Myocardial Carbohydrate Metabolism in Normal Dogs, with Effects of Hyperglycemia and Starvation

By Walter T. Goodale, M.D. and Donald B. Hackel, M.D.

Myocardial metabolism of Nembutalized normal intact dogs was studied with the aid of the coronary sinus catheterization technic. Oxygen, glucose, lactate and pyruvate were extracted by the heart in direct relation to the arterial level of each substance, independently of the others. Pyruvate and lactate showed a high myocardial extraction coefficient, but the normal low arterial levels at rest prevented them from together accounting for more than 50 per cent of the total myocardial energy requirements. Glucose was not utilized below a mean threshold of 54 mg. per cent, but with normal arterial levels of 70 to 120 mg. per cent, glucose extraction was sufficient to provide the major potential source of fuel for myocardial oxidative energy. During starvation, the heart probably derived its energy from fat, as indicated by a myocardial respiratory quotient near 0.70, and a low myocardial carbohydrate extraction.

The quantitative contribution of various metabolites to the energy production of the heart has not been specifically determined. Studies to date, well reviewed by Lovatt Evans,1 Visscher2 and Wollenburger,3 have dealt chiefly with myocardial carbohydrate metabolism either in vitro preparations, or after varying degrees of operative trauma, or after isolation of the heart from neurohormonal influences, and circulating substrate concentrations have often been unphysiologically high. Under these conditions, there is general agreement that circulating lactate and pyruvate can be extracted by heart muscle in sufficient quantity to provide a major source of fuel for oxidation. However, it was rarely demonstrated that lactate and pyruvate alone could fulfill the total substrate requirements for the simultaneously observed oxygen consumption. The amounts of circulating glucose, fatty acids, ketone bodies, amino acids and other substrates spontaneously extracted are uncertain.

An opportunity to study myocardial metabolism under normal physiologic conditions has become available with the recent development of a technic for catheterizing the coronary sinus in intact dogs and man.4,5 Initial results from this laboratory4 confirmed the relative importance and consistency of lactate and pyruvate extraction, as well as the less consistent, but often greater, extraction of glucose.

The present report is an analysis of pyruvate, lactate and glucose extraction by heart muscle in intact, lightly Nembutalized dogs, studied 12 to 24 hours postprandially, during induced hyperglycemia, and during starvation.

Methods and Definitions

Normal dogs were studied under the same conditions of light Nembutal anesthesia as described in the preceding paper.5 Similar technics were used for intubating the coronary sinus, pulmonary artery, and a peripheral artery and for measuring coronary blood flow, myocardial oxygen consumption, cardiac output, left ventricular work, and left ventricular efficiency. In addition, blood was drawn simultaneously from an artery and the coronary sinus in duplicate or triplicate syringes, and each sample was analyzed in duplicate for lactate,6 pyruvate7 and true glucose.8 The coefficient of variation between duplicates for all of these colorimetric procedures...
proved to be approximately ±2 per cent. Following the completion of these determinations six dogs were given approximately 2 Gm. per kilogram of 50 per cent glucose intravenously, and coronary arterial and venous levels of glucose, lactate and pyruvate were determined at varying intervals during the next two hours.

Four dogs were starved by decreasing their diet gradually for a two-week period, and then they were given no food for 18 additional days. During this period they were given water ad libitum, 200 mg. of ascorbic acid orally every 14 days, plus the following vitamins given orally three times a week: 10 mg. thiamin, 3 mg. riboflavin, 60 mg. niacin, 6 mg. pyridoxine, 15 mg. pantothenic acid, 300 mg. choline, 9 mg. inositol, and 9 mg. paraminobenzoic acid. In addition, 200 mg. of crystalline thiamin hydrochloride were given subcutaneously three times a week.

Definitions. Myocardial extraction coefficient equals the coronary A-V difference × 100, divided by the arterial level of the same metabolite. Myocardial utilization of a metabolite equals the product of coronary A-V difference and coronary blood flow (expressed as cubic centimeters or milligrams per 100 Gm. of myocardium per minute), for it is assumed that any metabolite removed from the coronary circulation must be utilized in one way or another by the myocardium. The data for myocardial utilization were obtained only from experiments in which analyses for lactate, pyruvate, glucose, and oxygen were carried out on blood samples drawn simultaneously with a coronary blood flow determination.

Myocardial respiratory quotient equals the myocardial carbon dioxide production divided by the myocardial oxygen consumption. Since the same coronary blood flow figure is used to calculate production and consumption in numerator and denominator by the Fick principle, flow cancels out. Myocardial respiratory quotient may thus be calculated by dividing the coronary V-A carbon dioxide difference by the A-V oxygen difference, without the necessity of measuring coronary blood flow flow. There are many objections to judgments of total body respiratory quotient from V-A CO2/A-V O2 differences. The myocardial respiratory quotient is affected little by respiratory variations. Also, changes in arterial carbon dioxide content are rapidly reflected in coronary venous blood because of the high vascularity and speed of diffusion in the myocardium. The relatively large coronary V-A carbon dioxide and A-V oxygen difference make the analytic procedures more reliable. The small oxidation of protein by the myocardium minimizes the need for correcting the myocardial respiratory quotient for nitrogen balance.

The per cent of the myocardial oxygen requirement available from carbohydrate extraction was calculated in the following manner: A-V differences of the metabolites were converted to their oxygen equivalents by multiplying the A-V differences of glucose and lactate by the factor 0.75 and those of pyruvate by the factor 0.67. These factors indicate cubic centimeters of oxygen required to oxidize completely 1 mg. of each metabolite. The oxygen equivalent thus obtained was divided by the simultaneously obtained value for the coronary A-V oxygen difference. The coronary blood flow could also be omitted from this calculation since it was common to both numerator and denominator.

Results

Table 1 presents the mean coronary A-V differences of pyruvate, lactate, glucose and oxygen at the mean arterial levels found in 36 normal dogs. In figures 1 to 3, the coronary A-V differences are plotted against the simultaneous arterial level for each observation. It is apparent that the A-V difference of any metabolite was almost entirely a direct function of the arterial level of that metabolite. Neither coronary blood flow nor left ventricular work correlated significantly with any of these coronary A-V differences. In every case the probability was less than one chance in 20 that it was significant (p < .05).

Since coronary A-V lactate difference was negligible at arterial levels of 2.56 ± 0.9 mg. per cent or below, 2.56 mg. per cent represented the lactate utilization threshold. Statistically this threshold varied from 0.8 to 4.4 mg. per cent (2.56 ± 2σm). The A-V lactate difference rose linearly from this point to a mean value of approximately 10 mg. per cent at an arterial lactate level of 21 mg. per cent with a high correlation coefficient (r, A/A-V) of 0.88. The mean lactate A-V difference was 5.8 ± 0.4 mg. per cent at a mean arterial lactate level of 13.3 ± 0.6 mg. per cent. The lactate coefficient of extraction (A/V/A) was 41.1 ± 1.7 per cent. The total utilization of lactate in milligrams per 100 Gm. of left ventricular myocardium per minute was 7.8 ± 1.3 mg. per cent.*

* This value does not correspond exactly to the product of the mean coronary blood flow (147.1 ± 11.3 cc./100 Gm./min.) and the mean lactate arteriovenous difference (5.8 ± 0.4 mg.%), since, as already pointed out, the value for total utilization was taken from a more limited group in which the coronary blood flow measurements were made simul-
TABLE 1.—Myocardial Extraction Values, Normal and during Starvation

<table>
<thead>
<tr>
<th></th>
<th>Lactate</th>
<th>Pyruvate</th>
<th>Glucose</th>
<th>Oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Art.</td>
<td>13.3 ± 0.6</td>
<td>1.91 ± 0.08</td>
<td>75.8 ± 1.8</td>
<td>17.4 ± 0.4</td>
</tr>
<tr>
<td>A-V</td>
<td>5.8 ± 0.4</td>
<td>0.88 ± 0.06</td>
<td>4.6 ± 0.7</td>
<td>12.9 ± 0.4</td>
</tr>
<tr>
<td>C. Ext.</td>
<td>41.1 ± 1.7</td>
<td>43.0 ± 2.0</td>
<td>5.7 ± 0.9</td>
<td>74.1 ± 1.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Inanition (Mean ± σm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Art.</td>
<td>15.5 ± 1.4</td>
</tr>
<tr>
<td>A-V</td>
<td>1.8 ± 0.5</td>
</tr>
<tr>
<td>C. Ext.</td>
<td>13.6 ± 2.9</td>
</tr>
</tbody>
</table>

**Abbreviations:** Art. = arterial level (mg. or vol.%). A-V = coronary arteriovenous difference (mg. or cc./100 gm. of left ventricle/minute). C. Ext. = Coefficient of extraction (%). N = number of observations. σm = standard error of the mean.

The coronary A-V pyruvate difference became statistically significant when the arterial level exceeded 0.61 ± 0.15 mg. per cent, and it rose linearly with rising arterial levels to a mean A-V difference of 1.62 mg. per cent at the upper normal arterial pyruvate level of 3 mg. per cent. The threshold of utilization varied from 0.31 to 0.91 mg. per cent (0.61 ± 2σm) and, considering the analytic errors, it is barely significantly greater than zero. The coefficient of correlation between the arterial level and A-V difference of pyruvate was high (0.86). The mean pyruvate A-V difference was 0.88 ± 0.06 mg. per cent at a mean arterial level of 1.91 ± 0.08 mg. per cent. The pyruvate extraction coefficient was 43.0 ± 2.0 per cent. The mean total utilization of pyruvate in milligrams per 100 Gm. of left ventricular myocardium per minute was 1.13 ± 0.18 mg. per cent.

Myocardial glucose extraction differed markedly from that of lactate and pyruvate; a much higher arterial glucose level was necessary before any extraction occurred consistently. No significant mean coronary A-V glucose difference was observed up to the glucose utilization threshold of 54.2 ± 14.3 mg. per cent. As the arterial level rose above this point, the glucose A-V difference became significant and increased in direct relation to

![Figure 1: Relation of lactate extraction to arterial lactate level.](http://circres.ahajournals.org/doi/abs/10.1161/01.CIR.51.2.511)
the arterial level, reaching a mean value of 10 mg. per cent at an arterial level of 100 mg. per cent and 14 mg. per cent at an arterial level of 120 mg. per cent. Taking all values in the normal series in which the arterial levels ranged from 47 to 121 mg. per cent, the slope of glucose utilization above the threshold of utilization was 0.21. The over-all coefficient of correlation between the normal arterial level and normal A-V difference of glucose was 0.56. The lower limit of the coefficient of correlation (p = 0.05) was 0.37, while the required coefficient of correlation for a significant correlation coefficient for the entire group was increased to the highly significant value of 0.79. The mean myocardial extraction coefficient similarly increased from 0 at fasting levels of 54.2 ± 14.3 mg. per cent to 13.7 per cent at 184.3 ± 12.8 mg. per cent.

A tendency of the coronary A-V glucose difference to level off at higher arterial glucose levels is apparent both on inspection and by statistical analysis. Assuming the relationship of arterial level and A-V difference to be exponential, the following formula was found to

\[
\text{Glucose Extraction} = \frac{\text{Arterial Glucose Level} - \text{Coronary A-V Difference}}{\text{Normal A-V Difference}}
\]

Fig. 3. Relation of glucose extraction to arterial glucose level. The values to the right of the broken vertical line were obtained in the fasting or postabsorptive state. The values to the right, above an arterial level of 120 mg. per cent, were observed after glucose infusion. The solid linear regression line represents the best linear correlation of both fasting and postabsorptive groups together. The broken line represents the best fit of an exponential curve taking all values as one series and illustrates the tendency for the curve to level off and the coronary glucose A-A difference to approach a limit of approximately 30 ± 10 mg. per cent at arterial glucose levels above 250 mg. per cent.

Hyperglycemia. The infusion of 50 per cent glucose led to a rise in lactate and pyruvate arterial levels in each experiment with a corresponding increase in coronary A-V differences. Figures 1 and 2 show that lactate and pyruvate extractions during hyperglycemia were not significantly different from extraction at the same arterial level when the glucose
provide the best fit for all observations as plotted, and the resultant curve is indicated by the broken line in figure 3:

\[ A-V = (45.51 \pm 2.35) - (67.03 \pm 4.07) e^{-0.064 A} \]

The mean arterial concentration of oxygen in the normal dogs was 17.4 ± 0.5 volumes per cent with a mean A-V difference of 12.9 ± 0.4 volumes per cent. The mean extraction coefficient was therefore 74 per cent. The total oxygen utilization in cubic centimeters per 100 Gm. of left ventricular myocardium per minute was 19.5 ± 1.5. This is not significantly different from the previously reported value of 19.1 ± 2.1 volumes per cent, which was based on a smaller series of observations.5

**TABLE 2.—Per Cent of Myocardial Oxygen Consumption Accounted for by Extraction of Different Metabolites.**

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Mean A-V</th>
<th>O₂ Equiv.*</th>
<th>O₂ A-V</th>
<th>2-3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate</td>
<td>5.83</td>
<td>4.38</td>
<td></td>
<td>34.0</td>
</tr>
<tr>
<td>Pyruvate</td>
<td>0.88</td>
<td>0.50</td>
<td>12.9</td>
<td>4.6</td>
</tr>
<tr>
<td>Glucose</td>
<td>4.6</td>
<td>3.5</td>
<td></td>
<td>27.1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td>65.7</td>
</tr>
</tbody>
</table>

**Abbreviations:** Same as table 1.

* Refers to number of cubic centimeters of oxygen required to burn the given amount of metabolite represented by its A-V difference.

Approximately two-thirds of the mean myocardial oxygen extraction was potentially accounted for by the mean values for lactate, pyruvate, and glucose extraction, assuming complete substrate oxidation (table 2). However, the utilization of each individual substrate was directly related primarily to its own arterial level (figs. 1 to 3), and arterial substrate level was not related to myocardial oxygen extraction. It follows that, as the arterial level of the metabolite increased, it accounted for a higher per cent of the myocardial oxygen consumption. In fact, at the higher arterial levels of lactate or glucose, their collective oxygen equivalents exceeded 100 per cent of the simultaneous oxygen extraction. From this it might be inferred that, at the higher arterial levels, metabolites were stored, while at lower arterial levels some of this endogenous source of energy could be utilized.

The mean value for 14 observations of the normal coronary arteriovenous (or myocardial) respiratory quotient (R.Q.) was 0.91 ± 0.03. A very high correlation (r = 0.90) was found between the myocardial respiratory quotient and the percentage of total oxygen extraction accountable to carbohydrate substrate extraction. At a respiratory quotient of 0.70 an average of only 12 per cent of the oxygen re-

**Fig. 4. Relation of myocardial respiratory quotient to percentage of myocardial energy requirements available from carbohydrate extraction in 17 dogs. Correlation coefficient, r_{A-V} = 0.90. Dots = postabsorptive or postprandial state; crosses = during starvation.**

It should be noted that approximately two-thirds of the oxygen requirement of the left ventricle could be accounted for by the utilization of lactate, pyruvate, and glucose whereas, at a respiratory quotient of 1.0, the amount of these carbohydrates utilized accounted for an average of 95 per cent of the myocardial oxygen requirement (fig. 4). The respiratory quotient during starvation varied between 0.66 and 0.70, while the oxygen consumption accounted for by carbohydrate extraction was only 2 to 32 per cent.

**Starvation.** There was an average weight loss of 27 per cent in the starved dogs. The main differences in the hemodynamic changes from previously reported normals4 were the
somewhat lower mean arterial blood pressure (120 mm. Hg), higher cardiac index (6.1 liters per square meter per minute) and lower peripheral arteriolar resistance (1.15) in the starved group. The coronary blood flow (142 cc. per 100 Gm. per minute), arterial oxygen content (19.8 volumes per cent), left ventricular oxygen consumption (20.9 cc. per 100 Gm. per minute) and coronary vascular resistance (55.4) were not significantly different from the normal group. Striking differences did occur in the metabolic findings (table 1). The arterial pyruvate levels were significantly elevated above normal (p < .02). The arterial lactate, and glucose levels were not significantly different from the normal series. However, for all three carbohydrate substrates, the A-V differences were significantly and markedly reduced (p < .01). Since the starvation arterial levels of glucose were somewhat lower than the normal, 37 observations were selected in which a mean arterial level of 66 mg. per cent glucose existed. The mean A-V difference for this special group was 2.3 ± 0.8, which is still significantly greater than the starvation A-V of -1.0 ± 0.5 mg. per cent. Table 3 emphasizes the abnormalities during inanition compared with values in the same animal during a normal control period.

**DISCUSSION**

The present in vivo experiments confirm the earlier work performed with heart-lung, or open chest preparations, and that of Olson and associates with surviving myocardial slices. We found several important differences, however, which probably reflect the more normal state of our preparation.

The most important observation in the present experiments was the close correlation between the arterial level and the coronary A-V difference of each metabolite, independent of coronary blood flow. Extraction of any one metabolite took place independently of arterial level or A-V difference of any other metabolite, even in hyperglycemia, in contrast with the results of Evans. Within normal ranges in vivo, the arterial level of each metabolite, per se, appeared to determine its myocardial extraction coefficient, independent of coronary blood flow or total left ventricular work. This independent correlation was much closer than has been previously observed in in vitro studies, or in experiments involving significant operative stress. It is still possible that at circulating substrate levels above normal in vivo ranges, a reciprocal relationship may exist between lactate, pyruvate and glucose extraction as suggested by Evans, and as demonstrated by Brin and Olson in surviving tissue slices.

In normal intact dogs glucose, lactate and pyruvate levels were normal, not elevated as in most previous studies. Yet there was a high myocardial extraction coefficient for all three substances.

The total amount of carbohydrate extracted, if fully oxidized to carbon dioxide and water,
could account for an average of 65.7 per cent of the simultaneous myocardial oxygen consumption. This figure corresponded well to the mean myocardial respiratory quotient of 0.91 which indicated that the heart was probably obtaining about two-thirds of its fuel for oxidation from carbohydrate and one-third from fat. The close correlation between myocardial respiratory quotient and the theoretic oxidation value of the extracted substrates suggested that the extracted carbohydrate was actually being oxidized, with production of carbon dioxide and water, rather than being used for nonoxidative or intermediary reactions. In an earlier work in which animals were either under severe operative stress, or a short-lived preparation was used, the extraction coefficients tended to be lower with higher circulating substrate levels. We have found a similar situation in intact dogs under severe stress and during anoxia.

The current confusion regarding the substrate which serves as the principal fuel for myocardial oxidation has arisen through failure to emphasize the primary importance of arterial substrate level. In many early experiments, the practice of exsanguinating the dog to obtain blood for perfusion, plus the varying degrees of lactate production from artificially ventilated lungs, led to high circulating lactate and low glucose levels. Under these conditions, lactate should and did appear to constitute the major substrate. In intact dogs and man, however, the normally low concentrations of lactate and pyruvate do not allow them to constitute the major source of fuel, even with high extraction ratios by the myocardium. It has been shown that ketone bodies can be burned by the myocardium, but with only 0.5 to 1.5 mg. per cent of total ketone bodies normally present in arterial blood, no more than 5 per cent of the total energy requirements could be derived from this source. In the presence of excessive levels of circulating ketones, as in diabetic acidosis, myocardial ketone utilization could be significant. The high threshold for glucose utilization is in sharp contrast to the negligible threshold for pyruvate, lactate, and oxygen. It is probable that oxygen and 3-carbon molecules can pass readily across the myocellular membrane and be metabolized directly. According to experiments by Park, however, the transfer of glucose across the cell membrane is under the endocrine control of insulin, and may be independent of phosphorylation and intracellular utilization. In diabetes this threshold for glucose is elevated.

Considerable support for the validity of myocardial respiratory quotients, in normal dogs in a steady state, has been gained from the independent simultaneous determinations of myocardial carbohydrate extraction:

1. In starvation, when myocardial carbohydrate extraction was very low, the myocardial respiratory quotient was consistently near 0.70.
2. There was a close linear correlation between respiratory quotient and the percentage of energy requirements available from carbohydrate extraction, with 95 per cent availability at a respiratory quotient of 1.0 (fig. 4).
3. Only in those cases with carbohydrate extractions in excess of 100 per cent of the simultaneous oxidative energy requirements have the respiratory quotients been greater than 1.0. At these higher arterial glucose levels, such as occur normally postprandially or after glucose infusions, some of this extracted glucose may be synthesized to fat, for the respiratory quotient for this anabolic reaction is near 1.2.

The variability of the hemodynamic status between dogs was discussed in a previous paper, and was attributed to Nembutal anesthesia. In the face of this variability, particularly of coronary blood flow, the close independent correlation between the arterial levels and coronary A-V differences of lactate and pyruvate appear even more significant. Furthermore, recent observations on man show no significant difference in the coronary A-V extraction coefficient, utilization threshold, or slope of utilization for pyruvate, lactate, glucose, or oxygen when compared with the present observations in dogs under light Nembutal anesthesia.

During starvation, the finding of abnormally
low myocardial extraction of carbohydrates, correlated with a low myocardial respiratory quotient of about 0.69, supports the contention that, in this situation, noncarbohydrate fuel is being utilized by the heart. The abnormally low myocardial extraction of lactate, pyruvate, and glucose in starvation, despite adequate arterial levels, suggests that some metabolic block in carbohydrate oxidation may be present. Since adequate vitamin supplements were given to the starved dogs, it is unlikely that vitamin deficiency was implicated.

SUMMARY AND CONCLUSIONS

1. The hearts of Nembutalized normal intact dogs extracted oxygen, glucose, lactate and pyruvate in direct relation to the arterial level of each substance and independently of the others.

2. Myocardial extraction, expressed either as coronary A-V difference or as an extraction coefficient, was independent of coronary blood flow and cardiac work. Total myocardial utilization of each metabolite was found to be the product of two independent variables: (a) coronary blood flow, and (b) coronary A-V differences.

3. During starvation, the heart probably derived its energy from fat, as indicated by a myocardial respiratory quotient near 0.70 and a low myocardial carbohydrate extraction.

4. At normal postabsorptive glucose, lactate and pyruvate blood levels, approximately two-thirds of the total oxidative energy requirements of the heart were available from simultaneous carbohydrate extraction (34 per cent from lactate, 5 per cent from pyruvate and 27 per cent from glucose). The average respiratory quotient of 0.91 suggested that fat could have supplied the remaining 34 per cent.

5. During hyperglycemia, the myocardial respiratory quotient was often greater than 1.0, and more than 100 per cent of the myocardial oxidative substrate requirements were available from carbohydrate extraction. The high respiratory quotient suggested that some carbohydrate was being stored as fat or utilized in some other nonoxidative way.

6. Pyruvate and lactate showed a high myocardial extraction coefficient with significant myocardial utilization, even at arterial levels close to zero. However, the absolute limitation of pyruvate and lactate extraction by the normal low arterial levels at rest prevents these metabolites from accounting for much more than 50 per cent of the total myocardial energy requirements.

7. Glucose was not utilized below a mean threshold of 54.2 ± 14.3 mg. per cent. But under some nonfasting conditions, with arterial glucose levels of 70 to 120 mg. per cent, glucose extraction was sufficient to provide the major potential source of fuel for myocardial oxidative energy.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the excellent technical assistance of Mr. Ernest Shiwanov, the statistical analyses by Mrs. Rosemary Gautier, and the cooperation and guidance of Drs. Thomas D. Kinney and Walter Fleischmann.

REFERENCES

9. Olson, R. E., Robson, J. S., Richards, H., and Hirsch, E. G.: Comparative metabolism of...

10 Brin, M., and Olson, R. E.: Metabolism of cardiac muscle. VI. Competition between L(+)-lactate uniformly labeled with C¹⁴ and C¹⁴-carbonyl-labeled pyruvate. J. Biol. Chem. 199: 475, 1952.


Myocardial Carbohydrate Metabolism in Normal Dogs, with Effects of Hyperglycemia and Starvation

WALTER T. GOODALE and DONALD B. HACKEL

_Circ Res._ 1953;1:509-517
doi: 10.1161/01.RES.1.6.509

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1953 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/1/6/509

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ 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 Research_ is online at:
http://circres.ahajournals.org/subscriptions/