Liver Function and Hypertension
Blood Pressure and Heart Weight in Chronic Hepatitis

By Flemming Raaschou, M.D.

The purpose of the present work was to study the incidence of arterial hypertension in a series of autopsied cases of chronic hepatitis. The frequency of patients with hypertension, examined according to three criteria (cerebral hemorrhage, hypertrophy of the heart, and incidence of hypertension as determined by actual measurements of blood pressure during life), is essentially lower in an autopsy series consisting of women who died of or with subchronic hepatitis than in a control series of autopsied female patients with the same age distribution who died of all other diseases.

CHAUFFARD, in 1892, was the first to point out that most icteric patients have a low blood pressure. About 1900, Gilbert and Garnier stressed low blood pressure as a characteristic feature of cirrhosis of the liver. In 1937 Loeper and in 1949 Spatt and Rosenblatt made the same observation. In 1930, Geill found strikingly low blood pressure values in acute, infectious hepatitis. Meakins, in 1932, was the first to show that the blood pressure in patients with arterial hypertension may show a pronounced fall when these patients develop acute, infectious hepatitis, and that this low blood pressure may persist for a prolonged period after the jaundice has subsided. In normotensive patients, too, there seems to be a tendency toward a lower blood pressure when they are attacked by acute hepatitis, a finding made by Selander in 1939 in a large series of patients with hepatitis.

The purpose of the present work was to study the incidence of arterial hypertension in a series of autopsied cases of chronic hepatitis. As a result of this study the hypothesis is put forward that a severely damaged liver function prevents the development of hypertension in man.

In a previous study the etiologic relationship of obstruction of the urinary tract (hydronephrosis) to the development of hypertension was investigated in a series of autopsied cases. During the period of this investigation (January 1944, to January 1948) there occurred in Denmark an epidemic of hepatitis during which numerous patients died. The livers of these patients showed the gross and microscopic characteristics of subchronic atrophy of the liver. With but few exceptions the patients who died were women over 45 years of age. Death occurred, on the average, 8.2 months after the appearance of the first symptom and was the result of severe, chronic hepatitis with ascites, edema, jaundice, hemorrhagic diathesis and, at last, hepatic insufficiency with hepatic coma. In this large group of women, the great majority of whom had reached an age at which essential hypertension is very frequent, the incidence of hypertension was amazingly low. It occurred to me, therefore, that in some way the severe hepatic disorder either prevented the development of hypertension in patients who were to be expected to be hypertensive or caused an already developed hypertension to subside again.

Material
This comprises a series of cases of hepatitis and a control series. In the course of the period mentioned in the preceding paragraph, 108 patients with subchronic atrophy of the liver were autopsied in Kommunehospital, Copenhagen; 102 were women. Since so few males died of this disease, only the series of women has been analyzed. The age incidence in the female patients is shown in figure 1: the curve rises abruptly after the forty-fifth year, the summit occurring between 65 to 75 years. The control series comprises 93 unselected women over 45 years of age who died during the same period and came to necropsy. The patients of this series died of many
diseases, but none of them had subchronic atrophy of the liver; patients with hypertrophy of the heart considered to have been caused by affections other than essential hypertension (e.g., valvular heart disease, chronic glomerulonephritis, chronic cor pulmonale, pheochromocytoma) were retained in both series. The age incidence in the control series corresponds fairly well with that of the series of cases of hepatitis (Fig. 1).

The incidence of hypertension was examined in the two series, and the following three criteria were used in determining the presence or absence of hypertension: (1) The frequency of cerebral hemorrhage, (2) the frequency of hypertrophy of the heart, and (3) the frequency and degree of hypertension as shown by the recorded blood pressure determinations in the patients.

RESULTS

Incidence of hypertension in patients with hepatitis

(1) The Occurrence of Cerebral Hemorrhage in the Two Series. None of the patients with hepatitis died of cerebral hemorrhage, whereas 11 patients in the control series (11.8 per cent) died of this condition.

(2) Frequency of Hypertension as Determined by the Finding of Hypertrophy of the Heart at Necropsy. Hearts weighing more than 400 Gm. were considered to be hypertrophied. Figure 2 shows the distribution of heart weights in 95 female patients with subchronic atrophy of the liver and in 93 women over 45 years in the control series. Five out of 95 women (5.3 per cent) with subchronic atrophy of the liver had hearts which weighed more than 400 Gm.; the average weight of these five hypertrophied hearts was 425 Gm. In the control series there were 33 out of 93 women (35.5 per cent) whose hearts weighed more than 400 Gm. the average weight being 475 Gm.

The number of cases with hypertrophy of the heart was thus about seven times greater in the control series than in the series with hepatitis, and the hypertrophied hearts in the control series weighed on an average 50 Gm. more than those found in the case of hepatitis.

(3) Frequency and Degree of Hypertension, as Determined by Actual Measurements during Life. This criterion is defective because not all the patients had had their blood pressure measured. However, since 89.2 per cent in the
control series and 83.4 per cent in the series with hepatitis had had their blood pressure measured, and as it was apparently quite accidental that no such measurement had been performed in the other cases, it was considered justifiable to draw certain conclusions from this part of the investigation.

(a) Systolic blood pressure. In the series of patients with hepatitis 15 (or 17.7 per cent) had pressures of 160 mm. Hg or higher, and three (or 3.5 per cent) had systolic pressures of 180 mm. Hg or higher. The corresponding figures in the control series were: 39 patients (47 per cent) with pressures of 160 mm. Hg or higher and 21 (25.3 per cent) with pressures equal to or above 180 mm. Hg. From these findings it can be concluded that if 160 mm. Hg is accepted as the lower limit of elevated systolic blood pressure, the number of hypertensive patients is about three times greater in the control series, than in the hepatitis series, and if 180 mm. Hg is accepted as the lower limit of systolic hypertension, the number is about seven times greater in the former series than in the latter. In both instances the average blood pressure of the hypertensive patients is higher in the control series than in the series with hepatitis.

(b) Diastolic blood pressure. The same conclusions can be drawn from an examination of the diastolic blood pressure. If 100 mm. Hg is fixed as the lower limit of diastolic hypertension, the series of cases of hepatitis contains 12 patients (or 14.8 per cent) whose pressures were over this value; but if 120 mm. Hg is accepted as the beginning of diastolic hypertension, only one patient (1.2 per cent) had too high a diastolic pressure. In the control series 21 patients (or 26.3 per cent) had pressures above 100 mm. Hg, and nine (11.3 per cent) had pressures over 120 mm. Hg. This analysis of the diastolic pressure, suggests that the severe cases of hypertension do not occur in the patients with hepatitis.

The chief conclusion of this analysis is that the frequency of patients with hypertension, examined according to the three criteria mentioned above (cerebral hemorrhage, heart weight and incidence of hypertension), is essentially lower in an autopsy series consisting of women who died of or with subchronic hepatitis than in a control series of autopsied female patients with the same age distribution who died of all other diseases. Severe, diastolic hypertension practically does not occur in patients with this disorder of the liver.

Of the three criteria, the first two (cerebral hemorrhage and heart weight) are presumably the most important, since these could be studied in the whole series of patients. With regard to the criterion of blood pressure as measured during life, its value is diminished, first, as already mentioned, because one-tenth to two-tenths of the patients of our series had not had their blood pressure measured, and second, because the number of blood pressure determinations in the individual patients varied greatly. The incidence of hypertension found in the control series agrees fairly well with the expected incidence in an average population. Robinson and Bruer assumed that the incidence of hypertension in adults is at least 40 per cent, and Søbye stated that a hereditary predisposition to hypertension was found in about 30 to 40 per cent of the population.

Possible Alleviation of Hypertension after Development of Hepatitis

If unquestionable cases of permanent hypertension which disappeared when the patient developed chronic hepatitis can be demonstrated, this will lend support to the hypothesis of a causal relationship between severe hepatic disorders with reduced liver function and the low incidence of hypertension. All case records in the hepatitis series have been gone through

![Fig. 2. The distribution of heart weights in the hepatitis and control material.](image-url)
with a view to this, and only the following case could be found. It may be mentioned that, with regard to the blood pressure of these patients with hepatitis, unfortunately prehepatitis details often were not available. M. E. B. was a woman 68 years of age. (Department III, Kommunehospital, case record no. 1468/1946, and the Institute of Pathology, case record no. 817/1946.) She gave the following history. Since 1936 (her fifty-eighth year) she had been suffering from dyspepsia on exertion, restlessness and precordial pain usually due to emotional disturbance, and had also had a tendency to edema of the ankles in the evening. In 1938 hypotension (210 to 250 mm. Hg systolic pressure) was first recorded. In 1941 the blood pressure ranged between 280/180 and 220/140. On March 15, 1946, it was 240/150. In June, 1946, the patient became ill with fatigue, dyspepsia and slight jaundice. She was admitted to Department III of Kommunehospital, where she remained from Aug. 29 to Oct. 24, 1946. The diagnosis was chronic hepatitis. She developed ascites and edema of the leg, and had anemia, a positive Takata-Ara test and a positive thymol test. In the course of the disease of the liver the following blood pressures were measured: 170/110 on August 15, 160/90 on September 2, 140/90 on September 5, 165/95 on October 18, 135/75 on October 21. An electrocardiogram (Aug. 30, 1946) showed only left axis deviation; a roentgenogram of the heart (Sept. 10, 1946) showed the width of heart to be 14 cm. and of the thorax, 26 cm. There was slight hypertrophy of the left ventricle.

On Oct. 24, 1946, about five months after the appearance of the first symptom, the patient died of hepatic insufficiency with hepatic coma. Necropsy showed subchonic atrophy of the liver, severe ascites, slight jaundice, enlargement of the spleen, and moderate pulmonary edema. The heart weight was normal (310 Gm.; body weight: 61 Kg.). The wall of the left ventricle measured 15 mm.

Comment. This case was thus one of hypertension of at least eight years’ duration in which a high diastolic pressure had been recorded. When this patient developed chronic hepatitis, an essentially lower blood pressure was found, and at necropsy there were no signs of hypertrophy of the heart.

Discussion

The question that immediately arises is whether the low incidence of hypertension in this severe hepatic disorder is specific and, therefore, attributable to special biochemical changes in the blood which determine the low blood pressure, or whether it is due to non-specific causes, such as, for instance, impairment of general health, emaciation or other factors incidental to such disease. It may be mentioned in this connection that hypertension is seldom seen in various forms of cancer presumably owing to the cachexia which develops.16

The Role of the Liver in Experimental, Renal Hypertension

That the liver plays such a role is strongly suggested by work such as that of Braun-Menendez and colleagues.4 In all probability hypotensinogen is produced in the liver15, 10 since the content of hypotensinogen in the blood of normal and hypertensive dogs is reduced or disappears completely after hepatectomy or injury to the liver (by carbon tetrachloride and ethyl alcohol). Moreover Haynes and Dexter17, 13 found that the content of hypotensinogen was reduced in human plasma in six out of nine patients with hepatic insufficiency. Renin, likewise, is generally considered to be destroyed, in part at least, in the liver since hepatectomy will delay its removal from the blood.13 Likewise hypotensinase, the hypotensin splitting enzyme, is also said to be present in liver as well as in many other parts of the organism; however, its concentration in the blood is said not to be changed in hepatic insufficiency.13

Shorr and associates23 put forward another theory about the occurrence of two antagonistic substances: vasoexcitor material (VEM) and the vasodepressor material (VDM), the function of which should be to regulate the peripheral blood flow and blood pressure. Vasodepressor material is produced in the liver, the spleen and the skeletal muscles in the case of tissue anoxia, and is destroyed in the liver under aerobic conditions. These authors found increased quantities of vasodepressor material in the blood and the liver tissue of rats with experimental cirrhosis of the liver; increased proportions of vasodepressor material are also said to be found in the blood of patients with cirrhosis of the liver.27

Finally, it may be mentioned that recently
Davis and co-workers\textsuperscript{8, 9} have published the results of experiments on dogs subjected to the Goldblatt procedure which, both with regard to the procedure and the results of experiments, closely resemble the experiments on dogs, which have been reported by Raaschou and Trautner\textsuperscript{22} in Goldblatt dogs; Davis and co-workers have undertaken partial clamping of the portal vein and the hepatic artery, either separately or simultaneously. When the flow of blood through the liver had been sufficiently reduced (which manifested itself, \textit{inter alia}, by the appearance of fatty infiltration in the liver), they observed that the blood pressure fell.

The strikingly low frequency of arterial hypertension in subchronic atrophy of the liver, and the fact that the function of the liver is found to be normal in essential hypertension in man,\textsuperscript{8} form the basis of the hypothesis on which the experimental work of Raaschou and Trautner\textsuperscript{22} was based: a normal or only slightly damaged liver function is a necessary condition for the development of hypertension in man, whereas a severely damaged liver function will prevent the development of hypertension or eliminate already existing hypertension. The object of Raaschou and Trautner’s work was to study in dogs the effect of a severe hepatic injury (caused by obstruction of the common bile duct) upon previously produced experimental renal hypertension. Briefly, it can be said that six hypertensive dogs (with experimental renal hypertension produced according to Goldblatt’s method), four with hypertension of short duration, two with more prolonged hypertension, displayed a gradual fall in the blood pressure toward, or to, the normal preoperative values after obstruction of the common bile duct had been established. These falls in the blood pressure were observed in dogs which had been in good health and which were sufficiently fed. In one normotensive dog the obstruction of the common bile duct produced no material changes in the blood pressure. The cause of the fall of the blood pressure after obstruction of the common bile duct could not be explained, but the experimental results are in accord with the clinical experience which has been summarized in this paper.

\textbf{Summary}

A comparison with regard to the incidence of arterial hypertension has been made between an autopsy series consisting of 102 women who had died of chronic hepatitis (subchronic yellow atrophy of the liver) and a control series of autopsied patients who did not have liver disease. By means of three criteria of arterial hypertension [(1) the incidence of cerebral hemorrhage, (2) the incidence of hypertrophy of the heart, and (3) the incidence and degree of arterial hypertension] study of these series demonstrated that the frequency of arterial hypertension is considerably lower in patients with severe hepatic disease than in patients without liver disease.

The hypothesis has been advanced that severely impaired liver function is able to prevent the development of arterial hypertension, or can eliminate already existing hypertension.

\textbf{Sumario Español}

Una comparación con relación a la incidencia de la hipertensión arterial se ha hecho entre una serie de autopsias consistiendo de 102 mujeres que murieron de hepatitis crónica (atrofia amarilla subcrónica del hígado) y una serie control de pacientes a quienes se les practicó autopsia que no tenían enfermedad hepática. Por medio de tres criterios para la presión arterial [(1) la incidencia de hemorragia cerebral, (2) la incidencia de hipertrofia del corazón y (3) la incidencia y el grado de hipertensión arterial] el estudio de estas series demostró que la frecuencia de hipertensión arterial es considerablemente más baja en pacientes con enfermedad severa hepática que en los pacientes sin enfermedad hepática.

La hipótesis se ha propuesto que la función hepática severamente deteriorada es capaz de evitar el desarrollo de hipertensión arterial o que puede eliminar la hipertensión ya existente.

\textbf{REFERENCES}

2. \textsc{Bjørneboe, M., and Brøchner-Mortensen, K.}:
11 Gilbert, and Garnier: cited by Loeper.17
Liver Function and Hypertension: Blood Pressure and Heart Weight in Chronic Hepatitis

FLEMMING RAASCHOU

Circulation. 1954;10:511-516
doi: 10.1161/01.CIR.10.4.511

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/10/4/511

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/