the rise in arterial pressure. Less is known about the contribution of peripheral vascular resistance to the rise in arterial pressure occurring with maturation. When standardized for body surface area, total peripheral vascular resistance increases with age in early childhood (Rudolph, 1974). If absolute total peripheral vascular resistance also increases with age, this factor, as well, would contribute to the rise in arterial pressure.

Of the numerous vasoactive substances that affect peripheral vascular resistance, angiotensin II is one of the most potent humoral vasoconstrictors. Despite previous reports that suggested that vascular sensitivity and/or reactivity to angiotensin II increases with age (Hebert et al., 1972; Boatman et al., 1975; Gray, 1976; Moore, 1980), we found no evidence of such a change. Our data, therefore, are in agreement with those of Pipkin (1971) who studied groups of rabbits at different ages. Our study, however, has the advantage of its longitudinal de-
sign and its performance in conscious animals that were maintained on a controlled sodium diet. This distinction is important, since the vascular sensitivity and response to angiotensin II varies with sodium intake (Strewler et al., 1972; Williams et al., 1976). It is likely that the effects of species differences, anesthesia, uncontrolled sodium balance, and/or experimental design contributed to the findings in previous studies, suggesting that an increase in vascular responsiveness to angiotensin does occur with increasing age (Boatman et al., 1965; Hébert et al., 1972; Gray, 1976). Our data demonstrate that no change in vascular responsiveness to angiotensin II occurs with maturation in the lamb. Therefore, other mechanisms must be responsible for the rise in arterial pressure that we observed over the first 8 weeks of life.

If total peripheral vascular resistance actually does increase with age, then factors other than angiotensin II-induced vasoconstriction are likely to be responsible. Other possible factors include vasopressin, sympathetic nervous system activity, number or affinity of vascular adrenergic receptors, prostaglandins, concentrations of various vasodilators such as histamine or bradykinin, and anatomic considerations such as the number of arterioles and the cross-sectional diameter of the vascular tree. Woods et al. (1977) were unable to demonstrate a change in the pressor responses induced by exogenous norepinephrine in lambs from 1 to 8 weeks of age. In the same study, α-adrenergic receptor blockade with phentolamine or ganglionic blockade with trimethaphan produced a smaller decrement in arterial pressure in the older lambs. Thus, the contribution of the sympathetic nervous system to the maintenance of arterial pressure appears to diminish with maturation, but no change in α-adrenergic responses apparently occurs in the lamb. However, other investigators, using different species, have found that vascular responses to norepinephrine either increase (Knight and McGregor, 1974) or decrease (Pipkin, 1971) with maturation. Therefore, this question remains unresolved.

Of the various prostaglandins, fetal blood vessels synthesize predominantly prostacyclin (PGI₂), which is thought to act as an endogenous vasodilator (Friedman et al., 1978). This agent appears to play an important role in maintaining patency of the ductus arteriosus in fetal life. A decline in PGI₂ synthesis, perhaps coupled with a relative increase in synthesis of prostaglandins with pressor activity such as thromboxane A₂, may occur with maturation (Friedman et al., 1978; Terragno and Terragno, 1978) and might then be responsible for the rise in blood pressure. However, the role of prostaglandins, various other vasoactive agents, and anatomic factors in the age-associated rise in arterial pressure remain to be explored.

Contrary to previous reports, we did not find elevated plasma renin activity or plasma aldosterone concentrations in the newborn lamb. Further more, we observed no significant age-related decrease in plasma renin activity or aldosterone concentration as the lambs matured. The difference between our observations and those reported in the literature again may reflect the fact that our animals were in balance at a relatively high sodium intake, which would be expected to lead to depression of the renin-angiotensin-aldosterone system. Dexamethasone-induced suppression of ACTH was not responsible for these observations, since in the three animals studied without prior treatment with dexamethasone, plasma aldosterone concentrations remained low.

Although other investigators have been unable to demonstrate an inverse relationship between components of the renin-angiotensin-aldosterone system and sodium intake or excretion in infants, either the range of sodium intake has been narrow (Siegel et al., 1974) or sodium excretion has been corrected for body weight (Siegel et al., 1974; Raux-Eurin et al., 1977; Van Acker et al., 1979). However, if the relationship between plasma renin activity or aldosterone concentration and sodium balance is examined over a wider range of sodium intake, or if sodium excretion is not factored for body weight or surface area, an inverse relationship is apparent (Siegel et al., 1974; Giovannelli et al., 1976; Hiner et al., 1976; Van Acker et al., 1979). Presumably, we did not find an association between basal plasma renin activity and basal plasma aldosterone concentration or between sodium and potassium excretion and either plasma renin activity or plasma aldosterone concentration because the intake of sodium and potassium of our lambs was held constant on a weight basis such that relatively little variation in any of these parameters occurred. Because the basal plasma renin activity and aldosterone concentrations we observed were low, our data suggest that the renal juxtaglomerular apparatus in the newborn lamb is indeed sensitive to sodium intake. It is possible that a low sodium intake in early life followed by a progressive increase in sodium intake may have been responsible for the elevated concentrations of the components of the renin-angiotensin-aldosterone system previously reported in neonatal organisms and for the progressive decline in these concentrations observed with maturation in cross-sectional studies.

Renin and aldosterone responses to angiotensin II also were studied. The increased aldosterone responses observed in lambs 28–31 days old remain unexplained, but are of doubtful physiological significance, since the response in this age group differed from that of both younger and older ages in which the zona glomerulosa responded in a similar fashion. Therefore, no consistent age-related change in the aldosterone response to angiotensin II is apparent in the lamb. Thus, if angiotensin II receptors in the zona glomerulosa increase with maturation postnatally in the lamb, as has been reported in the rabbit (Pernollet et al., 1980), this
would appear to have no physiological significance in terms of aldosterone response. This conclusion, of course, is based on the assumption that the metabolic clearance rate of aldosterone does not change with maturation. We did not study metabolic clearance rates in our lambs. However, Kowarski and Migeon (1977) concluded that, when corrected for body surface area, the metabolic clearance rate of aldosterone does not change significantly between 11 days and 15 years of age in the human.

The attenuation of the angiotensin II-induced suppression of plasma renin activity observed in the oldest age group (58–66 days) was limited to this age group alone and may have been due to decreased sodium intake. Since this was the oldest age group that we studied, it is difficult to judge the physiological significance of this observation. Older age groups would have to be studied to determine whether a pattern of decreasing plasma renin activity in response to exogenous angiotensin II occurs beyond 58–66 days. Even if such a pattern were identified, however, it could not explain the age-related decrease in plasma renin activity reported by others. It is apparent that the juxtaglomerular apparatus does not become more sensitive to negative feedback inhibition by angiotensin II as lambs mature between birth and 8 weeks of age.

We conclude that, in the sodium-replete newborn lamb, (1) arterial pressure increases with maturation, (2) age is a stronger determinant of arterial pressure than is weight, (3) altered vascular responsiveness to angiotensin II does not contribute to the rise in blood pressure that occurs with maturation, and (4) plasma renin activity and aldosterone concentrations are not elevated and do not demonstrate a sequential, age-related change in responsiveness to angiotensin II.

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References


Influence of Length Changes on Myocardial Metabolism in the Cat Papillary Muscle

GEORGE COOPER, IV

SUMMARY Myocardial oxygen consumption (MVO₂) increases in proportion to the cumulative product of active tension and time throughout the normal isometric contraction. However, rapid shortening at any time during a contraction prevents further tension generation and oxygen consumption during the remainder of that contraction. My hypothesis is that, under physiological conditions, shortening produces this effect by reducing the extent and duration of the energy-dependent events subserving contraction. I tested this hypothesis by minimizing the potential reduction of metabolism via muscle shortening during contraction; this was done by lowering temperature (23°C), reducing shortening rate (0.8 muscle length/sec) and increasing myoplasmic calcium (7.5 mM Ca²⁺ + 10 mM caffeine). Twelve right ventricular cat papillary muscles were released from that length at which maximum active force was developed to a slack length at increasing intervals after stimulation. Under these conditions, absolute MVO₂ increased significantly, but the relative increase with progressively longer stimulus-release intervals was greatly attenuated. At a 0-msec stimulus-release interval under the present conditions, MVO₂ was 8.26 nl/mg dry wt per contraction; for a full contraction MVO₂ was only 27% greater. Under the more physiological conditions employed in a prior study, this increase, from 0.41 to 2.97 nl/mg dry wt per contraction, was 624%. The addition of 10⁻⁷ M norepinephrine under otherwise physiological conditions increased MVO₂ at all times during contraction, but the relationship between MVO₂ and length was not altered. These data suggest that, both under normal conditions and after inotropic augmentation, shortening of cardiac muscle during contraction decreases the level of the energy-dependent events supporting contraction; this may be the mechanism by which MVO₂ is regulated by length-dependent changes in metabolism throughout contraction. Circ Res 49: 423-433, 1981

IT has been accepted generally (Braunwald, 1971; Lambert and Posner, 1979) on the basis of previous data (Monroe, 1964) that the relaxation phase of myocardial contraction requires very little energy. However, recent studies (Cooper, 1976; Cooper, 1979) on the regulation of myocardial metabolism have led to two new conclusions. First, there is no energy-independent portion of the isometric myocardial contraction. Second, the level of metabolism, measured as the net energy utilization of the processes required to initiate and sustain the myocardial contraction, varies directly with changing muscle length from the time of stimulation through that of complete relaxation.

These two conclusions have led to the hypothesis that length-dependent variation in metabolic activity regulates myocardial oxygen consumption (MVO₂) during the normal cardiac contraction. The present investigation of this hypothesis is based both on my previous finding that MVO₂ is reduced when heart muscle is allowed to shorten during contraction, with a progressive reduction in MVO₂ with earlier shortening, and on the supposition that one possible mechanism for such a reduction would be a decrease in the level of intracellular calcium effecting cross-bridge activation. If oxygen consumption primarily reflects the action of calcium on the contractile apparatus, the effect of such a decrease would be obscured as the calcium concentration approaches the level required to saturate the contractile apparatus. The present experimental conditions include the presence of high calcium and caffeine in an effort to cause such a saturation. The effect of these experimental conditions was assayed both metabolically and mechanically throughout contraction. Under these circumstances, absence of major length-dependent effects on myocardial me-
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T A Wilson, D L Kaiser, E M Wright, Jr, M J Peach and R M Carey

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