Etiology of the Negative Chronotropic Responses to Transient Coronary Artery Occlusion in the Anesthetized Rhesus Monkey

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SUMMARY Etiology of the negative chronotropic response to coronary artery occlusion was studied in chloralose-anesthetized monkeys. One-minute occlusion of the circumflex (CIRC) coronary artery resulted in marked negative chronotropic responses and consistent alterations in atrial electrograms. These responses were dependent on interruption of flow to a small proximal CIRC branch, and postmortem examination revealed that it perfused the sinus node region. The negative chronotropic response was not dependent on any apparent neural reflexes because it was not affected by autonomic blockade. Coronary artery occlusion in anesthetized monkeys can result in significant decreases in heart rate and changes in atrial electrical activity when flow to the pacemaker region is interrupted. We suggest that (1) rhesus monkeys may be suitable for study of the sick sinus syndrome, and (2) atropine-resistant bradycardia and atrial arrhythmias observed in postinfarction patients may be due to sinus node artery blockade.

CHANGES IN HEART RATE after either myocardial infarction in man or experimental coronary artery occlusion in other species have been reported. In the cat, occlusion of any of the three main coronary arteries results in marked bradycardia. In the dog, on the other hand, several investigators have reported that coronary artery occlusion resulted in a tachycardia, bradycardia, or no heart rate change. Webb et al. reported that patients, examined within hours after suffering a myocardial infarction, frequently demonstrated either a tachycardia or a bradycardia. They further associated the direction of the heart rate change with the site of infarction, i.e., tachycardia was seen most often after anterior infarction, whereas bradycardia usually occurred after posterior infarction. Lippestad and Martin also reported that blockade of flow in the sinus node artery can lead to sinus arrest and A-V nodal rhythm in patients after posterior infarctions.

Bradycardia after myocardial infarction may further exacerbate myocardial hypoperfusion due to a reduced cardiac output. In contrast, postinfarction tachycardia may increase the size of the infarct by further comprising ischemic tissue in the border zones and may also increase the incidence of ventricular fibrillation. The cause for these chronotropic responses and their effect on cardiac function are of major importance in post heart attack therapy. This study was undertaken to determine the etiology of the chronotropic responses to coronary artery occlusion in the nonhuman primate (Macaca mulatta). In addition, the effect of occlusion-induced heart rate changes on regional blood flow and contractile force was also studied to determine if these changes affect the magnitude of the ischemic insult.

Methods

Adult rhesus monkeys weighing 3-5 kg, unselected as to sex, were sedated with phencyclidine HCl (1-2 mg/kg, i.m.) and then anesthetized with alpha-chloralose (75 mg/kg, i.v.). The femoral artery and vein were catheterized for recording aortic blood pressure and for drug administration, respectively. Animals were paralyzed with pancuronium (0.1 mg/kg) and artificially respired. Blood samples were drawn every 30 minutes to insure that blood gases and pH were maintained within normal limits. To analyze overall cardiac function, the blood pressure, lead II electrocardiogram, and heart rate were recorded. The latter was detected by a cardiograph triggered by the systolic blood pressure peaks.

To study regional cardiac function, a transternal thoracotomy was performed, and the heart was stabilized in a pericardial cradle. Using a dissecting microscope, the bifurcation of the left coronary artery was exposed. Particular care was taken to avoid any visible pericoronary nerves in this region. Regional mechanical activity was measured by miniature Walton-Brodie strain gauges attached parallel to the epicardial fibers. One strain gauge was placed on the anterior apical surface in the region normally perfused by the anterior descending (LAD) branch of the left coronary artery, while the second was secured to the epicardium near the base of the left ventricle in the region normally perfused by the circumflex (CIRC).

The hydrogen polarograph technique was used to determine regional myocardial blood flow. Two platinum wire electrodes (tip diameter 0.2 mm) were secured within the epicardium near each foot of the strain gauges. This method for measuring myocardial blood flow was first reported by Aukland in 1964. Recent reports by Gross and Winbury and Kjekshus demonstrated that flows determined by this method are in agreement with those determined by either an electromagnetic flow probe or microspheres, respectively.

Briefly, the hydrogen polarograph technique measures blood flow by the Fick principle. Hydrogen gas is added to the inhaled air (maximum concentration less than 5%) until the tissues are saturated. Concentrations of hydrogen gas in tissues are detected by the platinum electrodes which are each polarized to a +0.65V DC potential relative to an indifferent electrode on the sternum. Inhalation of hydrogen is then discontinued and subsequently washed from the tissues. The slope of the hydrogen washout curve is calculated according to a first-order reaction with a rate constant k = (0.693/T½) x 100, where T½ is the time in minutes for hydrogen levels to decrease by one-half. Myocardial blood

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flow is expressed in ml/min/100 g tissue and is calculated by
the equation $MBF = \frac{K}{w}$, where $w$ is the weight of the
tissue and $\lambda$ is the blood-tissue partition coefficient for
hydrogen which is approximately equal to 1.9

To insure that the platinum electrodes did not damage the
surrounding myocardium, the output of each polarograph
channel was AC-coupled to a storage oscilloscope and the
resulting local epicardial electrograms were examined. Any
significant ST-segment deviation was taken as evidence of
myocardial damage, and blood flows were not calculated
from these electrodes.

In a few animals, right atrial electrical activity was
detected by silver electrodes secured to the epicardial surface
of the right atrium near its junction with the superior vena
cava and attached to a standard ECG preamplifier.

During the course of the experiment, each of the major
branches of the left coronary artery (left anterior descending
and circumflex) were occluded several times. To permit
repeated occlusions of these arteries, a modified Heifetz
aneurysm clip was utilized. Application of the clip to a cor-
ronary artery effectively eliminated any flow through the
vessel but did not appear to damage nearby pericoronary
nerves. Support for the latter stems from studies in
anesthetized cats in which a similar experimental technique
is being utilized to study the vagal cardio-cardiac reflexes
during coronary artery occlusion. In this study, repeated
occlusions with the same occlusion clip fail to alter the
magnitude of this neurally mediated reflex (Alter, unpub-
lished observations).

A one-hour control period was allotted prior to studying
the effects of coronary artery occlusion. Several occlusions
of both the LAD and circumflex arteries were then
accomplished with 10-minute control periods between
occlusions. Preliminary studies revealed that most of the
chronotropic responses reached their maximum within the
first minute after coronary artery occlusion. In addition it
was found that the incidence of ventricular fibrillation was
markedly reduced for these brief occlusions. Therefore, one
minute was selected as the occlusion period in these
experiments. To determine the role of autonomic reflexes in
any chronotropic responses to occlusion, atropine sulfate
(0.5 mg/kg) and propranolol (0.5-1.0 mg/kg) were ad-
ministered and occlusions were then repeated. Postmortem
analysis of the distribution of the coronary arteries was con-
ducted after filling them with colored latex solutions
(Cementex). It was found that manual injections of the latex
consistently filled vessels with diameters as small as 80 to
100 microns.

Results are reported as mean values ± standard error of
the mean. Statistical significance between data groups was
determined by Student’s $t$-test for paired data and was con-
sidered significant when $P < 0.05$.

Results

Physiological data obtained from 13 chloralose-anesthe-
thetized rhesus monkeys will be discussed in this report.
Baseline heart rate, prior to LAD occlusion, averaged
186 ± 7 beats per minute (BPM) while aortic pressure was
134 ± 4/73 ± 7 mm Hg. Control myocardial blood flow
(MBF) near the apex of the anterior left ventricular wall
averaged 118 ± 10 ml/min/100 g tissue, while that near the
base of the left ventricle was 122 ± 7 ml/min/100 g. There
were no significant differences in the baseline parameters
prior to occlusions of other coronary arteries (table 1).

Occlusion of the left anterior descending coronary artery
(LAD) resulted in a 12 ± 3% decline in systolic aortic pres-
sure which was accompanied by a small increase in heart
rate (6 ± 1 beats/min) in nine of 13 animals. An example of
these changes is shown in figure 1. In this animal, evidence
of regional ischemia and dysfunction was obtained near the
apex of the anterior left ventricular wall where myocardial
blood flow declined 74% below baseline values. This
ischemia resulted in a 75% decrease in contractile force.

After one minute, flow was restored to the LAD, result-
ing in a return of heart rate and aortic pressure to preoccu-
lation values. A marked reactive hyperemia was recorded in
the previously ischemic region. In this animal (fig. 1),
myocardial blood flow rose 67% above baseline; contractile
force also underwent a significant postocclusion overshoot
of 50%. Results from all animals indicate that LAD occlu-
sion failed to elicit any significant changes in myocardial
blood flow and contractile force in the basal region perfused
by the circumflex artery. The data are summarized in table 1.

Occlusion of the circumflex branch of the left coronary
to coronary artery occlusion.

<p>| Table 1. Cardiac Responses to Coronary Artery Occlusion |
|--------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Heart rate (beats/min)</th>
<th>Aortic pressure (mm Hg)</th>
<th>Contractile force (change from preocclusion values)</th>
<th>Myocardial blood flow (ml/min/100 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anterior descending artery occlusion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 186 ± 7</td>
<td>134 ± 4/73 ± 7</td>
<td>-74 ± 4</td>
<td>118 ± 10</td>
</tr>
<tr>
<td>During +6 ± 1*</td>
<td>117 ± 6/63 ± 7†</td>
<td>-55 ± 7</td>
<td>25 ± 4†</td>
</tr>
<tr>
<td>Post §</td>
<td>138 ± 5/72 ± 9</td>
<td>+4 ± 3</td>
<td>267 ± 49†</td>
</tr>
<tr>
<td><strong>Circumflex artery occlusion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 191 ± 7</td>
<td>136 ± 5/74 ± 7</td>
<td>-12 ± 9</td>
<td>121 ± 9</td>
</tr>
<tr>
<td>During -45 ± 6†</td>
<td>108 ± 6/54 ± 6†</td>
<td>-58 ± 7</td>
<td>99 ± 11</td>
</tr>
<tr>
<td>Post +4 ± 1*</td>
<td>137 ± 6/75 ± 7</td>
<td>+7 ± 4</td>
<td>132 ± 7</td>
</tr>
<tr>
<td><strong>Sinus node artery occlusion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 192 ± 10</td>
<td>131 ± 9/81 ± 10</td>
<td>-10 ± 4</td>
<td>134 ± 18</td>
</tr>
<tr>
<td>During -48 ± 6†</td>
<td>130 ± 9/77 ± 10</td>
<td>-10 ± 2</td>
<td>137 ± 25</td>
</tr>
<tr>
<td>Post +3 ± 1*</td>
<td>129 ± 9/75 ± 16</td>
<td>+5 ± 2</td>
<td>132 ± 22</td>
</tr>
</tbody>
</table>

*Change in heart rate.
†Difference from pre-occlusion value is significant at the 0.05 level.
‡Returned to preocclusion values.
artery also resulted in a decrease in systolic aortic pressure. In contrast to the small tachycardia observed during LAD occlusion, circumflex occlusion resulted in a marked slowing of heart rate (45 ± 6 beats/min) in 11 of 13 animals. Figure 2 shows an example of the responses to circumflex occlusion obtained in the present study. For this animal, occlusion resulted in a 46% decline in systolic aortic blood pressure and a 45% decrease in heart rate. Within the ischemic region at the base of the left ventricle, MBF decreased 85% and the contractile force trace indicated systolic expansion during the occlusion period. Restoration of flow to the circumflex resulted in a return in both heart rate and blood pressure. Within the previously ischemic region, a 109% increase in MBF was recorded and a postocclusion overshoot of contractile force (49%) was also observed.

Circumflex occlusion in this particular animal resulted in a 33% decline in MBF and a 40% decrease in contractile force in the apical region. Restoration of flow resulted in a 68% increase in MBF which was accompanied by a 17% overshoot in contractile force. The results obtained from all animals, however, indicated that restoration of flow in the circumflex did not result in significant alterations in myocardial blood flow and contractile force in the apical region. Results from circumflex occlusion are also summarized in table 1.

The most notable difference between the responses to the two occlusions was the marked decrease in heart rate which occurred during circumflex occlusion. This bradycardia may have affected regional cardiac function and blood flow in either the ischemic or nonischemic regions. Table I shows, however, that there were no significant differences in the average MBF and contractile force data from the ischemic regions for either occlusion except for the postocclusion overshoot in contractile force in the basal region after circumflex occlusion. This was significantly less than that obtained from the apical region after LAD occlusion.

To determine if the autonomic nervous system was involved in any of these changes resulting from coronary artery occlusion, atropine and propranolol were administered in three animals and the occlusions were repeated. Autonomic blockade resulted in a significant decline in baseline heart rate and contractile force for the left ventricle. These results are summarized in table 2. LAD occlusion after autonomic blockade elicited a 13 ± 4% decrease in systolic aortic pressure without any significant change in heart rate. In contrast, circumflex occlusion also elicited a decrease in systolic aortic pressure and a marked slowing of heart rate (32 ± 7 beats/min). Changes in regional contractile force and myocardial blood flow during these occlusions were similar to those observed prior to autonomic blockade. Due to the fact that only three animals
were studied after autonomic blockade, no statistical analysis of these data was performed.

Another possible mechanism for the bradycardia observed during circumflex occlusion may be ischemia to the sinoatrial node. To evaluate this hypothesis, proximal branches of the circumflex artery were exposed and individually occluded. This revealed that occlusion of the first lateral branch (diameter ≤ 1 mm) of the circumflex resulted in a bradycardia whose magnitude (48 ± 6 beats/min) was not significantly different from that recorded during occlusion of the proximal circumflex artery. Figure 3 depicts an example of these responses. Occlusion of the circumflex branch resulted in a marked bradycardia (70 beats/min) with no consistent changes in aortic pressure or regional contractile force. Myocardial blood flow was down somewhat during this occlusion, but the average response for all animals (table 1) failed to show any significant difference in regional myocardial blood flow during occlusion of this branch of the circumflex artery. After autonomic blockade, occlusion of this circumflex branch still elicited a decrease in heart rate (29 ± 6 beats/min) without any significant change in other cardiac parameters. Since occlusion of this branch resulted in a bradycardia which was not mediated by any apparent neural pathway, this artery was tentatively designated as the sinus node artery (SNA).

To further analyze the effects of sinus node artery occlusion on cardiac pacemaker function, surface electrodes were secured to the lateral wall of the right atrium near its junction with the superior vena cava. Occlusion of either the proximal circumflex artery or the sinus node artery resulted in negative chronotropic responses which were accompanied by changes in the ECG and the right atrial electrogram (AEG). Examples of these changes are shown in figures 4 and 5. The upper traces are aortic pressure, and indicate when electrical activity resulted in mechanical systole. In figure 4, occlusion of the circumflex artery proximal to the origin of the sinus node artery resulted in a 55 beats/min decrease in heart rate with an onset latency of 16 seconds. After 30 seconds of occlusion, there was an atrial depolarization which failed to conduct to the A-V node. This was then followed by a premature ventricular contraction with retrograde conduction to the atrium. For the remaining period of occlusion, the atrial electrogram indicated a sustained shift in the atrial depolarization wave vector, as was evident by the decrease in magnitude of the P wave of the AEG. This was also reflected in a smaller P wave in the lead II ECG. In addition, circumflex occlusion resulted in a marked ST elevation and hypotension. In contrast, sinus node artery occlusion (fig. 5) failed to significantly alter systolic aortic pressure despite an 88 beats/min decrease in heart rate. Once again, the onset latency for the heart rate decline (13 sec) was approximately one-half that for the change in the P wave of the AEG. In this example, sinus

![Cardiovascular responses to a one-minute occlusion of the sinus node artery in an anesthetized rhesus monkey. Interruption of flow to the sinus node region failed to cause any major changes in regional myocardial blood flow or contractile force in the left ventricle, but did result in a marked decline in heart rate.](image-url)
node artery occlusion resulted in both a reduced P wave magnitude and decreased PR interval, which suggests a shift in the pacemaker site. Since the left ventricular muscle was not ischemic, the QRS complex of the ECG remained unchanged. Right atrial electrograms were recorded in a total of four animals, and in all cases, sinus node artery occlusion resulted in a significant alteration in the atrial depolarization wave, the latter having an onset latency significantly longer than that for the bradycardia.

Postmortem examination of the latex-filled coronary arteries was conducted on 11 animals. In four of these, the sinus node region was perfused by a single artery which originated from the circumflex branch of the main left coronary artery. After arising as the first lateral branch of the circumflex, the sinus node artery gave off branches to the epicardial surface of the left atrium. It then traversed within the epicardium of the interatrial septum to the superior medial surface of the right atrium, reaching the area of the junction of the right atrial appendage and the superior vena cava. In five animals (fig. 6), the sinotubular region appeared to be perfused by this circumflex branch as well as one or more smaller branches of the right coronary artery. On most occasions, the sinus node artery (origin from circumflex) also continued onto the lateral surface of the superior vena cava, forming a loop around it. In this small number of animals, there did not appear to be a correlation between the magnitude of the negative chronotropic response to sinus node artery occlusion and the presence of additional sinus node perfusion from a nonoccluded right coronary artery branch. In the remaining two animals, the first lateral branch of the CIRC terminated near the interatrial septum. In these animals, right coronary branches reached the sinus node region; and in one, the right coronary branch looped around the superior vena cava. Physiological evidence was obtained from one of these animals that the right coronary artery might occasionally serve as the sole source of sinus node perfusion. Circumflex artery occlusion failed to elicit a bradycardia, but right coronary artery occlusion resulted in a 20 beats/min bradycardia which was not eliminated by autonomic blockade. Therefore, in 85% of rhesus studied, the CIRC is the origin of the sinus node artery, whereas the latter originates from the proximal right coronary in the remaining 15%. In either case, interruption of flow in the sinus node artery results in an ischemia-induced bradycardia.
Discussion

The results of this study indicate that chronotropic responses to coronary artery occlusion in the rhesus may be mediated by at least two mechanisms. During LAD occlusion, a small cardioacceleration was observed which was eliminated by autonomic blockade. It was concluded that this positive chronotropic response results from a baroreceptor reflex to the hypotension which occurred during LAD occlusion. It was surprising that the size of the response was small, considering that systolic aortic pressure fell significantly. A possible explanation for this finding comes from the recent report by Feola et al., who demonstrated that despite hypotension, cardiac sympathetic efferent discharge decreased during the first 30 minutes of circumflex artery occlusion.

Cardiac pacemaker ischemia is another mechanism which may be responsible for heart rate changes during coronary artery occlusion in the rhesus. In the present study, interruption of blood flow in the parent CIRC or its sinus node branch resulted in a marked bradycardia accompanied by an alteration in the P wave of the right atrial electrogram. Atropine (vagolytic) and propranolol (sympatholytic) administration failed to alter these responses, thus indicating that the changes were not dependent on any autonomic neural reflex.

A suitable model for the study of the effect of sinus node ischemia on cardiac function has not been previously reported. Early studies in the dog11 contended that bradycardia was produced by sinus node artery occlusion, but James and Reentsma12 were unable to confirm these findings. This difference was finally resolved by Billette et al.,13 who were able to obtain bradycardia in the dog by occluding the sinus node artery as well as all collaterals to the pacemaker region. This necessity for removing collateral blood flow before inducing any disruption in pacemaker function does not appear to be necessary in the rhesus. In the present study, five animals appeared to receive sinus node perfusion from branches of both the circumflex and right coronary arteries, and yet occlusion of just the circumflex branch was capable of inducing marked slowing of the heart rate. It is possible that occlusion of both blood supplies to the sinus node region may have induced even more dramatic pacemaker changes. However, the fact that occlusion of just the sinus node artery leads to pacemaker dysfunction may make this animal particularly useful in the study of the sick sinus syndrome. A recent report on patients with coronary artery disease by Jordan et al.14 has demonstrated a relationship between sinus node dysfunction and obstruction of the sinus node artery or its parent vessel. The rhesus monkey may be a useful animal model for the study of sinus node function after permanent interruption of sinus node artery blood flow.

In the rhesus, occlusion of the sinus node artery produced both bradycardia and alterations in the atrial electrical activity, with the latter having a latency approximately twice that of the former. The prolonged latency for change in the P wave of the AEG may be explained on the basis of the spread in ischemia in this region. Interruption of flow in the SNA first leads to sufficient ischemia in pacemaker tissue to decrease spontaneous rate, but the region of ischemia must further enlarge before any noticeable change in the atrial depolarization vector can be detected. Atrial arrhythmias, however, were not observed in the present study. The production of altered atrial electrical activity certainly suggests that occlusions for longer than one minute may lead to these arrhythmias. Studies are currently underway to determine if prolonged sinus node ischemia will lead to atrial arrhythmias. In addition, it is possible that simultaneous ischemia in both ventricular myocardium and the sinus node region may predispose to an increased incidence of ventricular arrhythmias as was suggested by Webb et al.8

The distribution of sinus node arteries in experimental animals shows a significant difference among species. In the dog, the sinus node artery originates as a distal branch of the right coronary artery in 90% of the cases,15 while arising from the proximal circumflex in the remaining animals. On the other hand, sinus node perfusion in the cat is usually from a proximal branch of the right coronary artery (90%) with the remainder coming from a CIRC branch.1 In man, James16 has shown that the sinus node is perfused by a proximal branch of the right coronary artery in 60% of the hearts examined, whereas the CIRC was the origin in 40% of the cases. In the present study, physiological and anatomical data indicate that the CIRC was the source of sinus node perfusion in approximately 85% of rhesus monkeys. In the other two monkeys, it appears that the sinus node received its blood supply from branches which arose near the origin of the right coronary artery. Anatomically, the course of the sinus node artery in the rhesus was quite similar to that reported in man;17 that is, the artery passed to the sinus node region and then formed a loop around the superior vena cava.

Based on the rather dramatic changes in heart rate and P waveform of the AEG, during just a one-minute interruption of flow in the sinus node artery, it appears that the rhesus monkey will serve as a useful model in studying the long-term effects of sinus node ischemia. It will be interesting to see if prolonged ischemia will lead to important atrial arrhythmias or if sufficient collateral flow exists to permit the sinus node region to continue in its role as the cardiac pacemaker.
It was somewhat surprising that coronary artery occlusion in the rhesus failed to initiate a neurally mediated bradycardia. This cardio-cardiac reflex has been demonstrated in cats, and appears to be responsible for most incidents of bradycardia seen in post-myocardial infarction patients. In both man and cat, atropine usually eliminated or markedly reduced the bradycardia. Other studies in nonhuman primates have also failed to observe any vagally mediated bradycardia during coronary artery occlusion. It is possible that these studies in baboons and rhesus monkeys did not report any ischemia-induced bradycardia during occlusion because their experiments did not involve proximal CIRC occlusion.

It is also possible that in the present study, the afferent pathways involved in this cardio-cardiac reflex were inadvertently interrupted during exposure of the coronary arteries. This is not likely, however, because studies are currently underway utilizing the same preparation in which we are studying the negative chronotropic response to coronary artery occlusion in the cat. This preparation consistently provides an experimental model in which occlusion results in a neurally mediated bradycardia (Alter, unpublished observations). Another possible cause for the lack of vagally mediated bradycardia during occlusion is the selection of anesthetic. However, the present study utilized the same anesthetic (chloralose) as in cat studies. Therefore, at this time, we must conclude that in the rhesus monkey, coronary artery occlusion may lead to either a small cardiovascular mediated by the autonomic nervous system or a bradycardia due to pacemaker ischemia, the latter occurring when either the CIRC or its sinus node branch is occluded.

Brief occlusions of coronary arteries resulted in marked changes in myocardial blood flow and contractile force within the ischemic region. In contrast, nonischemic regions failed to demonstrate any significant changes in contractile force. These results differ from those reported by Pashkow who showed that nonischemic myocardium demonstrated an increased contractile force during brief occlusions of the LAD in anesthetized pigs. This may be related to a species and/or anesthetic difference in the two studies. In addition, increased myocardial blood flow in regions outside an ischemic region have been reported in anesthetized dogs, however, once again, coronary artery occlusions failed to elicit such changes in the anesthetized rhesus.

Removal of the occlusion clip resulted in a marked reactive hyperemia and postocclusion overshoot in contractile force (table 1) in the previously ischemic region whereas no changes were seen in these parameters in the nonischemic region. The only significant difference in response seen after coronary artery occlusion was a decreased overshoot in contractile force at the base of the left ventricle (25 ± 7%) after CIRC occlusion as opposed to that observed at the apex after LAD occlusion (55 ± 7%). Several possible causes for this decrease can be proposed. The decreased response may reflect a decreased magnitude of ischemia in the basal myocardium during CIRC occlusion when compared to that seen for LAD occlusion. This is not likely, however, because myocardial blood flow and contractile force decrease were comparable for both occlusion sites. An alternative explanation might be the lesser involvement of sympathetic inotropic reflexes after CIRC occlusions. This does not appear to be a realistic hypothesis because postocclusion overshoot in contractile force persisted after autonomic blockade as has been reported by Pagani et al.

Indeed, the overshoots in contractile force still demonstrated a greater magnitude after LAD occlusion. Another possible mechanism may lie in the decrease in total ischemic insult during CIRC occlusion. Due to the presence of a bradycardia, the total energy requirements during CIRC occlusion might be expected to be less than those experienced during LAD occlusion where heart rate was unchanged or slightly increased. If the magnitude of the overshoot in contractile force is somewhat dependent on this ischemic insult, then as a consequence of the bradycardia, it would be expected that the overshoot in contractile force would be less. Support for this last possibility awaits additional experiments.

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