Fig. 4. Relationship between Hepatic Blood Flow and Splanchnic O_2 Extraction in Normal Subjects

function, the splanchnic oxygen consumption was only slightly increased almost equally with hepatitis patients. These findings seem to suggest that the cases of subgroup A of pulmonary tuberculosis have had latent disturbances of the hepatic function which were not detected with routine tests.

Then, observing the splanchnic oxygen consumption in relation to the hepatic blood flow and the splanchnic oxygen extraction, it was as follows. The splanchnic oxygen consumption under induced hypoxemia was remarkably increased from the range of 30–50 cc/min./m² at rest to the range of 65–85 cc/min./m² owing to marked increase of hepatic blood flow and slight increase of splanchnic oxygen extraction in normal subjects (Fig. 4). On the other hand, in

Fig. 5. Relationship between Hepatic Blood Flow and Splanchnic O_2 Extraction

patients with pulmonary tuberculosis or liver disease, the splanchnic oxygen consumption at rest was almost equal to the one in normal subjects, but in the majority of them, it did not reach the range of normal subjects during the induced hypoxemia (Fig. 5). From this viewpoint, it was considered that the healthy liver performed well the regulation of the metabolism in response to the oxygen insufficiency, while the liver with disturbed function was deficient in such a metabolic compensation; particularly this was nil in the cirrhotic liver.

REFERENCES

- 1) Ohbayashi, A., *J. Osaka Med. Coll.* **19**: 640, 1960.
- 2) Takasu, T., *Jap. Circul. J.* **24**: 1018, 1960.
- 3) Bradley, S. E. and Ingerfinger, F. I., *Clin. Invest.* **24**: 890, 1945.
- 4) Levy, R. L., *Am. J. M. Sc.* **197**: 241, 1931.

3. Metabolic Effects of Hypoxia and Hypercapnia on the Liver Related with Hepatic Circulation[†]

ISAO SUEMITSU, KOJUN IKEDA AND SHIGEO HOSHIYA

[The Department of Internal Medicine (Director: Prof. K. Hara), Osaka Medical College, Takatsuki, Osaka]

AS AN ALTERNATIVE and a preliminary study of the behavior of hepatic circulation and metabolism especially that of carbohydrates during respiratory insufficiency, investigations of these functions during hypoxemia of arterial oxygen saturations of 65–55%, induced by 10% O_2 inhalation were carried out. This induced condition is not identical with, but is closely related to that of acute clinical respiratory insufficiency.

METHODS AND MATERIALS

A total of 30 subjects (group I: healthy controls,

group IIA: pulmonary tuberculosis without hepatic dysfunction, group IIB: pulmonary tuberculosis with hepatic dysfunction, group III: recovery phase of acute hepatitis, group IV: chronic hepatitis, group V: hepatic cirrhosis) were studied.

10% O_2 was administered by the Levy's method¹⁾ and necessary blood samples were obtained before and 15–20 minutes after the beginning of the hypoxemia by hepatic vein catheterization to determine the hepatic circulation^{2,3)} and metabolism.

On the other hand, as a fundamental experiment the effect of hypoxemia on the methylenblue reducing ability of tissue (liver, heart, brain and kidney) was studied by having mice breath 5 and 10% O_2 and a mixture containing 5% O_2 + 5% CO_2 .

[†] (Received for Publication, Aug. 30, 1963)

RESULTS

I) Relationship between hepatic glucose release, splanchnic oxygen consumption and estimated hepatic blood flow. (Fig. 1)

Fig. 1. Relationship between Splanchnic O₂ Consumption, Hepatic Glucose Release and Hepatic C₃-acid Uptake or Release

1) Healthy controls: During hypoxemia, the total body O₂ consumption decreases, but the splanchnic O₂ consumption increases remarkably (80%).

The hepatic glucose release also increases.

2) Cases with slight to mild hepatic dysfunction: The splanchnic O₂ consumption increases only to a slight extent (17–19%).

3) Cases with moderate to severe hepatic dysfunction: The splanchnic O₂ consumption decreases to some extent (–28%). In these groups, the increase in hepatic glucose release due to the hypoxemia is smaller than that of normal controls and especially no increase is seen in the group with cirrhosis.

II) C₃ acids (Fig. 1)

Relationship between the percentage change of splanchnic O₂ consumption and hepatic uptake or release of lactate and pyruvate due to

the hypoxemia.

1) Normal controls: Lactate and pyruvate are consumed well by the liver in this group where the splanchnic O₂ consumption increases markedly.

During the induced hypoxemia, the release of C₃ acids from other organs increase, and this is consumed well by the liver in the normal controls.

2) Cases with hepatic dysfunction: The disposal of these C₃ acids especially that of pyruvic acid is decreased or moreover released in the resting state. During induced hypoxemia lactic and pyruvic acids are released from the damaged liver, so in those with hepatic dysfunction the increased amounts of C₃ acids liberated from other organs during hypoxemia can not be dealt with effectively.

III) Hepatic glucose release and mobilization of potassium during hypoxemia⁵⁾. (Fig. 2)

Fig. 2. Correlation between Hepatic Glucose Release and Hepatic Potassium Mobilization During 10% O₂ Inhalation

A positive correlation is seen between these two in cases without hepatic dysfunction, i. e. glucose and potassium are released together in paralld amounts. When hepatic dysfunction is present, this correlation does not exist, and even those with a large potassium mobilization have small glucose releases.

IV) Uptake or release of albumin⁶⁾ (Fig. 3)

Albumin is released by the liver in a resting state, whereas it is taken up during hypoxemia.

The albumin uptake during hypoxemia is larger in normal controls with a large glucose release than in cases with hepatic dysfunction with less glucose release.

V) In cases with no hepatic dysfunction, the change in hepatic release of glucose due to the hypoxemia is not related to the blood sugar level, but a negative correlation was

Fig. 3. Relationship between the Albumin Uptake or Release of the Liver and the Other Organs, During 10% O₂ Inhalation

Fig. 4. Correlation between Hepatic Glucose Release and Glucose Supply to the Liver During 10% O₂ Inhalation

found between the amount released and the amount supplied or returned to the liver. (Fig. 4)

VI) Relationship between the carbohydrate uptake and release of the liver and brain⁴⁾. (Fig. 5)

In a resting state, the liver releases glucose at the rate of 97 mg/min, and 86% of this is utilized by the brain. During the hypoxemia, the glucose release increases markedly and about 40% is used by the brain, the rest contributes towards the rise in the blood glucose level and as an energy source for other organs where anaerobic glycolysis takes place.

In a resting state, lactate is dealt with mostly by the liver. During hypoxemia, the release from the brain increases (42 mg/min), and almost all of this is also disposed by the liver.

VII) Tissue oxidation ability (Thunberg's method) (Fig. 6)

The ability of mice tissues to oxidize methylenblue with or without substrate added changes after hypoxia is induced. With 10% O₂ respira-

Fig. 5. Relationship between the Carbohydrate Uptake and Release of the Liver and Brain (Healthy Control)

Fig. 6. Percentage Change of the Tissue Oxidation Ability (Thunberg's Method)

tion for 2 hours, no change is seen with heart and brain tissues, but that of the kidney and especially that of the liver increase definitely. With 5% O₂, the oxidation ability of the liver is maintained fairly well when substrates are added although the endogenous respiration decreases, but other organs show a decrease despite the addition of substrates.

When 5% O₂ + 5% CO₂ is administered, the severe decrease in the oxidation ability seen with only 5% O₂ does not occur, and even a tendency to increase was noted with hepatic tis-

sue.

DISCUSSION AND SUMMARY

The results show that the liver of normal subjects do not rely on anaerobic energy during the induced hypoxemia as seen in an increase in splanchnic O_2 consumption and the increased oxidizing ability of the liver seen in animal experiments. The glycolysis which occurs in the liver is for the purpose of supplying glucose to other organs especially the brain which need an extra supply for anaerobic energy production. And the releases of glucose and potassium parallel each other. (Fig. 7) On the other hand,

Fig. 7. Healthy Control

the liver of those with hepatic dysfunction tends to become hypoxic, as it can be seen from the decrease in O_2 consumption and in expulsion of potassium. Since the liver itself needs anaerobic energy in these cases, a large portion of the glucose produced by glycolysis is catabolized to C_3 acids and the rest is released from the liver. Therefore, the releases of glucose and potassium do not parallel each other in these cases. (Fig. 8) In other words, even during hypoxemia, in the liver of normal controls, glycogenolysis occurs along with gluconeogenesis from C_3 acids expelled from other organs, albumin, etc., which causes the O_2 consumption to increase.

As for this phenomenon a concept of the

Fig. 8. Case with Hepatic Dysfunction

metabolic compensatory function of the liver has been introduced by Prof. Hara¹⁰⁾.

However, in those with hepatic disease, the livers themselves need anaerobic energy to maintain their own metabolism. So a large part of the glucose produced by glycogenolysis is consumed by the liver and the glucose release is reduced.

In these cases, the oxidation and the anabolic disposal of C_3 acids by the liver are disturbed causing them to be expelled from the liver.

Thus, those with hepatic disease have less ability to perform the metabolic compensatory function of the liver which is seen in healthy subjects. The effect of such disturbances can be considered to be quite large on the brain⁹⁾ and diseased myocardium⁸⁾ where extra glucose is needed for the production of anaerobic energy.

REFERENCES

- 1) Levy, R. L. et al, *Am. J. Physiol.* **50**: 216, 1919.
- 2) Ohbayashi, A., *J. Osaka Med. Coll.* **19**: 640, 1960.
- 3) Takasu, T., *Japanese Circ. J.* **24**: 1018, 1960.
- 4) Hoshiya, S., *Japanese Circ. J.* **24**: 1152, 1960.
- 5) Suemitsu, I., *Japanese Circ. J.* **24**: 1079, 1960.
- 6) Kawakami, C., *Japanese Circ. J.* **25**: 139, 1961.
- 7) Ikeda, K., *Japanese Circ. J.* **24**: 1005, 1960.
- 8) Hayashi, T., *Japanese Circ. J.* **21**: 501, 1958.
- 9) Ohtani, H., *Japanese Circ. J.* **27**: 537, 1963.
- 10) Hara, K., The main point of the President's speech on the 24th annual meeting of the Japanese circulation society 1960.