The Effect of Lipemia upon Tissue Oxygen Tension in Man

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SUBSEQUENT to the observation that the intravenous infusion of fat emulsion caused a decrease in the myocardial oxygen tension of dogs having an experimentally produced myocardial infarction, it was shown that the hyperlipemia following a large fat meal may precipitate an attack of angina pectoris in patients with severe coronary artery disease.1-3 These attacks of angina developed about 5 hours after the fat meal, when lipemia was near its peak. Although sublingual nitroglycerin gave subjective relief, the lipemia-induced angina could also be relieved by the intravenous injection of heparin. The plasma turbidity and triglyceride level decreased following heparin, as expected, due to lipoprotein lipase activity.4-8 Therefore, it appeared that the level of lipemia had an effect upon the myocardium, i.e., anginal attacks developed at the time of hyperlipemia and were relieved by heparin, which induced "clearing" of plasma. Since increasing the blood fat level in the dog decreased myocardial oxygen tension, the present study was undertaken in order to determine whether the level of lipemia affects tissue oxygen tension in man.

The polarographic method of oxygen tension determination, which was used in the study of the dog myocardium during fat infusion, is also a useful tool for investigation of oxygen tension in accessible tissue of man. It has been particularly adaptable to determinations of skin oxygen tension, and thus used extensively in the study of peripheral vascular disease. The limitations of the polarographic method, and the considerable information that has been obtained by its use, have been well summarized by Montgomery.9

In preliminary experiments we had attempted to measure oxygen tension of the skin as lipemia developed following a fat meal. As might be expected, valid determinations of oxygen tension over the several hours of increasing lipemia after fat ingestion were difficult to make. The polarographic method is most accurate when the subjects remain quiet, the electrode position is not disturbed, and the experiment is brief enough so that the slight downward "drift" of readings which always occurs when electrodes are in place for long periods will not hamper interpretation of data. The following procedure was therefore adopted in which oxygen tension determinations were made over reasonably brief periods during which plasma turbidity either remained at a constant level or decreased after heparin administration.

Method

Twelve subjects, ranging in age from 33 to 77 years, were studied. The serum levels of cholesterol, total esterified fatty acid, and phospholipid were normal in the fasting state in all patients; although several had clinically evident peripheral arteriosclerosis. Six subjects (A.N., T.S., A.P., G.T., M.S., J.G.) had no palpable pulses in the feet and poor skin blood flow as measured by the vasodilatation test; 3 subjects (A.C., M.G., and V.R.) had claudication of one extremity but no objective evidence of decreased blood flow to the feet; and 3 subjects (C.A., E.D., and J.K.) had neither symptoms nor signs of peripheral vascular disease. The basic design of the experiment was as follows.

Subjects had not smoked and had taken nothing by mouth except water for 16 hours before each study period. Lipemia was induced by a fat meal containing 0.6 Gm. of butterfat per pound of body weight. Following this meal, consisting of heavy cream flavored with cocoa and cyclamate, subjects were permitted only water by mouth and did not smoke until the study was completed. They
remained at rest, sitting or lying down as desired, until measurements of skin temperature and oxygen tension were begun 4 to 4½ hours after the fat meal. Studies were made with subjects reclining in a room with air temperature of 23 ± 1°C, which did not vary more than ±0.5°C during any one study period. Skin temperature of the toes was recorded from thermocouples. Four platinum electrodes were inserted intradermally at the base of the toes for determination of cutaneous oxygen tension by the polarographic technique in use in this laboratory.¹⁰ Per cent changes in oxygen tension were calculated from the direct galvanometric readings obtained from the 4 electrodes. After a 20- to 30-minute control period of stable skin temperature and oxygen tension had been obtained, a sample of venous blood was drawn and an injection of heparin given through the same needle. Determinations of skin temperature and oxygen tension were continued at 5-minute intervals over the subsequent 40 minutes, at which time another venous blood sample was obtained. This terminated the study period.

The dose of heparin given 4½ to 5 hours after the fat meal was 1.5 to 2.5 mg. in 3 subjects (V.R., M.S., and J.G.). In all other studies using heparin a dose of 15 to 20 mg. was injected.

For the plasma turbidity study 8.5 ml. of venous blood were mixed with 0.5 ml. of M/10 sodium oxalate and immediately centrifuged for 10 minutes at 3,000 R.P.M. Readings of plasma against a water blank were obtained with a Klett-Summerson photoelectric colorimeter with a red (640-700mμ) filter.

To compare the oxygen tension during fairly stable levels of hyperlipemia with that observed during heparin-induced plasma clearing, 5 of the subjects who received a 15 to 20 mg. injection of heparin were studied on another day when the identical experiment was repeated, except that 1 ml. of saline was given instead of heparin. One additional subject (G.T.) was studied with saline injection but was unavailable for a comparative experiment with heparin.

To determine whether cutaneous oxygen tension is affected by heparin injection when the plasma is "clear," 4 of the subjects in whom studies had been made with heparin and saline injections during postprandial lipemia were studied on another day when the plasma turbidity was low subsequent to a 16-hour fast. A blood sample was obtained after the standard control period; 20 mg. of heparin were injected intravenously, and the usual measurements were made over the subsequent 40 minutes.

Results

The plasma turbidity and cutaneous oxygen tension of the 3 subjects given less than 3 mg. of heparin 4½ hours after the standard fat meal are summarized in figure 1. M.S. and J. G. received 1.5 mg. of heparin; V.R. received 2.5 mg. A downward "drift" in oxygen tension was found in all 3 subjects; the plasma turbidity 40 minutes after heparin was not significantly decreased from the preheparin value in any patient. The trend of the oxygen tension in V.R. was similar to that of the 2 other patients, although this 57-year-old woman had diarrhea the day of the test and her plasma turbidity did not reach the level usually attained. In all 3 subjects, the skin temperature remained stable during the course of the experiment. The presence of severe peripheral arterial disease did not appear to affect the results. M.S. and J.G. had absent foot pulses and poor skin flow, as measured by the vasodilatation test. V.R. complained of claudication of one calf, but had a normal response to vasodilatation and excellent pulses in the feet.

The findings in all other experiments are summarized in table 1. A gradual increase in oxygen tension was recorded during the 40 minutes following heparin injection in all 8 subjects given 15 to 20 mg. of heparin 4½ to 5 hours after a fat meal. The increase in

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cutaneous oxygen tension ranged from 4 to 56 per cent, with a mean of 21.7 per cent. As expected, plasma turbidity was appreciably decreased following the injection of this dose of heparin.

It was not possible, however, to establish a direct relationship between the magnitude of change in oxygen tension and the per cent of clearing of plasma or absolute decrease in plasma turbidity. For example, A.N. and A.P. each showed a 51 per cent decrease in turbidity; but A.N. had an increase in oxygen tension of 56 per cent in contrast to the 8 per cent increase of A.P. The greatest decrease in absolute turbidity was shown by the 2 subjects (A.N. and C.A.) having the greatest increase in oxygen tension. However, the 2 subjects (A.P. and M.G.) having the least increase in oxygen tension showed a decrease in turbidity similar to that of E.D. and T.S., who each had a more than 20 per cent increase in oxygen availability. Also, there was no correlation between oxygen tension change and the level of plasma turbidity at the time of heparin injection. The plasma turbidity (Klett units) at the time of heparin injection in 3 subjects representing greatest oxygen tension change, near mean change, and least change was: A.N. –310, T.S. –175, and M.G. –270.

The change in oxygen tension did not appear to be influenced by the presence or absence of peripheral artery disease. As noted above, A.N., T.S., A.P., G.T., M.S., and J.G. had no palpable pulses in the feet and very poor skin flow by the vasodilatation test. The other 6 subjects had no objective evidence of impaired peripheral blood flow.

There was no significant change in the skin temperature of the toes in any of the subjects.

In contrast to the effects observed after the injection of 15 to 20 mg. of heparin, there was no increase in cutaneous oxygen tension when 1 ml. of saline was injected 4½ to 5 hours after a fat meal. As noted in table 1, a slight, insignificant increase or decrease in plasma turbidity was found 40 minutes after the placebo injection. Figure 2 presents a comparison of the effects of saline and heparin injections in all studies performed after a fat meal. The mean turbidity before injection was somewhat lower in the saline experiments than in the heparin series due to subject G.T. having a low postprandial lipemia curve with a peak of 150 units and E.D. having a lower turbidity reading on the day of saline than on the day of heparin injection.

The results of the 2 studies in subject E.D. are shown in figure 3. It should be emphasized that the oxygen tension determinations in this
study were done with uncalibrated electrodes, since calibration of these electrodes in human skin is subject to a 25 per cent error. Therefore, studies obtained on different days with different electrode placement should not be considered to reflect absolute oxygen tension on the different days. The technic is ideally suited for the measurement of changes in oxygen tension over brief periods, as was seen following heparin injection in E.D. and the other subjects. Each study should be considered against its own control period. For example, the absolute cutaneous oxygen tension during the entire saline study in E.D. may have been higher than the absolute level 40 minutes after heparin. What should be emphasized is that there was an increase from the control level following heparin injection and no increase after saline injection.

Another representative response to heparin injection following a fat meal is shown in figure 4, which summarized 3 of the 4 studies in patient T.S. The increase in tissue oxygen tension following heparin injection and the lack of increase following saline injection is similar to the response of patient E.D. and the other subjects. In addition, the consistency of the postprandial lipemia curves in patient T.S. made it possible to obtain measurements of oxygen tension during his spontaneous clearing of lipemia. The increase in oxygen tension during the first hour of spontaneous clearing from the peak of lipemia is plotted on the right in figure 4. Therefore, an increase in oxygen tension was found during spontaneous clearing as well as during heparin-induced decrease in lipemia.

As a fourth study in this patient, he received 20 mg. of heparin intravenously after a 16-hour fast. The results obtained in T.S. and the 3 other subjects given 20 mg. of heparin when the plasma turbidity was low due to a 16-hour fast are charted in figure 5. The injection of heparin in subjects having low-plasma turbidity due to fasting did not result in the increase in oxygen tension seen following the injection of heparin when there was significant gross lipemia. An increase in oxygen tension was found only in those situations in which there was clearing of gross lipemia.

**Discussion**

From these studies, it would appear that tissue oxygen tension in man is affected by the level of lipemia. The cutaneous oxygen tension of the toes increased coincident with heparin-induced clearing of plasma turbidity.
In 1 subject a similar increase of oxygen tension was demonstrated during the spontaneous decline of postprandial lipemia.

This increase in skin oxygen tension that occurred during heparin clearing is appreciable, exceeding that produced in normal and ischemic limbs by change from the horizontal position to dependency for 20 minutes.\textsuperscript{11} The changes in tissue oxygen do not appear to have been due to the administration of heparin per se, since injections given to fasting subjects had no demonstrable effect.

The measurements obtained with the intracutaneous electrodes used in this study are believed to reflect oxygen tension of tissue rather than of blood. The delivery of oxygen to the tip of an electrode inserted into skin is dependent upon several potentially variable factors. These are (1) flow of blood to the skin, (2) oxygenation of the blood, and (3) diffusion of oxygen from the erythrocytes to the electrode. It is quite unlikely, although possible, that the changes in tissue oxygen tension that occurred during plasma clearing resulted from changes in cutaneous blood flow. The presence or absence of apparent peripheral artery disease, and the response of the subjects to the vasodilatation test, could not be correlated with the oxygen changes noted during plasma clearing. For example, subject T.S. (fig. 4) had very ischemic feet. The vasodilatation test showed no evident capacity for increase in cutaneous flow when our studies were performed. He later had a sympathectomy and the vasodilatation test was repeated following the intravenous injection of Priscoline. Again, no capacity for increase in cutaneous flow could be detected.

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Also, all of our subjects had stable skin temperature readings during the course of the experiments. Minor changes in flow may occur without changes in skin temperature. However, the skin temperature has been found to bear a good relationship to the blood flow determined by plethysmography when room temperature is the same (23 ± 1°C) as that employed in our studies.12

If, as seems likely, the level of lipemia does affect oxygen diffusion, it may well influence oxygen uptake in the lungs as well as release to the other tissues. We had previously noted an unusual increase in rate and depth of respiration which seemed characteristic of lipemia-induced angina pectoris.1,2 In 2 subjects with hyperlipemia and congestive failure, arterial oxygen saturation apparently increased when the serum triglyceride level was decreased by several weeks of strict diet.13

The coexisting congestive failure in these 2 patients may have made detectable an impairment of blood oxygenation not demonstrable in hyperlipemic subjects with normal heart and lungs. Several years ago Martin and Hueper reported a decreased rate of oxygen uptake by the erythrocytes of hypercholesteremic rabbits.14 Coating of the red blood cells or streaming of chylomicrons might hinder the diffusion of oxygen between erythrocytes and tissues. Other effects of lipemia have been reported which might hinder diffusion. Increased adhesiveness and aggregation of red blood cells have been observed.15 Lipemia may affect blood viscosity. An increase in viscosity has been reported during lipemia, but another study failed to demonstrate an increase in viscosity during lipemia or a decrease in viscosity after heparin injection.15,16 Sludging of blood may be important, particularly in smaller vessels.3,17 Any of these factors, or others, may be responsible for the observed effect of varying levels of lipemia upon tissue oxygen tension.

The results of the present study indicate that the oxygen tension of at least one tissue in man—the skin—is affected by the level of plasma lipemia. A decrease in oxygen availability in the myocardium may be responsible for the angina which can be induced by postprandial lipemia.

**Summary**

The effect of varying levels of lipemia upon tissue oxygen tension has been investigated in human subjects with normal and decreased peripheral blood flow. Oxygen tension of the skin was determined during rapid clearing of lipemia to avoid the difficulties inherent in prolonged study over the several hours of increasing lipemia following a fat meal. Regardless of whether peripheral blood flow was normal or decreased, a mean increase of 21.7 per cent in skin oxygen tension occurred during heparin-induced clearing of plasma turbidity. In addition, skin oxygen tension increased during the spontaneous decline of lipemia in 1 subject. Oxygen tension was not increased after a saline placebo injection during lipemia or following heparin injections in subjects with “clear” fasting serum.

The observed increase could not be attributed to changes in blood flow. Skin temperature remained stable during the experiments and the subject’s response could not be correlated with skin blood flow as measured by the vasodilatation test. The increase in tissue
oxygen tension that occurs during clearing of plasma seems most probably to be due to increased diffusion of oxygen to or from the erythrocytes.

Acknowledgment

We are indebted to Miss Julia Van Horn, Dietitian, Hospital of the University of Pennsylvania, for her assistance in this study.

Summario in Interlingua

Le effecto de varie nivellov de lipemia super le tension de oxygeo tissular esseva investigate in subjectos human con normal e reduce fluxos de sanguine peripheric. Le tension de oxygeo del pelle esseva determinate durante le rapide claran de lipemia pro evitar le dificultates inherente in le prolongo studio a transverso le plure horas de crescente lipemia post un repasto grassee. Sin reguardo a si le fluxo de sanguine peripheric esseva normal o reduce, un augmento medie de 21,7 pro cento occurreva in le tension oxygeo del pelle durante le heparino-induce claran del turbiditate del plasma. In plus, le tension oxygeo del pelle cresceva durante le declino spontane del lipemia in un del subjectos.

Le tension de oxygeo non esseva aumentate post le injection de un placebo salin durante le lipemia o post injectiones de heparina in subjectos con sero "clar" in stato jejun.

Le observate augmento non poteva esser attribuite a alterationes del fluxo de sanguine. Le temperatura del pelle remaneva stabile durante le experimentos, e le responsa del subjecto non poteva esser correlareate con le fluxo de sanguine in le pelle como illo esseva mesurate per le test del vasodilatation. Le augmento del tension de oxygeo tissular que occurre durante le claran del plasma es probabilisime causeate per un augmento del diffusion de oxygeo ad o ab le erythrocytos.

References


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Circulation. 1960;22:901-907
doi: 10.1161/01.CIR.22.5.901

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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/22/5/901

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