CARDIOVASCULAR FUNCTION IN LIVER DISEASES

I. MECHANOCARDIOGRAPHIC STUDY

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AS REGARDS the cardiovascular function of the patients suffering from liver diseases, attention has been paid to the problems of "dys-proteinaemische Myokardose"¹ and "energetisch-dynamische Herzinsuffizienz"². However, the studies made in this field are mostly concerned with the relation between abnormalities of serum protein and serum electrolytes, and electrocardiographic findings.³⁻⁶ While few reports have so far been made in regard to hemodynamic studies.⁷⁻⁹ Recently, with the remarkable progress and rapid propagation of non-invasive techniques for examination of cardiovascular functions such as mechano-cardiographic method,^{10,11} measurements of cardiovascular hemodynamic values have become relatively easy in various pathologic status. On the other hand, the importance of latent heart insufficiency or metabolic heart failure have come to be realized in recent years.¹² It is estimated that there should be considerable number of cases of liver diseases where metabolic cardiac insufficiency is overlooked.

Therefore, with the purpose of researching on the actual status of cardiovascular function in patients with hepatic diseases, the authors designed present mechanocardiographic study.

METHODS

1. Subjects

Key Words:

Mechanocardiogram
Acute hepatitis
Chronic hepatitis
Cirrhosis
Metabolic heart failure
Energeto-hypodynamic heart failure

Healthy control group: Forty five healthy subjects having no complaints, working normal, being free from diseases in respiratory and circulatory systems, indicating no anomaly in physical signs, blood pressure, chest X-ray and electrocardiogram were selected as control (Table I).

Liver disease group: Thirteen cases of acute hepatitis, 13 cases of chronic hepatitis and 12 cases of cirrhosis were studied (Table I). These patients were diagnosed by their clinical history, physical signs and laboratory tests of liver functions and in many cases, the findings of peritoneoscopy and needle biopsy of the liver were also referred to in determining diagnosis. The cases having complications were excluded.

2. Technique for recording the mechanocardiogram

For this study, mechanocardiography was so designed that it can simultaneously record electrocardiogram (ECG), apexcardiogram (ACG), phonocardiogram (PCG) and carotid arterial pulse tracing (Car). As pre- and main amplifier, multipurpose bioelectrograph (Fukuda-Electro-MR 400 series) was employed. The tracings were recorded at a paper speed of 100 mm/sec with time lines of 10 msec.

The subject was kept at rest supine position for about 30 min. and then mechanocardiographic tracing was done in the left lateral decubitus position. Electrocardiogram was taken in the lead II. PCG was picked up at medium frequency from aortic area or Erb's area. Microphone was held by the hand of examiner and applied to the said area. ACG was recorded by Fukuda-electro TY-302 at the point of maximal apical pulsation. Pick up for carotid

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TABLE I. SUBJECTS

Age	Sex	Healthy persons	Acute hepatitis	Chronic hepatitis	Cirrhosis	Total of liver diseases
15-19	M F	4				
20-29	M F	23 11	4 3	4		8 3
30-39	M F	3	2	2	4	8
40-49	M F	4	2	1 1	2 1	5 2
50-59	M F		1	1 4	4 1	5 6
60-	M F		1			1
Total		45	13	13	12	38

pulse tracing was applied to the right common carotid artery with the head of the subject turned to the left. The pick up was fixed by a supporting mechanism. For simultaneous recording, the subject suspended respiration at half point of expiratory phase.

3. Measurements and calculations

Fig. 1 indicates the nomenclature of the time points and time intervals in mechanocardiogram used by the authors.

R-R interval (R-R; msec) and heart rate (HR; per min): HR was expressed as 60,000 per beat divided by the preceding R-R interval.

Q-T interval (Q-T; msec): Corrected Q-T interval (Q-Tc; sec) for HR was calculated from Bazett's formula,¹³ viz.: $Q-T/\sqrt{RR}(\text{sec})$. Corrected value for HR of the other left ventricular systolic time intervals was also obtained by the similar method.

Electromechanical systole (EMS; msec): Time period from the onset of the QRS-complex of the ECG to the onset of aortic valve closure (II_A) of PCG, i.e., Q-II time. Corrected value is EMSc or Q-IIc.

Mechanical systole (MS; msec): The time period from the onset (C point) of the systolic wave of ACG to the onset of II_A . Corrected value is MS_c.

Left ventricular ejection time (LVET; msec):

Time period from the true onset (S' point) of the upstroke of the carotid pulse wave to its dicrotic notch (Nd).

Electro-mechanical interval (EMI; msec): Time period from the onset of QRS complex to the onset of systolic wave of ACG. It was calculated by EMS-MS. Corrected value is EM_{ic}.

Pre-ejection period (PEP; msec): It was calculated as EMS-LVET. Corrected value PEP_c.

Isovolumetric contraction time (ICT; msec): It was obtained by MS-LVET. ICT was not corrected by heart rate.

Q-II/Q-T, PEP/LVET and ICT/LVET_c: They were calculated from the respective measured values.

A wave ratio (a/EO; %): A wave height (a) is the height from the starting point of A wave to the crest of it. A wave ratio was calculated by dividing "a" by the amplitude (EO) from horizontal line passing through point O up to point E.

The above measurements were made on 5 continuous heart beats and the average value was taken. The authors regarded the mean value of the measured values obtained on 45 healthy control subject $\pm 2SD$ as normal range. The mean value and standard deviation of each group of hepatic patients were calculated and the significance of their deviation from mean value of

Fig.1. Schema of the cardiac cycle and of the relationship between valve openings and closures, ECG, ACG, PCG, and carotid pulse tracing.

EMS (electro-mechanical systole) = $Q - II_A$

MS (mechanical systole) = $C - II_A$

EMI (electro-mechanical interval) = $EMS - MS$

LVET (left ventricular ejection time) = $S' - Nd$

IET (isotonic ejection time) = $S' - P$

RET (reduced ejection time) = $P - Nd$

PEP (pre-ejection period) = $EMS - LVET$

ICT (isovolumetric contraction time) = $MS - LVET$

ICT_2 (Druckanstiegszeit; DAZ) = $(Ia - II_A) - LVET$

IRP (isovolumetric relaxation period) = $II_A - O$

RFW: rapid filling wave

SFW: slow filling wave

PSP: pre-systolic period

A: aortic valve

M: mitral valve

healthy subjects was statistically tested.

RESULTS

1. Measurements of mechanocardiogram in each group

Figs. 2 and 3 indicate the measured values of individual cases of healthy control group, acute hepatitis group, chronic hepatitis group and cirrhosis group. Table II indicates the mean value $\pm$ ISD of each item of measurements classified by group.

Acute hepatitis: When compared with control group, it indicated significant prolongation of

EMIC and significant increase of PEP/LVET ($p < 0.05$).

Chronic hepatitis: The cases of this group indicated no significant changes in the values of mechanocardiographic measurements. The results of tests were more resembled to healthy group than the case of acute hepatitis group.

Cirrhosis: Cirrhosis group indicated the most evident anomaly among all groups of liver diseases. Many patients indicated remarkable prolongation of Q-Tc. Regarding Q-Tc, mean value of cirrhosis group was significantly different from those of the healthy group ($p < 0.01$), of

Fig. 2. Mechanocardiographic measurements in each group. QTc, MSc, LVETc, and EMlc.

Fig. 3. Mechanocardiographic measurements in each group. ICT, PEP, PEP/LVET, and a/EO.

the acute hepatitis ($p < 0.05$) and of the chronic hepatitis ($p < 0.05$), respectively. Change in LVETc was not remarkable but PEPc indicated significant prolongation at $p < 0.05$. Q-II/Q-T also indicated significant decrease at $p < 0.05$.

2. Correlations between mechanocardiographic measurements and results of clinical examination

Without discriminating the patients group and healthy group, correlation coefficient between the values of mechanocardiographic measure-

TABLE II MECHANOCARDIOGRAPHIC MEASUREMENTS (Mean $\pm$ 1 SD)

Measurements		Healthy persons n = 45	Acute hepatitis n = 13	Chronic hepatitis n = 13	Cirrhosis n = 12	Total of liver diseases n = 38
Q-Tc	(msec)	393 $\pm$ 18	405 $\pm$ 25	407 $\pm$ 24	432 $\pm$ 29**	414 $\pm$ 28**
EMSc (=Q-IIc)	(msec)	408 $\pm$ 20	407 $\pm$ 25	410 $\pm$ 25	417 $\pm$ 25	411 $\pm$ 25
MSc	(msec)	375 $\pm$ 18	368 $\pm$ 23	375 $\pm$ 23	376 $\pm$ 27	373 $\pm$ 24
LVETc	(msec)	302 $\pm$ 16	294 $\pm$ 21	305 $\pm$ 20	300 $\pm$ 17	299 $\pm$ 20
EMic	(msec)	33 $\pm$ 7	39 $\pm$ 9*	36 $\pm$ 8	41 $\pm$ 16	38 $\pm$ 11**
PEPc	(msec)	106 $\pm$ 11	113 $\pm$ 14	106 $\pm$ 14	118 $\pm$ 17*	112 $\pm$ 15
ICT	(msec)	69 $\pm$ 12	69 $\pm$ 10	64 $\pm$ 14	70 $\pm$ 19	68 $\pm$ 14
Q-II/Q-T		1.04 $\pm$ 0.06	1.01 $\pm$ 0.06	1.01 $\pm$ 0.06	0.97 $\pm$ 0.08*	1.00 $\pm$ 0.07**
PEP/LVET		0.35 $\pm$ 0.05	0.39 $\pm$ 0.05*	0.35 $\pm$ 0.05	0.39 $\pm$ 0.06	0.38 $\pm$ 0.06*
ICT/LVETc		0.23 $\pm$ 0.04	0.24 $\pm$ 0.04	0.21 $\pm$ 0.05	0.24 $\pm$ 0.06	0.23 $\pm$ 0.05
a/EO (%)		6.4 $\pm$ 3.0	6.4 $\pm$ 3.4	5.9 $\pm$ 2.6	8.0 $\pm$ 4.5	6.8 $\pm$ 3.6

* Significantly different from the group of healthy persons ($p < 0.05$)** Significantly different from the group of healthy persons ($p < 0.01$)

ments and values obtained by clinical examinations was studied (Table III). Enzyme activities of GPT, GOT, alkaline phosphatase and cholinesterase did not indicate significant correlation with the values of measurement of mechanocardiogram. Total serum protein concentration, albumin fraction and γ -globulin fraction respectively showed significant correlation with Q-Tc. Significant negative correlation was noticed between total serum protein and EMic, and between γ -globulin fraction and Q-II/Q-T. Hematocrit value, hemoglobin concentration and red blood cell count indicated high negative correlation ($p < 0.01$) with Q-Tc, EMSc, MSc and LVETc and also indicated significant correlation ($p < 0.05$) with PEPc and a/EO. As for plasma electrolytes, significant negative correlation was observed between Ca and Q-Tc ($p < 0.01$) and between Ca and EMSc ($p < 0.05$).

DISCUSSION

1. Liver diseases and cardiac function

Peripheral circulatory abnormalities and increase of cardiac output in cirrhosis: Among various liver diseases, cirrhosis is characteristic in that it accompanies increase of cardiac output

and reduction of peripheral vascular resistance,^{7,9} (Fig. 4). Cardiac function becomes hyperdynamic to maintain the increase of output and it is overloading status. Such increase of cardiac output is supposed to occur as an adjusting mechanism to cope with the increase of peripheral blood flow and circulating blood volume.^{8,14} It is considered that the change in peripheral circulatory hemodynamics is caused by parenchymal liver cell damage and intra- and extra-hepatic circulatory abnormalities, and that the mechanism is probably responsible for the formation of vasodilator material (VDM) by liver and/or for the deterioration of the hepatic VDM inactivation system,¹⁵ and for the hindrance of inactivation of estrogen and ADH in the liver.⁹ Besides, occurrence of peripheral arterio-venous shunts,¹⁶ pulmonary arterio-venous shunts¹⁷ and porto-pulmonary venous shunt¹⁸ and reduction of the arterial oxygen saturation are also concerned with its mechanism. The details of it had already been described in the authors' previous paper.²⁰

Metabolic heart failure¹²: In the chronic hepatitis or cirrhosis, the changes in substrates of body fluids caused by extensive hepatic dysfunction result in metabolic disturbances in the myo-

TABLE III CORRELATION COEFFICIENTS BETWEEN MECHANOCARDIOGRAPHIC MEASUREMENTS AND CLINICAL EXAMINATIONS

	QTc	EMSc	MSc	LVEtc	EMlc	PEPc	ICT	$\frac{Q-II}{Q-T}$	$\frac{PEP}{LVEt}$	$\frac{ICT}{LVEtc}$	$\frac{a}{EO}$
GPT	-0.29	-0.19	-0.13	-0.16	-0.15	-0.14	-0.005	0.12	-0.04	0.15	-0.31
GOT	-0.06	-0.05	0.003	-0.009	-0.12	-0.14	0.13	0.005	-0.06	0.13	-0.32
ALPase	0.30	0.09	0.09	-0.05	-0.01	0.18	0.29	-0.21	0.22	0.26	-0.02
Ch-E	-0.26	-0.09	-0.0002	-0.12	-0.19	0.13	0.10	0.15	0.07	0.17	-0.21
Total protein	-0.36*	-0.03	0.22	-0.06	-0.53**	0.06	0.30	0.30	0.04	0.29	-0.15
Albumin (%)	-0.40*	-0.12	0.02	-0.02	-0.30	-0.14	0.07	-0.29	-0.15	0.07	-0.20
γ Glob (%)	0.48**	0.16	0.08	0.12	0.19	0.07	-0.07	-0.33*	0.03	-0.11	0.07
Total cholesterol	0.03	-0.04	0.02	-0.10	-0.12	0.08	0.08	-0.07	0.18	0.12	-0.06
Ht	-0.58**	-0.59**	-0.43**	-0.50**	-0.23	-0.30	-0.08	0.07	-0.06	0.06	-0.37*
Hb	-0.62**	-0.55**	-0.49**	-0.43**	-0.29	-0.33*	-0.09	0.14	-0.11	0.04	-0.45**
RBC	-0.49**	-0.59**	-0.50**	-0.47**	-0.25	-0.35*	-0.12	-0.03	-0.11	0.02	-0.35
p-Na	-0.09	0.02	-0.05	0.04	0.06	-0.08	-0.17	0.09	-0.07	-0.12	0.18
p-K	-0.18	0.46	-0.05	-0.11	-0.0009	0.06	0.06	0.13	0.11	0.10	-0.17
p-Ca	-0.68**	-0.49*	-0.23	-0.27	-0.08	0.14	0.24	0.13	0.33	0.37	0.21
BP max	-0.11	0.18	0.30	0.18	-0.24	0.08	0.09	0.24	0.17	0.002	0.09
BP min	-0.06	0.10	0.20	0.04	-0.20	0.14	0.15	0.12	0.08	0.11	0.10

* Statistically significant at $p < 0.05$ ** Statistically significant at $p < 0.01$

Fig.4. Schema showing the mechanism of changing cardiac function and peripheral circulation in cirrhosis of the liver.

cardium and may further cause metabolic heart failure. "Dysproteinaemische Myokardose" (WUHRMANN, F.¹) attributed to hindrance of metabolism and nutrition of myocardium due to dysproteinemia, in particular, decrease of albumin and increase of globulin is clinically important. When dysproteinemia continues for a long time, plasma protein gradually exudes into interstitial tissue of myocardium and the latter indicates the histological findings similar to serous inflammation. Then the influence of decrease of serum Ca and K is added to it and gradually the pathologic state of the so-called "Myokardose" is accomplished. In "Myokardose", abnormal electrocardiographic findings such as flattening and lowering of T wave, prolongation of Q-T interval, etc. are observed. Especially, confusion of ST-T is said to be characteristic.

In the end stage of cirrhosis, energy production in myocardium is weakened due to metabolic dysfunction and recovery from electrical activation of myocardium is delayed. In other words, energetic heart failure occurs and Q-T interval on the electrocardiogram prolongs. At the same time, mechanical contractility of myocardium decreases and ventricular contraction ends earlier. The signs which indicate extension of Q-T and appearance of II sound by, more than 0.04 sec. earlier than end point of T

wave like above is called HEGGLIN syndrome ("energetische dynamische Herzinsuffizienz: HEGGLIN, R.²). Unlike the case of congestive heart failure, this type of heart failure indicates only uncertain symptoms such as hypotension, fatigue, abnormal pulsation, difficulty of respiration, etc., and accompanies no noticeable congestive manifestation. On these cases, digitalis has no effect but it is known that when myocardial metabolism is improved by therapy, electrocardiogram returns to normal and uncertain symptoms disappear.

Organic changes in the heart: In the hepatic diseases, the heart not only undergoes the aforesaid functional changes, but sometimes organic pathologic changes may be accompanied. In cases of viral hepatitis²¹ and cases of cirrhosis with cardiac hypertrophy²² certain organic myocardial changes have been described. If the heart having such organic changes is forced to give high output and placed for a long time under overloading condition, it will gradually result in the insufficiency of myocardial contractility. Sinking of cardiac function will further aggravate hepatic dysfunction and vicious circle begins.

2. Liver diseases and mechanocardiogram

As the above, circulatory hemodynamics in the liver diseases vary according to the kinds of the disease or its stage. Therefore mechanocardiographic findings are also variable depending

upon the pathologic state. In the case of chronic hepatitis, ICT and PEP indicate the tendency of extension while in the early stage of cirrhosis, it rather shortens and LVET tends to prolong²³ and in the last stage of cirrhosis, decrease of cardiac force is observed.

Acute hepatitis: In the case of acute viral hepatitis, it is said that no increase of cardiac output is observed²⁴. According to the authors' results, acute hepatitis group indicated significant extension of EMic and increase of PEP/LVET when compared with healthy control group. No reference was observed as to the other measurements. The cause of EMic prolongation is dissolved but the increase of PEP/LVET suggests that acute hepatitis accompanies the decreasing tendency of cardiac force²⁵.

Chronic hepatitis: No significant difference was observed between this group and healthy control with regard to all items of measurements. It is clinically interesting that cardiac function of this group is closer to that of healthy group than acute hepatitis.

Cirrhosis: Prolongation of Q-Tc and PEPc and reduction of Q-II/Q-T were statistically significant in cirrhosis group. The prolongation of PEPc is evidently the sign of decrease in cardiac force^{26,27} and Q-Tc prolongation and Q-II/Q-T reduction suggest the "energetisch-dynamische Herzinsuffizienz". Therefore, many cases of cirrhosis should be considered to be in the status of the aforesaid metabolic heart failure.

It is reported that LVET has a positive correlation with stroke volume²⁶ while ICT and PEP have negative correlation with it^{26,28}. According to the authors' results, shortening of ICT and/or prolongation of LVETc were not observed and consequently it was hardly possible to judge that cardiac function was in a high output status. The discrepancy between the authors' observation and the reports of the predecessors may arise from the difference of the stage in patients with cirrhosis selected as subjects.

3. Correlation between clinical examinations and mechanocardiogram

In the clinical examinations of the patients with liver diseases, the closest correlation was observed between the anemia and abnormalities of mechanocardiogram. When anemia advances, prolongation of Q-T, EMS, MS, LVET and PEP, and increase of a/EO are observed. In other words, anemia accompanies decrease of cardiac force (compensatory stage) as observed on mechanocardiogram. It is unknown, however,

whether anemia is important as a direct cause of heart failure or it merely concerns indirectly with heart failure.

Dysproteinemia also has significant correlation with Q-Tc. Decrease of total serum protein concentration and albumin fraction and/or increase of γ -globulin fraction should have resulted the prolongation of Q-Tc. As for serum electrolytes, Ca concentration indicated negative correlation with Q-Tc and EMS i.e., the electrical activation and mechanical contraction in myocardium. These results are similar to some previous investigations^{1,5}. No significant correlation was found between mechanocardiographic findings and GOT, GPT, alkaline phosphatase, cholinesterase and cholesterol levels.

In the diseases of liver, as the above mentioned, patients with cirrhosis may suffer from metabolic heart failure i.e., energeto-hypodynamic heart failure. This pathologic conditions give rise similar degree of insufficiency of myocardial contractility at left and right ventricles. Therefore the symptoms of congestion is often concealed and the myocardial weakness progresses latently and it is apt to be overlooked. Attention should be paid therefore to the fact that the cases of cirrhosis which apt to cause heart failure are the ones which accompany anemia, dysproteinemia and decrease of serum Ca concentration.

SUMMARY

1. Mechanocardiograms of 45 healthy control subjects, 13 cases of acute hepatitis, 13 cases of chronic hepatitis and 12 cases of cirrhosis were measured and analysed.

2. Acute hepatitis group indicated prolongation of EMic and significant increase of PEP/LVET.

3. Chronic hepatitis group indicated no significant difference from healthy group as to any items of measurements.

4. Cirrhosis group indicated remarkable prolongation of Q-Tc and some extension of PEPc and decrease of Q-II/Q-T.

5. These changes in the measured values of mechanocardiogram indicated significant correlation with such clinical findings as anemia, dysproteinemia and change of serum Ca concentration.

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