Point of View

Myocardial Perfusion-Contraction Matching
Implications for Coronary Heart Disease and Hibernation*

John Ross Jr., MD

Laboratory and clinical investigations of reperfusion of ischemic myocardium have revealed several previously unrecognized phenomena concerning regional myocardial contractile function. Perhaps the most significant of these was the discovery in experimental and clinical studies that even after prolonged regional ischemia, recovery of contraction could occur in the involved zone. Two associated phenomena were also described, which have come to be known as myocardial “stunning”1 and myocardial “hibernation.”2,3 Stunning is a reversible form of contractile dysfunction that can occur after restoration of coronary blood flow following a relatively brief period of coronary occlusion, as originally described by Heyndrickx et al.,4 but can also be observed in a variety of other experimental and clinical settings ranging from postexercise to postthrombolytic conditions when an ischemic condition is followed by reperfusion. Whether its etiology is always the same in these various settings is unknown. Myocardial hibernation is a term first used by Rahimtoola2 for a postulated condition of chronic sustained abnormal contraction due to chronic underperfusion in patients with coronary heart disease in whom revascularization or an improved oxygen supply–demand relation could cause recovery of regional function. This postulated condition may bear some relation to the phenomenon of low-flow “perfusion-contraction matching” that we have described in several acute and sustained conditions of experimental ischemia in which there is some residual blood flow.5 Hibernation and stunning could occur separately or together during prolonged partial ischemia (either prolonged low flow, or periods of low flow alternating with reflow and stunning as the cause of sustained contractile dysfunction). However, it seems likely that whether perfusion and contraction are appropriately “matched” during the ischemic period will determine whether prolonged ischemic contractile dysfunction will be reversible.

In this brief discussion, I focus primarily on the role of perfusion-contraction matching in several acute and sustained ischemic states, its possible relation to hibernation (which has been variously defined), and its potential implications for clinical therapy. Emphasis will be placed on regional contractile function because regional rather than global ischemia usually occurs in the clinical setting and a number of features of contraction are unique to regional ischemia,6 although it is implicit that changes in regional contraction also usually affect global left ventricular function.

Acute Perfusion-Contraction Matching During Partial Coronary Stenosis

Flow–Function Relation Under Resting Conditions

The relation between regional transmural blood flow distribution (radiolabeled microspheres) and regional myocardial function assessed as systolic wall thickening (ultrasonic crystals) was examined in open-chest dogs during graded reductions in coronary flow, and changes in systolic wall thickening were shown to correlate closely with decreases in subendocardial blood flow but poorly with subepicardial blood flow.7 These studies demonstrated that the level of inner-wall perfusion during regional ischemia has a central role in determining transmural wall function. Studies by others8 showed function to correlate with inner-wall flow in different regions of the left ventricle at several time intervals after coronary occlusion in conscious dogs.

In resting conscious dogs trained to lie quietly, progressive steady-state reductions in total circumflex coronary artery inflow were produced by inflation of a hydraulic cuff, with return to control conditions between each flow change.9 A nearly linear relation was found between reductions in left regional ventricular subendocardial blood flow and regional systolic wall thickening in individual animals as well as in the grouped data. Again, there was a poor correlation between systolic wall thickening and outer-wall blood flow and a moderately good correlation with transmural blood flow.9 It was observed, for example, that when percent systolic wall thickening during

*All editorial decisions for this article, including selection of reviewers and the final decision, were made by a guest editor. This procedure applies to all manuscripts with authors from the University of California San Diego or UCSD Medical Center.
From the Division of Cardiology, Department of Medicine, University of California San Diego.
Supported in part by a Coronary Heart Disease SCOR grant HL-17682 from the National Heart, Lung, and Blood Institute and by an endowed chair from the American Heart Association, San Diego County Affiliate.
Address for correspondence: John Ross Jr., MD, Department of Medicine (M-013B), University of California, San Diego, School of Medicine, La Jolla, CA 92039.

Downloaded from http://circ.ahajournals.org/ by guest on April 23, 2017
ejection was reduced by 40%, subendocardial blood flow was reduced by approximately 50% while subepicardial flow remained normal, and severe contraction abnormalities developed only when epicardial blood flow began to diminish. A nonlinear relation between subendocardial flow and subendocardial segment function was described by Vatner in conscious dogs. In those experiments, grouped data showed a considerable decrease in regional flow before a change in segment function occurred, but it seems possible that some animals were nonbasal because the average resting flow was relatively high.

These studies on regional flow–function relations during ischemia at rest indicate that a close coupling exists between the supply of myocardial substrates, including O₂, of which the regional coronary blood flow provides a rough measure, and myocardial energy demand, as reflected in the steady-state level of regional contractile dysfunction. Thus, under these acute conditions, contraction decreased and remained at a reduced steady-state level commensurate with, or “matched to,” the available blood supply.

The reasons for the dominant role of inner-wall blood flow in determining regional wall contraction are not entirely clear but may relate to the fact that approximately two thirds of transmural wall thickening during ejection occurs in the inner one half of the left ventricular wall as well as to possible tethering effects of subendocardial dysfunction on outer-wall function.

Flow–Function Relation During Exercise

Graded levels of circumflex coronary artery stenosis were produced by means of a hydraulic cuff in conscious dogs exercising on a treadmill. Steady-state levels of reduced flow and contraction were produced for approximately 3 minutes during each exercise bout, with return to control conditions between runs, while regional systolic wall thickening and regional myocardial blood flow distribution were determined.

A curvilinear relation was found between subendocardial blood flow and regional wall thickening in the ischemic zone, the curvilinearity relating mainly to the relatively high resting flows in dogs standing on the treadmill without coronary stenosis. These data during exercise were then normalized by expressing wall thickening as a fractional value and subendocardial flow as a fraction of the resting value per beat to normalize for the large differences in heart rate between rest and exercise. These data were then plotted on the same graph as the resting flow–function data described above (similarly normalized), and the two relations were found to be nearly superimposable (Figure 1A).

This observation suggests that under these acute conditions of partial ischemia during exercise, perfusion-contraction matching also occurs. Thus, regional subendocardial blood flow per beat to the inner wall appears to determine the level of regional contraction not only at rest but also under conditions

**Figure 1.** Scatterplots of relations between regional transmural myocardial contraction and subendocardial blood flow. Panel A: Relations between regional subendocardial myocardial blood flow per beat and regional systolic wall thickening (%Wth) expressed as a decimal fraction of the resting value in conscious dogs. Δ, Data in a zone supplied by the circumflex coronary artery when the artery is subjected to progressive levels of coronary artery stenosis at rest. SD of normal resting flow is indicated; ○, data from other experiments in which exercise was carried out at graded levels of coronary artery stenosis. Modified and reproduced with permission of the authors and the American Heart Association. Panel B: Relations between regional systolic %Wth (expressed as a percent of the control value) in a region perfused by the anterior descending artery pump, which was perfused to allow changes in regional coronary flow over a wide range in swine. Effects of reduction of subendocardial blood flow per minute on regional function at a heart rate of 54 beats/min (●) are compared with data from a different group of swine in which heart rate averaged 120 beats/min (○). Panel C: Same data as shown in panel B plotted as subendocardial myocardial blood flow per beat. Reproduced with permission of the authors and the American Heart Association.
of exercise. Of course, the degree of contraction during ischemia will also be influenced to some degree by other factors, such as the loading conditions on the myocardium, but the finding of similar relations at rest and during exercise suggests a dominant influence of the absolute level of subendocardial blood flow per beat in determining contraction.

Flow–Function Relation and Changes in Heart Rate at Rest

In an open-chest porcine model, which allowed control of coronary blood flow to the anterior descending bed by means of a pump perfusion system, relations among regional myocardial blood flow distribution, regional function, and heart rate were further examined. Regional wall thickening was measured in the zone to be rendered ischemic; total coronary blood flow was measured by a flow meter in the pump circuit; and myocardial blood flow distribution was determined by regional injection of radio-labeled microspheres.

Coronary inflow was first reduced at a paced heart rate averaging 91 beats/min to diminish contractile function in the ischemic zone by approximately 70% (average percent systolic wall thickening, 6%; control value, 25%); regional blood flow to the subendocardium was reduced to 0.22 (ml/min)/g. After restoration of control conditions, the specific bradycardiac drug ULFB-49 was administered intravenously. This agent has been found to have no significant direct effect on myocardial contractility, although some negative inotropic response due to the force–frequency effect was observed at the slowed rate of 54 beats/min produced in these studies. Coronary inflow was then reduced at the slowed heart rate to exactly the same level as during control ischemia at a heart rate of 91 beats/min, and a marked improvement of systolic wall thickening was noted compared with the initial ischemic level (25% wall thickening, which is not significantly different from control). There was a small increase of subendocardial blood flow per minute compared with that at the higher heart rate, but the increase in subendocardial blood flow per beat was large.

The flow–function relation during ischemia at the slowed heart rate was then compared with the relation observed in another group of pigs studied over a range of reduced coronary inflows in the same manner but at a more rapid heart rate (average, 120 beats/min). During the slowed heart rate (54 beats/min), the entire flow–function relation was shifted upward (Figure 1B) so that at any level of subendocardial blood flow per minute there was increased regional function at 54 beats/min compared with that at 120 beats/min. However, when the percent wall thickening values at the two levels of heart rate were plotted against the corresponding levels of subendocardial blood flow per beat, the relations were superimposable (Figure 1C).

These observations support the concept that low-flow perfusion-contraction matching in the coronary circulation operates under a variety of conditions. In these acute studies, substantial slowing of the heart rate at the same level of reduced perfusion markedly improved regional contraction so that regional systolic contraction was again matched to the regional myocardial blood flow to the subendocardium. Although some redistribution of blood flow to the subendocardium occurred at the slowed heart rate, probably related to the increased diastolic perfusion time, this effect was not sufficient to explain the large improvement in contractile function because the entire curve was shifted upward (Figure 1C); however, there was a much larger increase in the subendocardial blood flow per beat at the same level of total coronary inflow. Therefore, under these conditions, the beneficial effect of slowed heart rate was likely due to both diminished O2 requirements per minute and increased O2 supply per beat.

Sustained Perfusion-Contraction Matching During Partial Coronary Stenosis

To study an experimental model that might resemble clinical settings in which there is prolonged ischemia with sustained low flow and regional contractile dysfunction, conscious sedated dogs were trained to lie quietly on a table while partial circumflex coronary stenosis was produced for a 5-hour period using an implanted hydraulic cuff. Regional myocardial wall thickening was assessed using implanted ultrasonic gauges, and regional myocardial blood flow was measured. Sufficient coronary stenosis was produced to reduce contraction by approximately 40% and was then continually adjusted to maintain the percent wall thickening relatively constant for the 5-hour period. Subendocardial coronary blood flow, measured near the end of the ischemic period, was reduced by approximately 50%. After reperfusion, delayed but complete recovery of function occurred during a 1-week period, and at postmortem examination no necrosis of the free wall was evident at the site where regional systolic wall thickening was measured, although some damage was noted in the posterior papillary muscle. The reversible nature of the dysfunction after reperfusion suggests that at some time during the ischemic period, conditions developed that were conducive to the occurrence of stunning upon reperfusion (see below).

These studies demonstrated that low-flow perfusion-contraction matching can occur over an intermediate term (hours). Whether an undefined metabolic adaptation occurred during this 5-hour period to help maintain cardiac muscle viability or whether reduced contraction per se at the lowered level of aerobic metabolism accompanied by increased anaerobic glycolysis was sufficient to protect the myocardium at this moderate level of ischemia will require further studies. Regardless, it appears that myocardial energy demands were diminished by reduction of contraction to a level appropriate to the
available substrate supply, allowing reversibility of the contractile dysfunction after reperfusion.

We have previously shown that reperfusion after 2 hours of complete coronary occlusion in the conscious dog could be followed by delayed partial recovery of regional function during 1–4 weeks. It seems likely that during such occlusions in the dog, a species in which epicardial collaterals exist, partial perfusion occurred in the outer wall during coronary occlusion and that the delayed recovery reflected the stunning phenomenon in that region; however, whether other mechanisms were involved as well remains uncertain.

It should be pointed out that reversible stunning has been observed not only after 15-minute periods of coronary occlusion but also after brief periods of exercise-induced partial ischemia. A number of mechanisms have been postulated to be involved in stunning, as recently reviewed by Bolli. Whatever mechanisms are responsible for postreperfusion stunning, they could become activated at some time during periods of ischemia or during reperfusion.

Myocardial Hibernation

There are differences in the definition of myocardial hibernation in the clinical and experimental literature. Rahimtoola first used the term “hibernating myocardium” in a discussion of the effects of coronary bypass surgery to differentiate between myocardium that is ischemic upon stress contrasted to that which is hibernating with persistently reduced contraction and decreased coronary flow at rest, terming it a “subacute or chronic stage of myocardial ischemia associated with decreased metabolism, which is reversible”; he also postulated that it may not represent ischemia “in the strict sense.” More recently, Rahimtoola emphasized that the occurrence of this phenomenon is often painless and that evidence of it should be sought in chronic stable angina without ischemia, in unstable angina pectoris, and after acute myocardial infarction because the associated regional dysfunction may be wholly or partially reversible by revascularization. Braunwald and Rutherford stated that “hibernating myocardium results from months or years of ischemia and ventricular dysfunction persists until blood flow is restored.”

Recent experimental studies have used the term hibernation broadly to encompass relatively brief periods of mildly reduced perfusion during which function is diminished but there is no metabolic evidence of ischemia, periods of severe global regional underperfusion for 2 hours during which the ischemic myocardium in which abnormalities of high-energy phosphate stores were initially present but resolved with continued underperfusion.

It seems possible that all of these definitions may be useful, although they appear to reflect the operation of different phenomena during perfusion-contraction matching, including a reduction in activator Ca²⁺ release, compensatory anaerobic metabolism, or recovery of aerobic metabolism by some mechanism. It is possible that the expression of these mechanisms depends on the severity and duration of the blood flow reduction. Likewise, in the clinical syndrome of hibernation, whether pain and other evidence of ischemia are present may depend in part on the degree and length of coronary hypoperfusion and whether some type of adaptation has ensued.

Based on these considerations, it is proposed that perfusion-contraction matching be conveniently considered in three categories: acute perfusion-contraction matching (not defined as hibernation); sustained perfusion contraction-matching, or “short-term hibernation”; and the hypothetical condition of chronic perfusion-contraction matching, or “chronic hibernation.” In all of these categories, the key features are reduced coronary blood flow, proportionately reduced regional contraction, and reversible contractile dysfunction.

Potential Clinical Implications

The findings in the above-cited laboratory research may mimic several acute and chronic clinical settings in which persistent regional hypoperfusion results in regional contractile dysfunction with low-flow perfusion-contraction matching.

Table 1. Acute Perfusion-Contraction Matching

<table>
<thead>
<tr>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low coronary blood flow lasting several minutes</td>
</tr>
<tr>
<td>associated with proportional reduction of contraction,</td>
</tr>
<tr>
<td>with steady-state matching of energy supply and demand;</td>
</tr>
<tr>
<td>rapidly reversible without tissue damage, although</td>
</tr>
<tr>
<td>brief stunning may occur</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Experimental models</td>
</tr>
<tr>
<td>Steady-state reductions in regional coronary blood</td>
</tr>
<tr>
<td>flow at rest</td>
</tr>
<tr>
<td>Exercise-induced regional ischemia</td>
</tr>
<tr>
<td>Effects of bradycardia on ischemia at rest</td>
</tr>
<tr>
<td>Effects of antianginal agents</td>
</tr>
<tr>
<td>Clinical examples</td>
</tr>
<tr>
<td>Coronary artery spasm</td>
</tr>
<tr>
<td>Exercise-induced regional ischemia</td>
</tr>
<tr>
<td>Effects of antianginal drugs</td>
</tr>
<tr>
<td>Significance</td>
</tr>
<tr>
<td>Rapidly reversible</td>
</tr>
</tbody>
</table>

Acute Perfusion-Contraction Matching

The features of acute perfusion-contraction matching and the experimental and clinical settings in which it can occur are summarized in Table 1. This phenomenon of transiently reduced flow and function, lasting minutes, can occur at rest in clinical conditions such as variant angina pectoris due to coronary artery spasm or during exercise-induced ischemia in the presence of a severe atherosclerotic coronary artery lesion. Perfusion-contraction matching occurs rapidly during the regional energy supply—
demand imbalance produced by exercise, and the degree of regional myocardial ischemia assessed by measuring regional or global contractile function by radionuclide ventriculography31 or by exercise echo-
cardiography32 is often used to detect ischemia and
for risk stratification in chronic coronary heart
disease. In the absence of myocardial infarction, the
degree of regional contractile dysfunction closely
reflects the degree of regional myocardial ischemia,
even when subcritical coronary stenosis is produced experimentally,33 which may be important in evaluating the functional effects of ischemia independent of the presence or absence of symptoms (silent ischemia). Furthermore, the level of the exercise
ejection fraction has been found to be an effective
predictor of prognosis in patients with chronic coro-
nary heart disease.34

In experimental models of critical coronary steno-
sis, subendocardial blood flow during exercise
decreases to below the resting value, and subepicardial
flow may increase somewhat without a change in mean transmural flow.35 As shown in experimental
animals with chronic coronary stenosis produced by
an ameroid constrictor, regional myocardial wall
function during such exercise decreases in proportion
to the level of subendocardial perfusion.5 Furthermore,
antianginal drugs that mainly decrease myocardial O2 demands, such as β-adrenergic blocking
agents,36 drugs that increase oxygen supply such as
calcium channel–blocking drugs,37 or their combina-
tion38 affect the matching of subendocardial flow and
function in a favorable and additive manner, leading
to improvements in regional contractile function
during exercise that are in proportion to the in-
creases in subendocardial blood flow (Figure 2). This
phenomenon may be reflected, for example, in the
improvement or normalization of the exercise eje-
c tion fraction in patients with coronary heart disease
who are treated with calcium channel blockers or
with β-adrenergic blockade.39

Sustained Low-Flow Perfusion-Contraction Matching
or Short-term Hibernation

The features of sustained perfusion-contraction
matching, which may be called “short-term hiberna-
tion,” and some experimental and clinical settings in
which it can occur are shown in Table 2. This
phenomenon (lasting 1 or more hours) undoubtedly
occurs in clinical settings such as unstable angina
pectoris and acute myocardial infarction in which
there is some residual myocardial blood flow. The
experimental observations described earlier with 5
hours of partial ischemia39 indicate that prolonged
partial ischemia can be accompanied by prolonged
regional dysfunction that is reversible. Both acute
and prolonged perfusion-contraction matching are
probably associated with reduced oxidative metabo-
lism and lactate production.28 The findings in the
5-hour ischemia model suggest that in patients with
unstable angina or acute myocardial infarction with
nontransmural ischemia, in whom there is sufficient
residual blood flow via coronary collateral vessels (or
a partially patent artery) to allow perfusion-contrac-
tion matching to occur, even delayed reperfusion may
have beneficial effects on contractile function. Al-
though the lower limit of such matching remains to
be defined, contraction will be absent and necrosis
obviously will occur if little or no residual blood flow

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Plot of relations between subendocardial regional myocardial blood flow (RMBF) per minute expressed as a decimal fraction of the control resting value flow plotted against regional systolic wall thickening (%WT), which is expressed as a percentage of the resting values. Data at rest and during exercise in three different groups of dogs with chronic coronary artery stenosis are shown. Effects of control exercise in all three experiments without antianginal drug are comparable (control running). Effects during exercise before and after administration of the β-adrenergic–blocking drug atenolol (○), the calcium channel–blocking drug diltiazem (●), and combined treatment with these two agents (△) are shown. Reproduced by permission of the authors and the American Heart Association.38

**Table 2.** Sustained Perfusion-Contraction Matching or Short-term Hibernation

<table>
<thead>
<tr>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low coronary blood flow lasting from 1 to several hours and associated with sustained reduction of contraction; perfusion-contraction matching occurs, provided there is sufficient residual coronary blood flow</td>
</tr>
<tr>
<td>Experimental models</td>
</tr>
<tr>
<td>5 hours of regional hypoperfusion at rest</td>
</tr>
<tr>
<td>Reperfusion after prolonged coronary occlusion in animal species with collaterals</td>
</tr>
<tr>
<td>Clinical examples</td>
</tr>
<tr>
<td>Unstable angina pectoris</td>
</tr>
<tr>
<td>Acute coronary occlusion accompanied by some residual coronary perfusion</td>
</tr>
<tr>
<td>Significance</td>
</tr>
<tr>
<td>Reversible by reperfusion without tissue damage, although prolonged stunning can ensue; may occur in outer wall, and transmural dysfunction may be partially reversible even if there is inner-wall necrosis</td>
</tr>
</tbody>
</table>
is available, as evidenced by the occurrence of nearly complete infarction within 1 hour after coronary occlusion in animal species without a collateral blood supply, such as the pig.49

In patients with unstable angina pectoris, several studies have shown reversal of wall motion abnormalities after revascularization by percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft surgery (CABG).41–43 In one of these reports, persistent negative T waves and regional dysfunction in patients with unstable angina due to left anterior descending coronary artery stenosis were shown to be reversible in studies carried out an average of 6 months after PTCA.43 Such observations could be related to reversal of “short-term hibernation” or to reversal of stunning related to repeated transient episodes of reduced coronary blood flow.

In acute myocardial infarction, the level of residual myocardial blood flow after coronary occlusion has been shown to be of importance for the success of reperfusion in restoring regional function in patients given streptokinase relatively late after the onset of chest pain (up to 7 hours) who were studied by left ventriculography early and again approximately 2 weeks later.44 Thus, in a group of patients without residual coronary blood flow before treatment with streptokinase, there was no improvement in regional myocardial function in the infarct zone at the late study, whereas in patients having collateral flow or a partially patent coronary artery at the time of the initial coronary angiogram, significant recovery of the regional ejection fraction occurred in the zone perfused by the infarct-related artery.44

In a number of other studies, improved regional and global functions have also been reported in patients with acute myocardial infarction treated by thrombolysis, provided treatment was initiated within 3–4 hours after the onset of acute infarction.45–47

Chronic Perfusion-Contraction Matching or Chronic Hibernation

Although suggestive evidence exists, such a phenomenon (which might last for days or months) has not been clearly documented either experimentally or in clinical coronary heart disease. Its potential characteristics and clinical expression are shown in Table 3. If such a clinical syndrome exists, it would result from prolonged and persistent reduction of regional coronary flow associated with decreased contraction. However, many chronic coronary artery stenoses are not associated with reduced coronary blood flow at rest, and the syndrome might be mimicked by intermittent episodes of low flow with a persistent stunning effect. The potential clinical significance of such long-term perfusion-contraction matching would appear to lie primarily in the setting of chronic coronary heart disease, when clinical evidence of ongoing ischemia is not present at the time of study but regional dysfunction is present and can be improved by a revascularization procedure. If one or more such regions of dysfunction can be successfully revascularized, an improvement in global left ventricular function could be anticipated. Documentation of such a syndrome, either experimentally or clinically, would require repeated measurements of both reduced regional blood flow and function over a prolonged period before revascularization. The term “chronic hibernation” might best fit such a condition.

As mentioned earlier, in proposing the term hibernation Rahimtoola2 suggested that it might not represent a true ischemic state. If hibernation is considered to represent in part an adaptive response due to prolonged underperfusion rather than a response to relatively short periods of hypoperfusion during which clear-cut ischemia is associated with perfusion-contraction matching, it is possible that delayed subcellular adaptive responses could occur. The concept of perfusion-contraction matching with reduced energy expenditure and contraction would explain the early phase of such an adaptation, which might later involve an adaptation via new enzyme synthesis or induction of fetal-type proteins to provide a beneficial adaptation. For example, we have found that messenger RNAs coding for heat shock protein appear in myocardial samples within 3 hours after production of ischemia in the dog;48 this class of proteins may have a protective role during ischemia.49

An example of reversal of regional wall motion abnormalities at rest of the chronic type is the improvement of regional wall motion that has been described in some patients with chronic stable coronary heart disease after coronary bypass surgery. Several reports have described such recovery relatively early (within 2 weeks) and later (at several months) after bypass surgery.41,50–53 As recently reviewed in detail by Rahimtoola,26 Recently, such reversibility has also been reported several days after PTCA in patients with chronic stable coronary heart disease.42

Improved understanding of the basis for these responses has been provided by studies using positron emission tomography (PET).54 Regions

<table>
<thead>
<tr>
<th>Table 3. Chronic Perfusion Contraction Matching or Chronic Hibernation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>A hypothetical condition of chronically reduced coronary</td>
</tr>
<tr>
<td>blood flow lasting days to weeks associated with reduction of</td>
</tr>
<tr>
<td>contraction</td>
</tr>
<tr>
<td>Experimental models</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Clinical example</td>
</tr>
<tr>
<td>Impaired regional perfusion with preserved indexes of viability</td>
</tr>
<tr>
<td>(metabolism) often in the absence of manifestations of acute</td>
</tr>
<tr>
<td>ischemia, with reversal of regional dysfunction after coronary</td>
</tr>
<tr>
<td>artery bypass graft surgery (CABG) or percutaneous transluminal</td>
</tr>
<tr>
<td>coronary angioplasty (PTCA)</td>
</tr>
<tr>
<td>Significance</td>
</tr>
<tr>
<td>Wholly or partly reversible regional dysfunction after</td>
</tr>
<tr>
<td>revascularization by CABG or PTCA</td>
</tr>
</tbody>
</table>
showing regional contraction abnormalities by radio-
uclide angiography preoperatively that were sub-
sequently shown to be reversible after CABG fre-
quently showed metabolic activity (fluorine-18 
deoxylucose [18F]FDG) uptake sometimes associ-
ated with reduced regional perfusion (nitrogen-13 
ammonia [13NH3]) at the preoperative PET study.54
Among the 17 patients studied, 11 were referred 
for CABG because of two- or three-vessel disease 
and a left ventricular ejection fraction of less than 40%, 
five had ischemia after myocardial infarction, and 
one had medically refractory angina pectoris; 16 of 
the patients had a history of prior infarction. 
Among 73 abnormally contracting regions preoper-
atively, 24 of 26 regions in which both 18F]FDG and 
13NH3 were depressed failed to show recovery of 
function. Among 41 abnormally contracting regions 
that were adequately revascularized by CABB, 25 
(60%) had normal or increased 18F]FDG uptake and 
normal 13NH3 uptake preoperatively; of these, 22 
(88%) showed improved wall motion 12–18 weeks 
postoperatively. Among the remaining 16 regions, 
18F]FDG uptake was normal or increased but 13NH3 
was decreased, and 13 (81%) showed improved wall 
motion at postoperative study.54
It is in the latter group, in whom there was reduced 
perfusion with evidence of persistent metabolism 
(with abnormally increased glucose uptake in some), 
that chronic or prolonged perfusion-contraction 
matching, or chronic hibernation, may be postulated 
to have existed. However, serial studies in such 
patients are needed to document the persistence of 
the perfusion abnormality. In the remaining patients 
with reversible contraction abnormalities who had 
normal or increased glucose uptake and normal 
perfusion preoperatively, the occurrence of persis-
tent stunning after prior episodes of regional blood 
flow reduction seems likely. Thus, clear-cut evidence 
for chronic hibernation remains elusive.

Summary
Experimental studies demonstrate that short-term 
regional perfusion-contraction matching, in which the 
energy demands of regional myocardial contract-
on are reduced to match the diminished myocardial 
substrate supply, occurs during states of low coronary 
flow blood flow under resting conditions and during 
exercise-induced ischemia. This phenomenon is rapidly 
reversible and appears to occur in several clinical 
settings. Sustained perfusion-contraction matching is 
observed in states of partial experimental ischemia 
of intermediate duration lasting several hours. This 
condition might be called short-term hibernation and 
resembles clinical conditions such as unstable angina 
pectoris or myocardial infarction with some residual 
perfusion in which the contractile defect can be 
improved by reperfusion provided the ischemia is not 
severe enough to cause transmural necrosis. Such 
experimental and clinical observations may or may 
not relate to the setting of regional dysfunction at 
rest in patients with chronic coronary heart disease,
in whom manifestations of acute ischemia may be 
absent but improvement of wall motion abnormal-
ties occurs after CABG or balloon angioplasty. This 
condition may constitute the hypothetical state of 
chronic myocardial hibernation, for which tentative 
evidence exists from metabolic and perfusion studies 
using PET. Whether such a condition of prolonged 
perfusion-contraction matching might be associated 
with adaptive processes that could allow its persis-
tence for long periods without manifest ischemia 
remains to be investigated.

References
1. Braunwald E, Klomer RA: The stunned myocardium: Pro-
longed, postischemic ventricular dysfunction. Circulation 
1982;66:1146–1149
2. Rahimtoola SH: A perspective on the three large multicenter 
randomized clinical trials of coronary bypass surgery for chronic 
stable angina. Circulation 1985;72(suppl V);V-123–V-135
3. Braunwald E, Rutherford JD: Reversible ischemic left ven-
tricular dysfunction: Evidence for the “hibernating myocar-
dium.” J Am Coll Cardiol 1986;8:1467–1470
MC, Vattner SF: Depression of regional blood flow and wall 
thickening after brief coronary occlusions. Am J Physiol 1978;234: 
H653–H659
5. Ross J Jr: Mechanisms of regional ischemia and antiangiual 
drug action during exercise. Prog Cardiace Dis 1989;31:455–466
6. Ross J Jr: Perspective: Assessment of ischemic regional myocar-
dial dysfunction and its reversibility. Circulation 1986;74: 
1186–1190
7. Gallagher KP, Kumada T, Koziol JA, McKown MD, Kemper 
WS, Ross J Jr: Significance of regional wall thickening abnor-
malities relative to transmural myocardial perfusion in anes-
characterization of left ventricular segmental responses during 
the initial 24 hours and one week after experimental myocar-
Jr: Regional myocardial perfusion and wall thickening during 
10. Vattner SF: Correlation between acute reductions in myocar-
dial blood flow and function in conscious dogs. Circ Res 
1980;47:201–207
WS, Ross J Jr: Nonuniformity of inner and outer systolic wall 
12. Weintraub WS, Hattori S, Agarwal J, Bodenheimer MM, 
Banka VS, Helfant RS: Relationship between myocardial 
bleed flow and contraction by myocardial layer in the canine 
Ross J Jr: Subepicardial segmental function during coronary 
stenosis and the role of myocardial fiber orientation. Circ Res 
1982;50:352–359
Jr: Effect of exercise on the relationship between myocardial 
bleed flow and systolic wall thickening in dogs with acute 
End-systolic dimension–wall thickness relations during myocar-
dial ischemia in conscious dogs: A new approach for 
defining regional function. Am J Cardiol 1983;51:1750–1758
Jr: Mechanisms of improved ischemic regional dysfunction by 
80:983–993
17. Guth BD, Heusch G, Ross J Jr: Elimination of exercise-
induced regional myocardial dysfunction by a bradycardic
agent in dogs with chronic coronary stenosis. *Circulation* 1987;75:661–667

**Key Words**: regional myocardial contraction • myocardial flow • ischemia • exercise • hibernation • stunning • regional function • coronary heart disease
Myocardial perfusion-contraction matching. Implications for coronary heart disease and hibernation.
J Ross, Jr

Circulation. 1991;83:1076-1083
doi: 10.1161/01.CIR.83.3.1076

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/83/3/1076

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/