Effects of Fat on Coronary Circulation in Dogs

By Peter T. Kuo, M.D., D.Sc., Arthur F. Whereat, M.D., Arthur A. Altman, M.D., and James W. West, Ph.D.

A number of investigators have observed, although somewhat inconstantly, an increase in the coagulability and viscosity of the whole blood, sludging of the red cells, and agglutination and adhesives of blood elements with lipemia. Clinically, an aggravation of the symptoms and signs of arterial insufficiency by hyperlipemia was observed in patients with severe coronary and peripheral vascular diseases.

The purpose of this communication is to describe the circulatory and biochemical alterations observed following the induction of lipemia in dogs with either an intact or an experimentally disrupted coronary circulatory system.

Methods

Myocardial scars were produced in dogs by ligating one or more branches of the anterior descending coronary artery. Twenty-eight dogs which had survived the operation for 4 to 12 weeks and 17 animals with intact coronary circulations were used for the study of the effect of an acutely induced lipemia upon the myocardial oxygen uptake and the coronary blood flow. During the collection of the data, 12 of the experiments (8 in the myocardial scar series and 4 in the control group) were unsuccessful due to technical difficulties.

All animals were given morphine premedication and were then anesthetized by intravenous injection of equal volumes of Dial and urethane* (100 and 400 mg/kg, respectively) and sodium pentobarbital (60 mg/kg), after 3 mg/kg of morphine subeutaneously. Duplicate coronary blood flow studies performed in this preparation at an interval of about 30 minutes have been found to be reasonably stable. Indwelling plastic catheters were placed in the femoral arteries. One of them was connected to a strain-gage transducer for continuous recording of atrial blood pressure and the other was connected to a manifold for anaerobic collection of arterial blood samples. The main pulmonary artery was catheterized to obtain mixed venous blood to estimate cardiac output by Fick method and for measuring pulmonary arterial pressure. Coronary sinus catheterization was performed according to the technic of Eckenhoff, Goodale and their associates, and the coronary blood flow was measured by the nitrous oxide method of Kety and Schmidt as modified by Eckenhoff, Goodale and their associates. The trachea was intubated and expired air was collected in a Tissot spirometer. Cardiac output was estimated over a 5-minute period. Then a measurement of coronary flow was immediately carried out over a 10-minute period.

A standard limb lead electrocardiogram, femoral arterial pressure and, at intervals, the pulmonary arterial pressure were recorded with a multichannel Hathaway oscillograph during each coronary blood flow measurement.

Blood samples drawn from the coronary sinus, main pulmonary artery and femoral artery were analyzed for oxygen and carbon dioxide contents by the technic of Van Slyke and Neill. An expired air sample was analyzed for carbon dioxide and oxygen contents by the method of Scholander.

Intravenous infusion of physiologic saline or fat-free emulsion base at the rate of 50 to 60 drops per minute were given during the control period. Immediately after the completion of the control set of observations, commercial fat emulsion (10 per cent sesame oil) or a 10 to 15 per cent specially prepared lipemic plasma obtained from donor dogs was administered in a similar manner to induce lipemia in preparation for the second flow study. Lipemic dog plasma was prepared as follows: Lipemia was produced in donor dogs either by repeated plasmaphoresis or

*Kindly supplied by Ciba Company, Summit, N. J.
by inducing experimental nephrosis with rabbit anti-dog-kidney serum. Six to 8 hours prior to the exsanguination, 600 to 800 ml. of heavy cream were given to the animal through a stomach tube. The lipemic plasma was separated from the red cells, and chylomicrons were harvested by high speed centrifugation. The concentrated “cream” was resuspended in a calculated amount of clear dog plasma to make up a 10 to 15 per cent emulsion.

A second set of coronary blood flow and hemodynamic measurements was performed in each animal within 25 to 35 minutes of the completion of the control run and of the start of the fat infusion. In each animal, blood samples were taken at the end of the control and fat infusion periods for total esterified fatty acid determinations.15

Results

Since the acute changes induced by the infusion of lipemic plasma were essentially the same as those produced by the infusion of a commercial fat emulsion, no attempt is made to evaluate each of the 2 preparations separately.

Circulatory Effects

This series of studies was made on 13 normal dogs. Ten of these animals received infusions of 10 per cent sesame oil and 3 of them received lipemic plasma from donor dogs. The data obtained are presented in table 1.* The mean hemodynamic and metabolic changes observed during the control and the lipemic periods of this series of animals are summarized in table 1-A. The t and sign† tests were used to determine the significance of the data.

The mean coronary blood flow of this group of animals during the control period was 96 ml. per 100 Gm. of left ventricle per minute with a mean myocardial oxygen extraction of 11.1 volume per cent and a myocardial oxygen consumption of 10.3 ml./100 Gm. of left ventricle per minute. Induction of lipemia in the same animals resulted in a highly significant decrease in the coronary blood flow (mean value 82 ml./100 Gm. left ventricle per minute). However, the mean myocardial A-V differential remained unchanged at 11 volume per cent. As a result, the calculated myocardial oxygen consumption of these animals was significantly lower than that of the control periods with a mean value of 8.9 ml./100 Gm. of left ventricle per minute.

When the fat emulsion was administered at the standard rate of 50 drops per minute and with the elapse of 25 to 30 minutes, the animals generally acquired a steady state. No significant change in the mean arterial pressure was demonstrable in this series of animals. Since both the coronary blood flow and the cardiac output were decreased, while the mean arterial pressure remained unchanged, both the calculated coronary and total peripheral vascular resistances were slightly increased with the intravenous fat infusion.

Blood Gas Changes

Several minutes after the intravenous fat injection had begun, all the animals in this series developed hypernea. Studies of the blood gases at this time showed a simultaneous fall in the arterial carbon dioxide and oxygen contents. The arterial oxygen saturation of this group of animals showed a mean decrease of 2.5 per cent and the average carbon dioxide content was lowered by 5.5 volume per cent. Repeated pulmonary arterial pressure measurements were made both before and after the induction of lipemia in 10 of the 13 animals. No significant changes in the dogs’ pulmonary arterial pressure levels were observed between the 2 periods of study.

Other Studies

The standard limb lead electrocardiograms were made in all experiments. All the dogs developed sinus arrhythmia and a few ventricular premature contractions during the first few minutes of the fat infusion. These arrhythmias soon subsided when the infusion.
FAT ON CORONARY CIRCULATION

Table 1-A*

Comparison of Data Obtained From the Same Dog Before and After Fat Infusion (13 Normal Dogs)

<table>
<thead>
<tr>
<th></th>
<th>Control run mean</th>
<th>After fat run mean</th>
<th>Mean difference</th>
<th>Probability of &quot;t&quot;</th>
<th>Sign test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary blood flow (ml./100 Gm./min.)</td>
<td>96</td>
<td>82</td>
<td>-14</td>
<td>&lt; .001</td>
<td>12-1</td>
</tr>
<tr>
<td>Coronary A-V difference (vol./100 ml.)</td>
<td>11.1</td>
<td>11.0</td>
<td>-0.1</td>
<td>&gt; .05</td>
<td>7-6</td>
</tr>
<tr>
<td>Cardiac O2 consumption (ml./100 Gm./min.)</td>
<td>10.3</td>
<td>8.9</td>
<td>-1.4</td>
<td>&lt; .001</td>
<td>13-0</td>
</tr>
<tr>
<td>Cardiac output (L./min.)</td>
<td>3.83</td>
<td>3.10</td>
<td>-0.73</td>
<td>&lt; .005</td>
<td>10-3</td>
</tr>
<tr>
<td>Mean arterial pressure (mm. Hg)</td>
<td>116.5</td>
<td>116.3</td>
<td>-0.2</td>
<td>&gt; .9</td>
<td>7-8-1</td>
</tr>
<tr>
<td>Cardiac rate</td>
<td>123</td>
<td>133</td>
<td>+10</td>
<td>&lt; .02</td>
<td>2-10-1</td>
</tr>
<tr>
<td>Total peripheral resistance (A.M.)</td>
<td>2,556</td>
<td>3,123</td>
<td>+567</td>
<td>&lt; .01</td>
<td>2-11</td>
</tr>
<tr>
<td>Coronary resistance (P/flow)</td>
<td>1.27</td>
<td>1.48</td>
<td>+0.21</td>
<td>&lt; .005</td>
<td>0-13</td>
</tr>
<tr>
<td>Arterial O2 saturation (%)</td>
<td>88.9</td>
<td>86.4</td>
<td>-2.5</td>
<td>&lt; .001</td>
<td>11-1</td>
</tr>
<tr>
<td>Arterial CO2 content (vol. %)</td>
<td>44.0</td>
<td>38.5</td>
<td>-5.5</td>
<td>&lt; .001</td>
<td>13-0</td>
</tr>
<tr>
<td>Total O2 consumption (ml./min.)</td>
<td>131.0</td>
<td>132.2</td>
<td>+1.2</td>
<td>&gt; .09</td>
<td>7-8</td>
</tr>
<tr>
<td>Respiratory quotient</td>
<td>0.89</td>
<td>0.90</td>
<td>+0.01</td>
<td>&gt; .05</td>
<td>7-5-1</td>
</tr>
<tr>
<td>Serum total esterified fatty acids (mEq./L.)</td>
<td>8.3</td>
<td>14.3</td>
<td>+6</td>
<td>&lt; .001</td>
<td>0-10</td>
</tr>
</tbody>
</table>

*See footnote (*), page 1158.

was continued at a slow rate. There were no significant displacements of the RS-T-T segments and waves in the electrocardiograms of these animals with the induction of lipemia.

Intravenous injection of the lipemic plasma or the vegetable oil emulsion did not produce a significant change in the respiratory quotient of the heart or in the hematocrit reading of animals studied.

Serum total esterified fatty acids of these dogs showed an average rise of 6 mEq./L. with a range of 3.4 to 10.4 mEq./L. following the fat infusions, indicating that a satisfactory lipemia had been produced in each case.

Acute lipemia was induced in 19 dogs with myocardial scars. In 14 of these dogs, infusions of artificial oil emulsion were employed, while lipemic plasma infusions were used in the remaining 5 animals. One of these animals received fat-free emulsion base before the fat infusion. One other dog in this series received only the fat-free emulsion base following the control period of infusion. The data obtained in this group of animals are presented in table 2.* Their mean values, mean differences and statistical analysis are seen in table 2-A.

Prior to the fat infusion, the mean coronary blood flow and the mean cardiac output of these dogs were somewhat lower than those of the control dogs. Six of the animals in this group had coronary blood flows below 80 ml./100 Gm. left ventricle/min. In animals with myocardial scars, the induced lipemia appeared to have caused a slightly more marked decrease in the coronary blood flow (a mean drop of 16 ml./100 Gm. of left ventricle/min.) and in myocardial oxygen consumption (a mean decrease of 1.7 ml./100 Gm. left ventricle/min.) than those in control groups (the decreases in coronary flow and myocardial oxygen consumption were 14 ml. and 1.4 ml./100 Gm. left ventricle/min. respectively). However, the differences between the 2 groups as a whole were found to be of no statistical significance.

Study of the blood gases during lipemia in these dogs again showed a simultaneous decrease in the arterial oxygen and carbon dioxide contents. The drop of 2.8 per cent in arterial oxygen saturation and 4.7 volume per cent in the arterial carbon dioxide content was also not significantly greater than the corresponding decreases observed in the animals of the control series. Respiratory quotient of the heart and the hematocrit of
The animals were unchanged during the short period of fat infusion.

No change in the coronary circulation and arterial blood gases from their respective control values was observed in 2 dogs which received fat-free emulsion base infusions.

The formalin-fixed hearts of dogs with myocardial scars weighed 101 to 228 Gm. (mean 167.5 Gm.) Their grossly visible scars were found to range from 0.8 to 13.7 Gm. with a mean of 7.5 Gm.

Arterial oxygen capacities of each animal in both groups were determined both before and during lipemia. The in vitro study failed to reveal a significant decrease in the ability of lipemic blood to pick up atmospheric oxygen. The oxygen consumption of all animals remained unchanged with the intravenous fat infusion.

Discussion

The present study indicates that acute induced hyperlipemia can exert very definite effects upon the circulation of dogs with or without myocardial scars. In the coronary circulation, the most outstanding effects are: a decrease in the coronary blood flow with little or no concomitant increase in myocardial oxygen extraction and consequently a decrease in the myocardial oxygen consumption. The mean cardiac output of these animals also shows a slight decrease with the development of lipemia. These changes are in many ways similar to those observed following intracoronary injection of plastic spheres suspended in gum acacia, human albumin, or dog plasma by Bing and his associates, and of lycopodium spores by West and his co-workers. In another experiment, the oil red O stained microscopic sections of the myocardium and of the lungs taken from lipemic animals showed large amounts of lipid in the capillaries. Although one cannot be certain that chylomicrons would behave like glass sphere and lycopodium sphere, it is perhaps reasonable to assume that the injected chylomicrons may produce mild blockage to the small coronary vessels similar to that of experimental coronary arterial embolization. Regan and his associates observed a similar decrease in myocardial blood flow and oxygen consumption in man during postprandial lipemia. In addition, these investigators found that this situation could be modified by lipolysis following heparin administration.

In studying the effects of lipemia, Swank reported a delayed increase in the viscosity of the whole blood and in the hematocrit reading of dogs following intravenous injection.

Table 2-B

Comparison of Data Obtained from the Same Dog Before and After Fat Infusion (19 Dogs with Myocardial Scars)

<table>
<thead>
<tr>
<th></th>
<th>Control run mean</th>
<th>After fat run mean</th>
<th>Mean difference</th>
<th>Probability of &quot;t&quot;</th>
<th>Sign test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary blood flow (mL/100 Gm/min.)</td>
<td>88</td>
<td>72</td>
<td>-16</td>
<td>&lt;.001</td>
<td>19-0</td>
</tr>
<tr>
<td>Coronary A-V difference (vol./100 mL)</td>
<td>10.8</td>
<td>10.9</td>
<td>+0.1</td>
<td>&gt;0.8</td>
<td>10-9</td>
</tr>
<tr>
<td>Cardiac O₂ consumption (mL/100 Gm/min.)</td>
<td>9.4</td>
<td>7.7</td>
<td>-1.7</td>
<td>&gt;0.01</td>
<td>17-2</td>
</tr>
<tr>
<td>Cardiac output (L/min.)</td>
<td>3.14</td>
<td>2.44</td>
<td>+0.7</td>
<td>&lt;.001</td>
<td>17-2</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>101.5</td>
<td>100.7</td>
<td>-0.8</td>
<td>&gt;0.7</td>
<td>8-9-2</td>
</tr>
<tr>
<td>Cardiac rate</td>
<td>120</td>
<td>119</td>
<td>-1</td>
<td>&gt;0.7</td>
<td>11-8</td>
</tr>
<tr>
<td>Total peripheral resistance (A.U.)</td>
<td>2,022</td>
<td>3,034</td>
<td>+112</td>
<td>&lt;.001</td>
<td>3-16</td>
</tr>
<tr>
<td>Coronary resistance (P/flow)</td>
<td>1.21</td>
<td>1.45</td>
<td>+0.24</td>
<td>&gt;0.01</td>
<td>2-17</td>
</tr>
<tr>
<td>Arterial O₂ saturation (%)</td>
<td>89.3</td>
<td>86.5</td>
<td>-2.8</td>
<td>&lt;.001</td>
<td>17-2</td>
</tr>
<tr>
<td>Arterial CO₂ content (vol. %)</td>
<td>42.3</td>
<td>37.6</td>
<td>-4.7</td>
<td>&lt;.001</td>
<td>19-0</td>
</tr>
<tr>
<td>Total O₂ consumption (mL/min.)</td>
<td>112.7</td>
<td>111.5</td>
<td>-1.2</td>
<td>&gt;0.8</td>
<td>10-9</td>
</tr>
<tr>
<td>Respiratory quotient</td>
<td>0.83</td>
<td>0.83</td>
<td>0</td>
<td>&gt;0.7</td>
<td>8-11</td>
</tr>
<tr>
<td>Serum total esterified fatty acids (mEq./L)</td>
<td>7.9</td>
<td>13.4</td>
<td>+5.5</td>
<td>&lt;.001</td>
<td>0-18</td>
</tr>
</tbody>
</table>

*See footnote (*), page 1158.
of various kinds of fat emulsions. He ascribed the changes observed, to an increase in vascular permeability resulting from a slowing of the circulation. In the present study, however, the circulatory and metabolic studies were completed within 25 to 35 minutes of the fat injection, when no significant increase in hematocrit was demonstrable. Furthermore, a simple slowing of the circulation would be expected to result in an increase in the A-V oxygen differential across the myocardium. Hence, it is safe to assume that these acute effects of lipemia as demonstrated in this series of studies are different from the delayed effects produced by the adhesion, sludging and agglutination of the formed elements in the blood.

The acute respiratory manifestations and blood gas changes of these animals following the induction of lipemia simulate closely those produced by experimental pulmonary embolization. Niden and Aviado found that their dogs quickly became hyperpneic after a brief period of apnea, following the intravenous injection of glass beads. There was a simultaneous fall in the arterial carbon dioxide and oxygen contents with pulmonary embolization. In this study, the slow infusion of fat suspension of small particulate size, did not produce a significant rise in the pulmonary arterial pressures as observed by Niden and Aviado in their pulmonary embolization experiments. In spite of the hyperventilation and the lack of evidence of severe obstruction of the pulmonary vessels, a slight but significant decrease in the arterial oxygen saturation was observed in both groups of animals following fat infusion. The possible mechanisms involved are: pulmonary capillary obstruction, opening of the pulmonary arteriovenous shunts and decrease in pulmonary diffusing capacity. The experiments of Swank and his associates may have a bearing on this study. These investigators have observed fat emboli in the blood vessels of the lung and other organs of rabbits following the feeding of high fat meals.

It is doubtful that hypocapnea induced by fat infusion was responsible for the fall in the coronary blood flow in this series of dogs. Whatever vasoconstriction effect the hypocapnea may have can be offset by the potent coronary dilatation effect of a reduction in arterial oxygen content.

Similar drop in arterial oxygen content following fat infusion both at high altitude and at ground level was observed by Stutman and his associates in dogs. These investigators also reported a drop in the oxygen capacity of the animal's blood during lipemia. It is entirely possible that lipemia might decrease the rate of oxygen uptake at a rarified atmosphere; however, a decrease in the arterial oxygen capacity was not demonstrated by the conventional laboratory method in the lipemic blood samples.

Based upon the observations made in previous open-chest animal experiments that intravenous fat injection would invariably produce a readily discernible dilatation together with a decrease in the amplitude and vigor of contraction of the freshly infarcted heart, the coronary arteries of a series of dogs were ligated to produce infarcts to use in this study. Later, it became apparent that the pathophysiology of the coronary circulation of these animals which had completely recovered from the simple ligation procedure can hardly be considered as analogous to either that of fresh myocardial infarction or that of coronary atherosclerosis. Hence, it is not surprising to find that even though fat infusion did produce significant hemodynamic and metabolic changes in each of the control and experimental groups, the induced lipemia did not produce a significantly greater effect upon the animals with myocardial scars than upon animals with an intact coronary circulation. Further investigation using atherosclerotic animals would be desirable.

**Summary**

The effects of lipemia upon the coronary circulation and myocardial oxygenation, and arterial oxygen and carbon dioxide contents were studied in 13 control dogs and 20 animals with myocardial scars. Acutely induced lipemia caused a significant decrease in the
cardiac output, coronary blood flow and myocardial oxygen consumption in both groups of animals. These changes were similar to those observed in experimental coronary artery embolization. The slow intravenous fat infusion did not cause a significant drop in the mean arterial pressures of these dogs. All animals in this series developed hyperpnea during fat infusion. There was a simultaneous lowering of the arterial oxygen saturation and carbon dioxide content. These changes were in some ways similar to those observed by other investigators in experimental pulmonary embolization. However, the slow fat infusion did not produce a significant elevation of the pulmonary arterial pressures of these dogs. These data suggest that the chylomicrons, like most macromolecular substances, may produce mechanical interference to the coronary blood flow and impose a limitation to myocardial oxygenation, while the total oxygen consumption of the animal is unaltered by lipemia.

Acknowledgment

We are grateful to Dr. Carl F. Schmidt for his help in making this study possible and in the preparation of this paper.

Summario in Interlingua

Le effectos de lipemia super le circulation coronari e le oxygenation myocardial e le contenuto arterial de oxygeno de bioksid de carbon essaeva studiate in 13 cases de controlo e in 20 caes con eletriscos myocardial. Le induction neute de lipemia causava un significativo declino del rendimento cardiae, del fluxo de sanguine coronari, e del consumption myocardial de oxygeno in ambe gruppos de animales. Iste alterationes esseva simile al alterationes observate in embolisation experimental de arteria coronarii. Le lente infusion intravenose de grassia non causava un declino significative del tension arterial medio in iste cases. Omne le animales in iste serie dissepolpava hyperpnea durante le infusion de grassia. Essva constatate un simultanea reduction del saturation oxygenie e del contenuto de bioksid de carbon in le arterias. Iste alterationes esseva simile, in certa aspectos, al alterationes observate per altere observatores in embolisation pulmonar experimental. Tamen, le lente infusion de grassia non producava un significative augmento del tension pulmo-arterial in iste cases. Le datos suggerire que le chylomicrones, de acordo con le majoritate del substantias macro-molecular, produce possibilemente un interferentia mechanic con le fluxo de sanguine coronari e impose un limitation al oxygenation myocardial, durante que le consumption de oxygeno total del parte del animal non es alterate per le lipemia.

References


Effects of Fat on Coronary Circulation in Dogs

PETER T. KUO, ARTHUR F. WHEREAT, ARTHUR A. ALTMAN and JAMES W. WEST

*Circ Res.* 1960;8:1157-1163
doi: 10.1161/01.RES.8.6.1157

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1960 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/8/6/1157

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/