CLINICO-PATHOLOGICAL CONFERENCE

A case of dilated cardiomyopathy with end-stage heart failure treated by prolonged continuous hemodiafiltration

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Abstract. A 55-year-old Asian man first visited to our hospital with complaining of exertional dyspnea eight years ago, and was diagnosed as having idiopathic dilated cardiomyopathy. One of his siblings also suffered from idiopathic dilated cardiomyopathy. His symptoms became worse gradually, and he was hospitalized again because of disturbance of consciousness on February 21, 2001. Hemodynamic monitoring with a Swan-Ganz catheter was started, which revealed that the cardiac index was 1.1 L/min/BSA, cardiac output 1.8 L/min, and pulmonary artery pressure 43/33 mmHg. The echocardiographic observation showed that the left ventricular ejection fraction was 32%, and serum BNP was elevated to 5,411 pg/mL. Multi-organ failure including renal and hepatic dysfunction developed because of the low cardiac output status. Continuous hemodiafiltration (CHDF) was introduced to reduce the volume overload, improve renal failure, and eliminate adverse cytokines. Although his hemodynamic status was temporarily improved after starting CHDF, weaning from CHDF was difficult and he finally died from cardiogenic shock after two month of intensive therapy. The autopsy showed thinning of the left ventricular wall, and histological examination revealed diffuse fibrous hyperplasia and myocardial fiber deficit in the ventricular myocardium. CHDF was effective in reducing the volume overload and improving renal function; however, heart transplantation is inevitable for the patients with severe heart failure due to dilated cardiomyopathy. (Keio J Med 51 (3): 165–177, September 2002)

Key words: dilated cardiomyopathy, continuous hemodiafiltration, autopsy, heart failure, unconsciousness

Dr. Ogawa (Moderator): I declare the 1042nd clinico-pathological conference (CPC) open. The case for discussion in today's CPC is a patient who died from gradual worsening of his cardiac function over a course of approximately 8 years. The physician-in-charge, Dr. Matsumura, will first describe the clinical course of this patient.

Dr. Matsumura (Internal Medicine): The patient presented complaining of exertion-related dyspnea on climbing stairs or walking up a slope since March 1993. He visited the Cardiopulmonary Division at our hospital in April 1993. After he was admitted to the hospital, cardiac catheterization and left ventriculography were performed, and revealed contractile dysfunction of the left ventricle, which was manifested by diffuse hypokinase and a reduced ejection fraction (EF, 11%). A myocardial biopsy further revealed hypertrophy of myocardial cells and interstitial fibrosis. There was no evident infectious, metabolic, systemic, or hereditary etiology. The patient was diagnosed as having dilated cardiomyopathy (DCM). Treatment with an anticoagulant (Warfarin®), digitalis glycoside, an angiotensin-converting enzyme (ACE) inhibitor, and furosemide was started. The patient was then discharged from the hospital and treatment was continued on an outpatient basis.

In the months of June and October of 1997, the patient developed acute exaggeration of his heart failure, precipitated by a common cold, and he was admitted to our hospital. Oral administration of pimobendan was

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started on October. From October 1998, his dyspnea on exertion (DOE) became progressively worse, and in April 2000, he developed the symptom of chest oppression at night. Holter ambulatory ECG recording performed in January 1999 revealed non-sustained ventricular tachycardia (max. 11 beats in a run). At 5:00 a.m. on February 21, 2001, his wife, who was sleeping beside him, noticed that he was breathing hard. He did not respond to her calls, and she immediately called for an ambulance. He was taken to Nihon University Surugadai Hospital. On initial examination, dyspnea and cyanosis were observed. His consciousness level was slightly below normal, and systolic blood pressure was about 70 mmHg. Following endotracheal intubation, artificial ventilation, and intravenous infusion of dobutamine and furosemide, the patient's consciousness improved rapidly. He was transferred to our hospital on February 27.

Dr. Ogawa: So, the clinical course of the patient's illness was as follows: The patient first presented with the clinical features of heart failure in 1993, and he was clinically diagnosed as having DCM. Despite intensive therapy, however, the heart failure became worse gradually and progressively. At one point, he was admitted with loss of consciousness to another hospital. Thereafter, he was again admitted to our Keio University Hospital for thorough examination and treatment.

Echocardiography performed in 1994 revealed end-diastolic and end-systolic left ventricular diameters of 5.9 cm and 4.4 cm, respectively, and cardiac pool scintigraphy (MUGA) revealed a left ventricular EF of about 40%. These dimensions improved slightly to 5.2 cm and 4.2 cm, respectively, in the year 1996, but they increased again in 1998 and 1999; in particular, the end-systolic diameter increased to 5.2 cm, indicating that the contractile function of the left ventricle had decreased considerably.

The patient first presented with dyspnea on exertion in March 1993. Are there data from earlier medical examinations?

Dr. Matsumura: There is one earlier mention of right axis deviation on ECG; however, no other ECG changes were recorded. The patient was apparently in good health in 1982, when he was involved in a traffic accident in the State of Kuwait and underwent surgery on his right lung. Subsequently, he developed slight dyspnea on exertion. The symptom worsened rapidly in 1993, and he was referred to our hospital.

Dr. Ogawa: As for the 11 beat run of non-sustained ventricular tachycardia revealed by the Holter ECG in 1999, was his morbid condition relatively stable during the period when the tachycardia was observed? Or was the non-sustained ventricular tachycardia associated with worsening of his heart failure?

Dr. Matsumura: In 1993, his symptoms of heart failure were relatively mild, classified as New York Heart Association (NYHA) functional class II. A little later, he presented with worsening of the heart failure due to a common cold, and he was admitted to our hospital. On admission, the NYHA functional class found to have worsened from Class II to Class III. When this improved again to Class II (IIM), he was discharged from our hospital. The symptoms thereafter gradually worsened again, and runs of non-sustained ventricular tachycardia were observed on the Holter ECG recording associated with worsening of the heart failure.

Dr. Ogawa: Was the treatment of the tachycardia detected by Holter ECG undertaken on an outpatient basis?

Dr. Matsumura: Yes, it was.

Dr. Ogawa: If so, can we understand that the Holter monitoring was not performed specifically during the period when his heart failure had become worse?

Dr. Matsumura: Yes, we can. Holter ECG monitoring was performed routinely and was not related to the worsening of his heart failure.

Dr. Ogawa: We can therefore say that the non-sustained ventricular tachycardia was incidentally detected.

The patient's chief compliant seems to have been consciousness disturbance; when his wife, who was lying beside him in bed, called out to him at 5:00 a.m. in the morning, she noticed that he did not respond. Is that right?

Dr. Matsumura: Yes, it is.

Dr. Ogawa: I wonder if the ambulance personnel detected any abnormalities in his vital signs that could be responsible for the consciousness disturbance on that occasion? Is there any record?

Dr. Matsumura: His consciousness level was slightly below normal, but it was apparently returning to normal when he was taken into the ambulance. The ECG recorded then also did not show any ventricular tachycardia or ventricular fibrillation. The possibility of low cardiac output due to DCM, or transient arrhythmias, such as spontaneously converted ventricular tachycardia that terminated spontaneously having caused the syncope, cannot, however, be ruled out.

Dr. Ogawa: How was the control of his coagulation parameters with the dose of Warfarin® during this period? Was he taking an appropriate dose of Warfarin®?

Dr. Matsumura: The thrombotest was supported to 10–20%, which suggests favorable control by the Warfarin®. Nor did echocardiography show any evidence of intracardiac thrombus during his course. This echocardiographic finding, together with the appropriate control by Warfarin®, indicate that it is unlikely that cerebral embolism may have been responsible for this syncopal episode. A brain CT was not conducted because the patient was in poor general condition.

Table 1 Vital Signs and Acute Clinical Settings

	Consciousness	Breathing	Pulsation
Normal	+	+	+
Peripheral Artery Occlusion	+	+	−
Coma	−	+	+
Apnea	−	−	+
Choke	±	−	+
Shock	±	+	±
Cardiac Arrest	−	−	−

Dr. Ogawa: What do you think of this case, Dr. Mitamura?

Dr. Mitamura (The Suntory Fund for Advanced Cardiac Therapeutics): I would like to make a few points. As for the labored breathing and absence of response to verbal commands, I doubt whether we can refer to the patient's state here as ''syncope''. When we use the term ''syncope'', it usually refers to a condition of complete muscular weakness associated with unconsciousness; labored breathing therefore is not characteristic of syncope. Syncope in this sense generally results from a transient and steep fall of blood pressure. It is also important to know how long the labored breathing was sustained in the patient. To sum up, rather than suffering from an episode of ''syncope,'' this patient was probably taken to the hospital in a so-called state of shock with sustained moderate hypotension, or the main cause of the patient's condition may have been dysfunction of the central nervous system (Table 1).

The following possibilities should be considered in this circumstance, other than DCM: (1) The possibility of ventricular tachycardia having spontaneously terminated when the patient was taken to the hospital should be considered as the most likely; (2) and, despite the favorable control of warfarinization, there is still the possibility of cerebral infarction having occurred due to a cerebral embolism derived from an intraventricular thrombus because of poor left ventricular function; (3) there is also the probability of cerebral hemorrhage having occurred due to an excess dose of Warfarin®; (4) the possibility of hemorrhagic shock having been caused by gastrointestinal hemorrhage or hemorrhage from other sites; and (5) the possibility of pulmonary embolism, in which condition the blood pressure of patients with very poor cardiac function who are bedridden over a long period of time, suddenly declines.

Dr. Ogawa: Thank you very much. How about his family history?

Dr. Matsumura: The patient's younger brother was diagnosed as having DCM at the age of 45 years.

Dr. Tsuji (5th-year medical student): Could the history of pulmonary contusion on the right side in 1982 be related to the slight decrease in respiratory sound on the right side?

Dr. Matsumura: As is evident from the chest X-rays, the patient had developed thoracic deformity and collapse of the right lung consequent to the pulmonary contusion. This is probably the cause for the muted respiratory sound on the right side.

Dr. Ogawa: What was the nature of this pulmonary injury? Could you explain it in greater detail?

Dr. Matsumura: When he was driving, his car collided head-on with another car. At that time, two other people who were in the car with him died instantly, so the accident was apparently a major traffic accident.

Dr. Ogawa: I wonder how we can correlate his morbid condition, DCM, with the accident. For instance, it has been reported that myocardial injury of the right ventricle or tricuspid regurgitation can occur following steering wheel injury. The patient, however, had not been detected as having any significant physical abnormalities in medical check-ups undertaken subsequent to the accident. Am I right?

Dr. Matsumura: Yes, that's right.

Dr. Ogawa: There is no history to suggest that the patient was a habitual drinker. The presence of a drinking history is very important in making a differential diagnosis. Now, will you please describe the patient's clinical condition on admission to our hospital?

Dr. Matsumura: The blood pressure was 110/80 mmHg, and the pulse was 100 beats per minute. The respiratory rate was 26 per minute. He was fully conscious. The external jugular vein was distended. In regard to the heart sounds, P2 was loud, and 3rd and 4th heart sounds were audible. A systolic murmur could be heard between the cardiac apex and the 4th intercostal space at the left margin of the sternum. Breath sounds were decreased on the right side of the chest, and there were no added sounds. The liver was palpable by 3 QFB and there was some tenderness below the right costal margin. There was no pretibial edema.

Laboratory examination revealed normocytic normochromic anemia and increase in the serum levels of fibrinogen and fibrin degradation products. The BUN and CRTNN levels were elevated, which was considered to be related to the administration of diuretics. The serum UA and K levels were also elevated; the serum K was 5.6 mEq/L. Furthermore, the serum levels of LDH, GOT, and GPT were elevated. Serum CPK was slightly increased. Serum CRP was increased to 4.56 mg/dL. Thyroid functions were normal. The serum concentration of digoxin was slightly high. BNP was revealed to be considerably elevated to 5,410.8 pg/mL.

Dr. Ogawa: Will you please explain the reason for the distended jugular vein observed in this patient on admission?

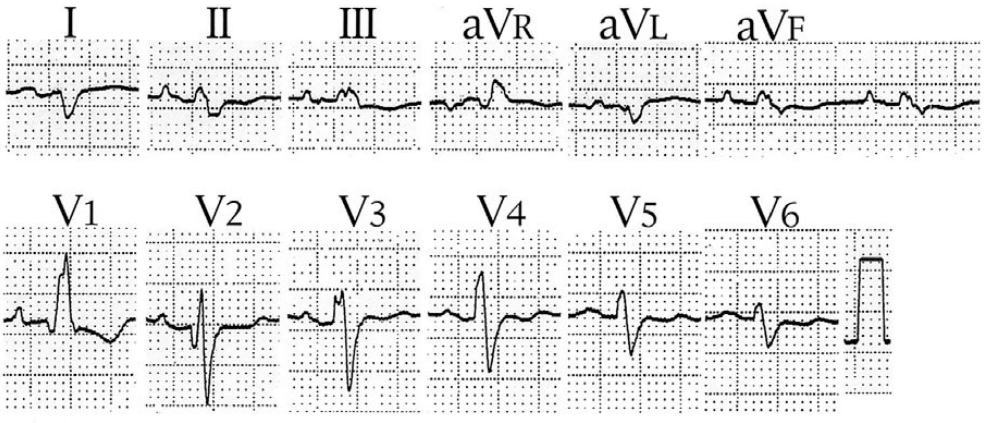


Fig. 1 The electrocardiogram has apositive P wave in lead II, and shows a normal sinus rhythm at the rate 60 beats per minute. Although the amplitude of P wave in leads II and III was not high enough to meet the criteria for right atrial overload, peaking of the first half of the P wave in lead VI may be a reflection of the overload of the right atrium. The PQ interval was within the normal range. The right axis deviation and clockwise rotation of the QRS complex may be due to right ventricular overload. The width of the QRS complex was 168 msec, and the rS pattern in V6 with a wide S wave suggests complete right bundle branch block (CRBBB); however, the QRS complex in V1 was not an typical CRBBB rsR pattern. There was an abnormal Q wave in V1 and V2, which raises the possibility of myocardial necrosis in the ventricular septum. Slight ST depression and biphasic T wave are seen in the left precordial leads.

Dr. Matsumura: The right jugular vein was found to be distended up to the level of the mandible, and *a* v wave was observed.

Dr. Ogawa: The marked distension of the jugular vein indicates that the filling pressure of the right cardiac system was high, doesn't it? The respiratory rate was also increased. How about the cardiac murmur?

Dr. Matsumura: The murmur was pansystolic. Echocardiography suggested the presence of mitral regurgitation (MR) and tricuspid regurgitation (TR), and the murmur was considered to be associated with these regurgitations.

Dr. Ogawa: Do you mean that the signs of right heart failure were rather significant?

Dr. Matsumura: Yes, that's right.

Dr. Ogawa: Will you please present the results of arterial blood gas analysis?

Dr. Matsumura: Under nasal administaration of 2 L/Min oxygen, the pH was 7.44; Pco_2, 31.4 Torr; Po_2, 144.4 Torr; HCO_3^-, 24.5 mEq/L; BE 1.5, mEq/L; and the Sao_2, 99.4%. These findings are suggestive of compensated respiratory alkalosis from hyperventilation.

Dr. Ogawa: How can we correlate the findings of the morbid condition reported in this conference with the ECG findings? What is your opinion, Dr. Mitamura? (Fig. 1)

Dr. Mitamura: The ECG fundamentally revealed a sinus rhythm. An occasional ventricular extrasystole was observed in the limb leads.

As to the P wave, the negative portion of P wave in lead V1 did not seem to be so clear. There seemed to be some peaking of the first half of the P wave, suggestive of right atrial overload.

The PQ interval was almost within the normal range. The QRS axis deviated to the right, and as stated earlier, the right axis deviation may be reflective of right ventricular overload. However, the axis might be influenced by a right bundle branch block. The first component in leads V1 and V2 in cases of right bundle branch block is essentially an upright r, but in this case there was a negative deflection, a ''q'' wave, in these leads. This matter weighs on my mind. The presence of the ''q'' wave in these two leads may suggest the possibility of myocardial necrosis in the ventricular septum. Mild non specific ST-T changes were observed in the chest leads.

The patient had a thoracic deformity, and there is the possibility that this also influenced the ECG changes. It would therefore seem difficult to make a definitive diagnosis based on the ECG findings alone in this patient.

Dr. Ogawa: The presence of abnormal ''q'' waves in leads V1 and V2 in a case with right bundle branch block should raise the possibility of cardiac sarcoidosis, which selectively damages the interventricular septum.

Dr. Matsumura: A chest X-ray taken in the year 2000, when the patient was being followed up as an outpatient, is shown here. There is thoracic deformity and collapse of the right lung, which are probably consequent to the traffic accident. The mediastinum is shifted to the left. There is no obvious evidence of pulmonary venous congestion, such as the presence of Kerley's B lines. There is no evidence of pulmonary venous re-distribution to the upper lung fields. The tracheal bifurcation angle is approximately 90°, which suggests the presence of left atrial dilatation.

In the lateral view, narrowing of the retrosternal space is observed, which suggests the presence of right

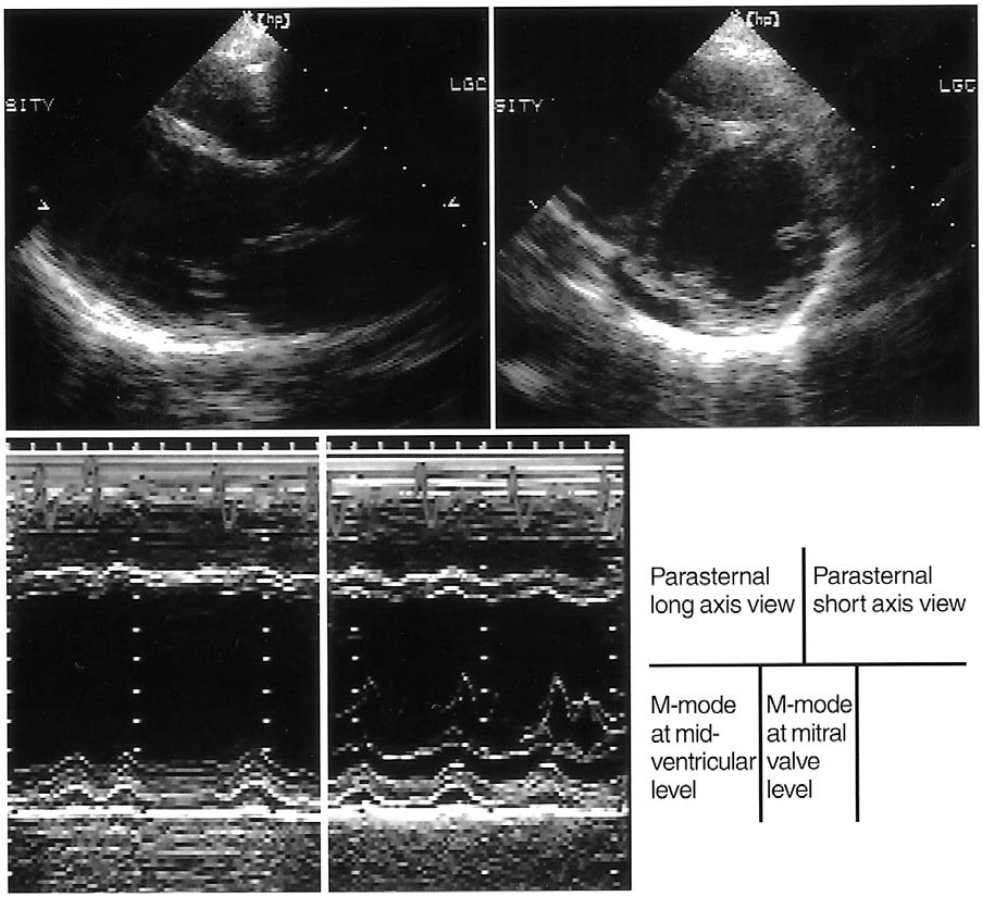


Fig. 2 The echocardiography was performed on March 28, 2001. Parasternal long axis view on the left upper panel shows dilation of the left and right ventricles. Thinning of the left ventricular wall and a small amount of pericardial effusion are also observed on the right upper panel, the parasternal short axis view. The two lower panels are M-mode traces at the mid-ventricular level (left) and mitral valve (right). Both traces revealed reduced excursion and thinning of the left ventricular wall. The calculated ejection fraction of the left ventricle was 23% by the method of Pombo, suggesting marked reduction of left ventricular systolic function. B-B′ step of mitral valve on the right lower panel suggests the elevation of left ventricular end-diastolic pressure.

ventricular dilatation. Dilatation of the left ventricle is also suspected from the point of intersection between the diaphragm and the inferior vena cava. The costophrenic angles are sharp, and there is no evidence of pleural effusion.

This X-ray taken on admission to our hospital shows opacity of the right lung field. The cardiothoracic ratio (CTR) is slightly high, and no Kerley's B lines are evident. These findings suggest that there was no significant pulmonary venous congestion. There is no evidence of pleural effusion. There is also evidence suggestive of dilatation of the left atrium and right ventricle.

Dr. Ogawa: The left ventricular function was significantly compromised in this patient, but findings of right heart failure were more remarkable on admission. There was no evidence of pulmonary congestion, either clinically or on chest X-ray. Will you present the echocardiographic findings in this patient and explain his heart condition as evaluated by this investigation, Dr. Iwanaga? (Fig. 2)

Dr. Iwanaga (Laboratory Medicine): This videotape shows the echocardiographic findings of this patient obtained on March 28. The parasternal long-axis view shows the right and left ventricles, left atrium, aorta, mitral valve, and the aortic valve. The short-axis view shows the right atrium and right ventricle. We can see a Swan-Ganz catheter inserted. At the level of the papillary muscle, the interventricular septum is slightly hyperechoic, which shows little or no wall motion. The motion of the posterior wall is also poor, and the left ventricle is dilated. As for the valves, moderate to severe MR is observed. The aortic valve shows atherosclerotic degeneration. The most significant findings are the dilated left ventricle and the poor contraction of the interventricular septum and posterior wall. The mitral regurgitation may be due to dilatation of the left ventricle and the mitral annulus. The left ventricular

diameter as measured by M-mode was 6 cm and 5.5 cm at end-diastole and end-systole, respectively, which reflects significant dilatation. A small amount of pericardial effusion is also observed.

The apical four-chamber view shows that the contraction of the interventricular septum is even worse than that of the free wall, even though there is significant thinning of the free wall. The left atrium is dilated. Wall motion of the free wall is relatively sustained, but, on the whole, left ventricular contractile dysfunction is diffuse. Based on these echocardiographic findings, the diagnosis of DCM is suspected. One problem, however, is localization of the wall thinning; the thinning is distributed in the areas supplied by the right coronary and left anterior descending arteries. Marked fibrosis is evident in these areas. It is impossible to completely rule out left ventricular contractile dysfunction due to ischemic heart disease from this finding.

Dr. Ogawa: What do you think of the possibility of cardiac sarcoidosis in this case?

Dr. Iwanaga: In cardiac sarcoidosis, a relatively localized contractile dysfunction of the left ventricle is observed, and wall motion remains relatively normal in other areas. Reports of diffuse hypokinesis of the left ventricle, as observed in the present case, are limited. A color Doppler image of the apical four chamber view is shown. Severe TR is evident from this image.

Dr. Ogawa: Is there any evidence of an organic legion in the tricuspid valve?

Dr. Iwanaga: The TR could be related to the presence of the Swan-Ganz catheter through the tricuspid valve and annular dilatation consequent to dilatation of the right ventricle. The patient had only mild pulmonary hypertension; the pulmonary arterial pressure was estimated to be 31/21 mmHg. This is reflective of postcapillary pulmonary hypertension due to left heart failure.

From the echocardiographic findings, DCM may be suspected as the first differential diagnosis, and in the present case, it was presumably severe and associated with hemodynamic decompensation. However, in the presence of thinning of the ventricular wall in the areas of the right coronary artery and left anterior descending artery, it is difficult to rule out so-called ischemic cardiomyopathy.

Dr. Ogawa: When DCM is suspected, primary DCM should be differentiated from secondary DCM. The ischemic DCM just mentioned by Dr. Iwanaga cannot be ruled out, either. While cardiac sarcoidosis may be kept in mind, the possibility is rather remote, because in this case, not only the interventricular septum, in which lesions usually develop, but also the free wall of the left ventricular myocardium, showed significant diffuse damage. The presence of a positive family history also points more towards the possibility of primary or hereditary DCM.

Now, Dr. Matsumura, could you please outline the treatment initiated in this case?

Dr. Matsumura: In 1993, when the patient was first admitted to our hospital, treatment with digitalis, Warfarin®, an ACE inhibitor, and furosemide was started. Thereafter, the patient was followed up on outpatient basis. Sometime in mid 1997, the patient was readmitted with symptoms of a common cold and worsening of his heart failure. On that occasion, administration of a β-blocker was initiated, and when the patient showed improvement, he was discharged. However, with the continuation of the β-blocker, the symptoms of heart failure, including leg edema and dyspnea on exertion (DOE), gradually became worse, and administration of the β-blocker was discontinued.

Subsequently, when the patient was admitted once again with worsening of heart failure, administration of Acardi® (pimobendan), a phosphodiesterase (PDE) inhibitor that also enhances the calcium sensitivity of myocardial cells, was initiated. In addition, the dose of the diuretic was increased and spironolactone was started. The subsequent course of the patient was again monitored on outpatient basis.

Dr. Ogawa: Do you have any comments about the course of treatment undertaken so far, Dr. Yoshikawa?

Dr. Yoshikawa (Internal Medicine): The standard treatment for all cases ranging from asymptomatic left ventricular dysfunction to severe heart failure includes administration of ACE inhibitors or angiotensin type I receptor antagonists. For mild to moderate heart failure classified as NYHA functional class II or III, diuretics are usually added to the treatment regimen, and in some patients, also digitalis. Some reports have shown that the prognosis is improved by the administration of a β-blocker in such patients. Furthermore, in severe heart failure classified as NYHA functional class III or IV, further improvement of prognosis has been reported with the addition of spironolactone to the treatment regimen. Although pimobendan does not decrease the mortality rate, clinical studies in Japan have shown that the drug decreases the number of patients who are admitted to hospitals due to worsening heart failure, *i.e.*, it improves the quality of life. With regard to Warfarin®, there is limited evidence to suggest improvement in the prognosis of these patients, as there have been no large-scale studies on the treatment of heart failure with this drug.

Dr. Ogawa: How about digitalis?

Dr. Yoshikawa: Some data have shown that digitalis significantly decreases the mortality associated with worsening heart failure. The overall mortality, however, has been reported to be similar between groups receiving digitalis and placebo. The reason for this is unclear, but digitalis probably increases the incidence

of sudden death. Accordingly, there has been a gradual tendency towards reduced usage of this drug.

Dr. Ogawa: Dr. Matsumura, could you please describe the course of this patient after admission?

Dr. Matsumura: The blood pressure on admission was 118/75 mmHg, and frequent non sustained ventricular tachycardia were observed. With a Swan-Ganz catheter, the pulmonary arterial pressure was determined to be 43/33 mmHg; the right atrial pressure, 19 mmHg; the cardiac index, 1.1 L/min/m^2 BSA; and the cardiac output, 1.8 L/min. Thus, all of these values were abnormal, and the pulmonary arterial oxygen saturation was markedly decreased to 33%. Intravenous injections of furosemide and continuous infusion of dobutamine, which had been initiated for the treatment of heart failure at the Nihon University Hospital, were continued. Administration of amiodarone for the treatment of ventricular tachycardia, and also of Adehl®, (colforsin daropate hydrochloride) as an inotropic agent, was started. The hemodynamic status improved slightly, the cardiac index and right atrial pressure improving to 1.4 and 16, respectively, however, oliguria and gradual deterioration of renal function were observed.

On March 9, elevation of the BUN/Cr and K levels to 93.5/6.0 and 6.0, respectively, were observed, and continuous hemodiafiltration (CHDF) was initiated. With the start of CHDF, the serum Cr and K levels decreased gradually to 2.7 and 3.9, respectively, while the heart rate started increasing.

With stabilization of the serum Cr and K levels, CHDF was temporarily discontinued on March 27. However, the patient could not be indefinitely sustained without CHDF, and the procedure was started again on March 31. Wide QRS tachycardia began to be observed on this day, and severe hepatic dysfunction was noted on April 3. Hemodialysis (HD) was started to wean the patient from CHDF, performed once every two days, and the course of the patient was carefully monitored. The wide QRS tachycardia and severe hepatic dysfunction improved slightly, but the patient's general condition continued to deteriorate. On April 14, elevation of the central venous pressure, deterioration of renal function, and decreased consciousness level were observed, and CHDF was started again.

The consciousness disturbance deteriorated on April 15. On April 17, in deference to the family's wishes, CHDF was discontinued. On the evening of the 18th, the patient started gasping, and developed respiratory arrest at 18:20 p.m. Thereafter, cardiac arrest occurred at 18:30 p.m., and the patient was declared dead.

Dr. Ogawa: The patient, who had DCM, was referred to our hospital with consciousness disturbance. He had severe cardiac dysfunction. How should the data collected with the Swan-Ganz catheter be interpreted?

Dr. Matsumura: According to Forrester's classification of hemodynamic disturbance in acute myocardial infarction, heart failure is classified as group IV. In this category of patients, not only diuretics, but also an inotropic agents are considered to be indicated.

Dr. Ogawa: Could you please explain the changes in the ANP and BNP data in relation to the severity of the heart failure?

Dr. Matsumura: The serum level of BNP was 2,356 in 1997, which decreased in subsequent examinations to 1,557 and 1,217. The level of ANP was 100 to 700, showing no remarkable changes thereafter. On admission, the BNP level was significantly elevated to 5,410, consistent with deterioration of the heart failure. BNP, which is a protein discovered from swine brain, is reported to be secreted mainly from the ventricular cardiomyocytes in humans. The normal serum BNP level is 15 or less, and the levels are elevated in heart failure. Our patient showed markedly elevated levels of BNP.

Dr. Ogawa: Initially, I thought that the present admission may have been directly related to the ventricular arrhythmia. However, judging from the course, the cardiac failure also seems to have worsened considerably, and there is the possibility that the nonsustained ventricular tachycardia was related to the worsening of the cardiac function. Am I right?

Dr. Matsumura: Yes, Sir.

Dr. Ogawa: What about other possibilities for the ventricular tachycardia, such as its being a possible proarrhythmic effect of one of the drugs used?

Dr. Matsumura: The possibility of pimobendan, an inotropic agent, having triggered the ventricular tachycardia cannot be ruled out.

Dr. Ogawa: What was the blood level of digoxin?

Dr. Matsumura: It was slightly elevated to 2.2. The echocardiographic findings showed that the size of the left ventricle was almost unchanged, but the short-axis view revealed deterioration of wall motion and thinning of the wall. These observations suggest the possibility that the frequent runs of ventricular tachycardia were triggered by increasing severity of the cardiomyopathy itself.

Dr. Ogawa: Cardiomyopathy itself in this case had progressed considerably, and such progression secondarily induced frequent episodes of tachycardia. This also may have contributed to the worsening of the morbid condition of the patient.

As a last issue regarding the clinical course of the patient, the serum Cr level in the patient on admission was 2.6. Thereafter, the renal function deteriorated rapidly, necessitating the introduction of hemodialysis (HD). I would like to now ask Dr. Kumagai to explain the patient's overall pathological findings in relation to the changes in the renal function and CHDF.

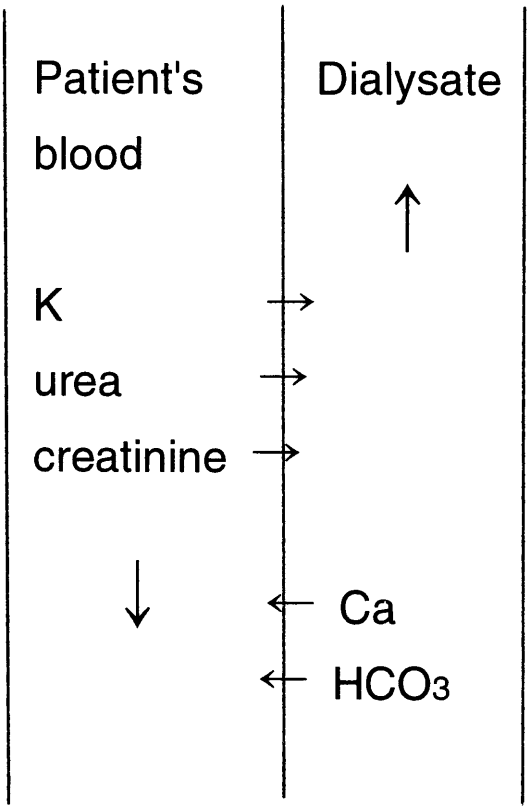


Fig. 3 The principle underlying the commonly performed hemodialysis (HD).

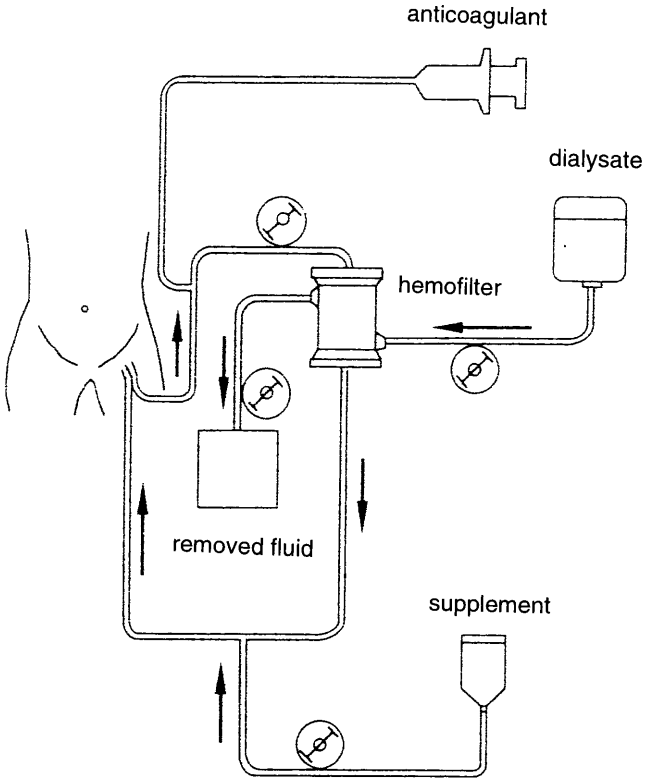


Fig. 4 A schema of continuous hemodiafiltration (CHDF). As in the commonly performed HD, the HD solution and the patient's blood are allowed to flow in reverse directions and to come in contact with each other; then a supplementary solution is added to the blood.

Dr. Kumagai (Internal Medicine): On admission, serum Cr level of the patient was 2.6 mg/dl and BUN level was approximately 60 ml/dl, but thereafter, the renal function deteriorated gradually. The deterioration can be explained by following mechanism: renal blood flow (RBF) is one-fourth of normal cardiac output despite their small size; it is well known that the RBF becomes extremely reduced in a situation of low cardiac output.

The BUN to Cr ratio is usually somewhere between 10:1 and 20:1. Thus given for a serum Cr level of 2.6, the corresponding BUN level should have been 30 to 40, whereas it was actually 60 in this patient. To explain this discrepancy, it is important to consider this patient's use of a diuretic (furosemide, Lasix®). Diuretics cause dehydration and vasopressin release, which makes water reabsorption at the collecting ducts of the kidneys. Vasopressin causes the reabsorption of urea from the tubules. On the other hand, Cr is filtered only at the glomeruli and is not reabsorbed in the renal tubules. Therefore, even though vasopressin is released, blood level of Cr does not increase. Since only urea is reabsorbed, the urea nitrogen level is relatively increased as compared with serum Cr level when a diuretic is used for the resolution of pulmonary congestion and in the presence of dehydration.

Although the cardiac function improved somewhat due to the use of furosemide, the cardiac index still did not reach 2, and the patient's renal function continued to deteriorate, and eventually CHDF became necessary.

In the conventional hemodialysis (HD) shown Fig. 3, the patient's blood and HD solution are allowed to flow as counter currents, and the excess K, urea, Cr, and water in the patient's blood are removed from the patient's blood into the HD solution. Conversely, substances that are beneficial for the patient (calcium, bicarbonate ion), which are contained in the HD solution, enter the patient's blood.

In CHDF, shown in Fig. 4, the mechanism is basically the same as in HD, but since it is a continuous system, the load on the patient's cardiovascular system is comparatively lighter. HD is impossible in the presence of a low cardiac output associated with hypotension, as in this patient. That is the reason why we chose the CHDF for this patient.

The two merits of CHDF are shown in Table 2. (1) the load on the cardiovascular system is lighter as compared to that during HD and hypotension is less common in CHDF. In the healthy humans, approximately 3

Table 2 Merits and Significance of CHDF

1. It imposes only a slight load on the cardiovascular system and scarcely causes a decrease in blood pressure.
   HD: 3 L of fluid is forced to be removed (volume normally removed over 2 days) in 4 hours. Electrolytes, such as Na, K are rapidly eliminated. Even though the molecular weight of these substances is low, a unit of osmotic pressure is decreased by elimination of one molecule. Consequently, with the decrease in the osmotic pressure, the blood pressure may decrease. This potential decline is not compensated for in HD.
   Normal kidneys: A volume of 3 L is removed in 2 days.
   CHDF: The volume of 3 L can be removed in 2 days. When one molecule is eliminated, the a unit of osmotic pressure is decreased; however, this decrease is compensated for in CHDF.
2. Substances with molecular weights of 1,000–15,000, which cannot be eliminated by HD, can be eliminated by CHDF.

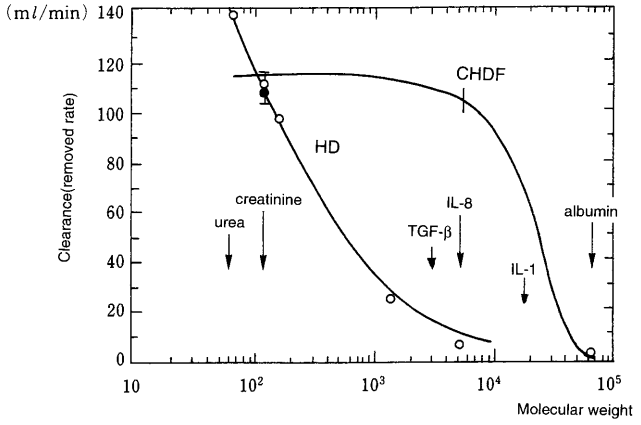


Fig. 5 Relationships between the molecular weights of substances eliminated by HD and CHDF and the elimination rates (clearance). Substances with molecular weights of 1,000 to 10,000 (e.g., TGFβ and IL-8) show a high clearance with CHDF.

L of urine are excreted from the capillaries of the renal glomeruli in 2 days. The same excretion can be obtained by CHDF. In contrast, in HD, 3 L of water are removed within 4 hours. (2) CHDF can remove substances with molecular weights between 1,000 and 15,000, which cannot be removed by HD. Cytokines and some growth factors are involved in the development of heart failure. As shown Fig. 5, the curve running steeply from the upper left side to the lower right side illustrates how substances are removed during HD, and the less steep curve alongside it on the right illustrates how substances are removed during CHDF. The molecular weights of the substances are plotted along the horizontal axis, and the volume (clearance) of the substances removed from the patient's blood is plotted along the longitudinal axis. Substances, such as urea, Cr and uric acid, of which molecular weights are 100 to 1,000, are removed efficiently by HD.

However, the substances of which molecular weights are 1,000 to 10,000 or 15,000, such as TGF-β, IL-8, and IL-1, cannot be removed by HD and can be by CHDF. Since these substances may be involved in the exacerbation of heart failure, removal of these substances by CHDF is desirable.

On the other hand, CHDF has some demerits; patients are connected to devices with tubes all day long, because it is a continuous process. This is a big disadvantage for patients. Usually, the procedure is performed over 24 hours a day for about 3 days, and when a significant improvement is observed, it is discontinued for the subsequent 2 days. CHDF can also be switched to the conventional HD (conducted for 4–5 hours every other day or every day). In the present patient, however, CHDF was successful; since the cardiac index increased slightly, and the pulmonary arterial wedge pressure decreased. The physician-in-charge wanted for CHDF to be continued. Throughout the treatment, the highly intelligent patient was conscious and alert. He and his wife hoped that the CHDF be continued for longer. Under these circumstances, CHDF was continued for subsequent 20 days, with only a few interruptions, although such long-term continuation of this procedure is quite exceptional.

Since the patient is connected to tubes and devices and the anticoagulant (heparin) is used during CHDF, the risk of hemorrhage should be always borne in mind. Therefore, the patient's condition has to be closely monitored. It is usually difficult to continue CHDF for a long term, but it was continued in this patient because he was extremely cooperative.

Dr. Ogawa: Heart failure is always associated with various degrees of renal dysfunction. While this new treatment was temporarily efficient, it could not influence the deterioration in cardiac function or improve the low cardiac output.

Dr. Sato, could you please comment on assisted circulation as a possible method of treatment, and also other novel methods of treatment for heart failure?

Dr. Satoh (Internal Medicine): We had administered almost all the drugs available for the treatment of heart failure, including CHDF. We had planned to make the patient register for a heart transplantation and wait for donors when his condition had improved a little more.

Dr. Ogawa: As for registration for heart transplantation, would this patient have met the criteria for such registration? What are the current criteria for registration?

Dr. Yoshikawa: There are various criteria: *e.g.*, it is recommended that the patient be younger than 60 years old, that the patient be on a β-blocker, that the pulmonary vascular resistance be less than 6 wood unit, and that there be no serious infectious diseases, such as human immunodeficiency virus infection.

Anyway, our patient had severe heart failure, with a serum BNP level of 5,000 pg/mL, and he would have been a good candidate for heart transplantation from the point of view of his age as well. We were discussing whether or not to apply for cardiac transplantation, but it turned out to be too late. If such a patient had been admitted to the institute where transplantation is actively carried out, he might have had a left ventricular assist device (LVAD) implanted and been ranked as status I in the transplantation registry, which means an urgent condition.

As a matter of fact, heart transplantation has been performed so far in 10 cases in Japan. Approximately 168 patients in total have applied to the Japanese Circulation Society transplantation sub committee, as of March 2001. Approximately 30 patients have died during the waiting period for elective transplantation. Eighty percent of these had DCM. Such patients can thus die without LVAD even while waiting for transplantation. In all, about 50% die in a year, and approximately 80% survive even in the presence of LVAD.

Anyway, the most serious problem is that there are very few organ donors available. Only a limited patients who undergo transplantation find themselves in the media spotlight. In reality, most patients die while waiting for transplantation.

Dr. Ogawa: As just mentioned, there are many patients with severe refractory heart failure, who die while waiting for cardiac transplantation. Our present patient might also have been a candidate for another form of non-drug therapy, *i.e.*, biventricular pacing. In this recently introduced treatment for heart failure, improvement of the cardiac function is sought by narrowing the QRS interval by pacing from both the right and left ventricles with a pacemaker, particularly in patients with a very wide QRS interval seen on ECG. What do you feel, Dr. Mitamura?

Dr. Mitamura: The method that Dr. Ogawa just referred to is called re-synchronization therapy; a lag of synchronism between the left and right ventricles induces abnormal motion of the interventricular septum; when the left ventricle contracts, for example, the interventricular septum protrudes into the right ventricle. To avoid this, innovations, such as simultaneous excitation and contraction of the right and left ventricles with a pacemaker have been introduced.

However, the present patient had a right bundle branch block, so his right ventricle in any event probably contracted later than his left ventricle. So, while there is the possibility that he would have felt slight relief with pacing of the right ventricle, the probability of improvement of his cardiac status is indeed rather limited, even if left ventricular pacing had been performed with a pacemaker introduced into the coronary sinus.

Table 3 Autopsy Finding

1. Dilated cardiomyopathy
   - A. Dilatation of the bilateral ventricles, severe
     Endocardial fibroelastosis
     Diffuse fibrosis in the left ventricle
   - B. Fibrinous fibroelastosis
   - C. Congestion of the lung
   - D. Congestion of the liver
   - E. Pleural effusion (left, 850 ml)
     + Ascites (290 ml)
2. Rectal cancer
   - A. Moderately differentiated adenocarcinoma, mp, ly0, v1, INFγ
   - B. No invasion or metastasis
3. Acute pancreatitis, severe

Dr. Ogawa: In regard to the differential diagnosis, the pathological study would ultimately determine whether the DCM in this patient was primary or secondary. However, the possibility of primary hereditary cardiomyopathy was clinically considered to be high. Dr. Umezawa, could you please describe the findings in this patient at autopsy.

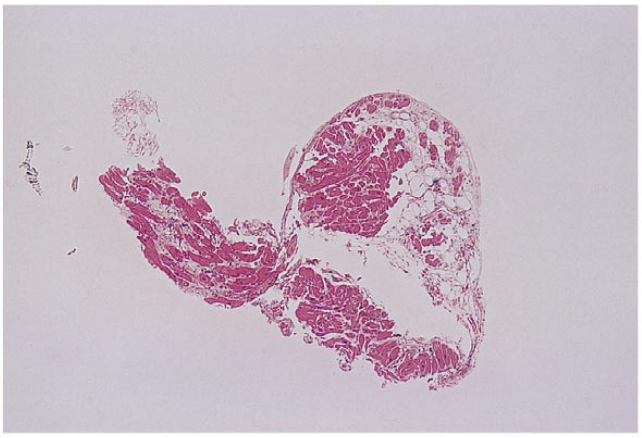
Dr. Umezawa (Pathology): I shall now describe the biopsy and autopsy findings in this patient (Table 3).

This is a heart biopsy slide prepared in April 1993 (Fig. 6). The myocardium is slightly hypertrophic and characterized by the presence of abundant collagen fibrils in the intermyocardial interstitial tissue. Thus, there was myocardial hypertrophy with interstitial fibrosis.

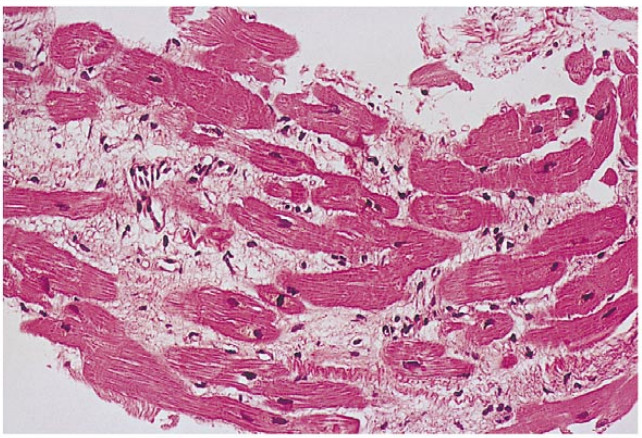
The heart weighed 450 g, which represented an increase over the normal heart weight of 300 g. Marked dilatation of both the ventricles was observed (Fig. 7). The left ventricular wall was 0.9 cm thick (normal at autopsy, 1.5 cm). Thus, there was considerable thinning of the ventricular wall. The right ventricular wall was 0.3 cm thick (normal, 0.3–0.4 cm at autopsy). Therefore, the right ventricle showed slight thinning. There was also fibrinous pericarditis and endocardial fibroelastosis.

Histologically, (1) there were no inflammatory changes, (2) there was no evidence of any granuloma suggestive of cardiac sarcoidosis, and (3) diffuse myocardial fibrosis was present (Fig. 8A, B).

Mallory's staining was conducted to show the proportions of the myocardial fibers and collagen fibrils (Fig. 8C, D). The myocardial fibers were stained red and the collagen fibrils blue by the stain. The myocardial fibers were very coarse, and the collagen fibrils filled the spaces between the myocardial fibers. Poor contractility of the wall observed by echocardiography was supported by the histological findings – myocardial fibers which are essential for contraction of the muscle were replaced by collagen fibrils, which explained the hypokinesia of the myocardial wall observed clinically.



A



B

Fig. 6 Histological findings of the heart biopsy specimen. H.E. staining. Original magnification, A. ×40. B. ×200.

Vacuolar degeneration around the nuclei and the disappearance of the violet color reflecting myocardial degeneration and deficit are shown by PTAH staining (Fig. 8E). The myocardial fibers disappeared singly, and not in bundles, while fibers replaced by collagen fibrils showed hyperplasia. There was no complicated arrangement. The deficit and hypertrophy of the myocardial fibers were marked. Based on these findings, the patient's condition was diagnosed as DCM.

In addition, the lungs were edematous and severe hepatic congestion was observed; 850 ml of pleural fluid was found on the left side and 0 ml on the right side. In the right lung, complete adhesion of the parietal pleura and visceral pleura, which was probably consequent to the traffic accident, was observed.

A second remarkable finding was the presence of advanced cancer of the rectum. Since this was detected at autopsy, it was a latent carcinoma. It was a moderately differentiated adenocarcinoma, which had infiltrated up to the tunica muscularis propria. Slight venous invasion was observed. There was no infiltration to the bladder or other organs and no metastasis to other organs. Therefore, there was presumably no causal relationship between the rectal cancer and the patient's fatal course.

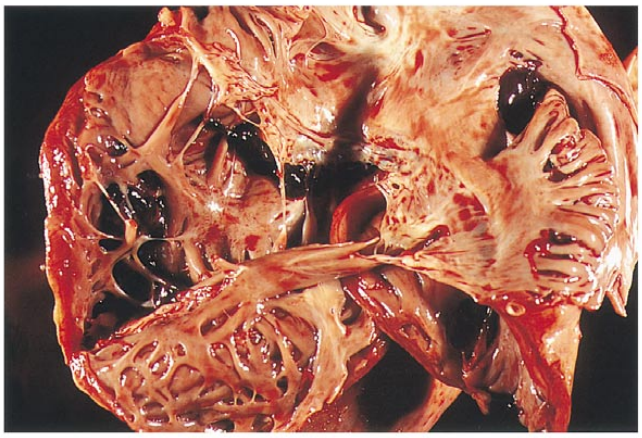


Fig. 7 Severe dilation of the right ventricle.

Dr. Yoshikawa: I got the impression that the histologically observed fibrosis was prominent, considering that this was a case of DCM. The tissue sample may have been collected from the site of fibrosis around the interventricular septum, which showed poor contraction echocardiographically. Administration of a β-blocker was attempted in this patient, but the heart failure deteriorated. Such patients often show severe interstitial fibrosis on histological examination. It is therefore noteworthy that DCM patients who have not respond satisfactorily to a β-blocker have also showed severe interstitial fibrosis on histology.

A β-blocker along with an ACE inhibitor is recommended prior to considering cardiac transplantation. Efforts were made with this patient, but introduction of the drug in this case was not successful. It is important to note that patients who do not tolerate β-blockers have a very poor prognosis.

Dr. Ogawa: This patient had mainly left heart failure, of course, but right heart failure was also a prominent clinical feature. In many cases with general DCM, the left cardiac system is mainly affected, and secondary pulmonary hypertension causes right heart failure. In this patient, however, the biopsy and autopsy findings revealed that the changes in the right ventricle were almost as marked as those in the left ventricle.

Dr. Umezawa: In this patient, fibrosis of the right ventricular wall was diffuse and severe. The dilatation of the right ventricle was slightly greater than that of the left ventricle.

Dr. Ogawa: This patient's condition was familial. Dr. Yoshikawa, could you please explain the characteristics of hereditary cardiomyopathy? One more thing I want

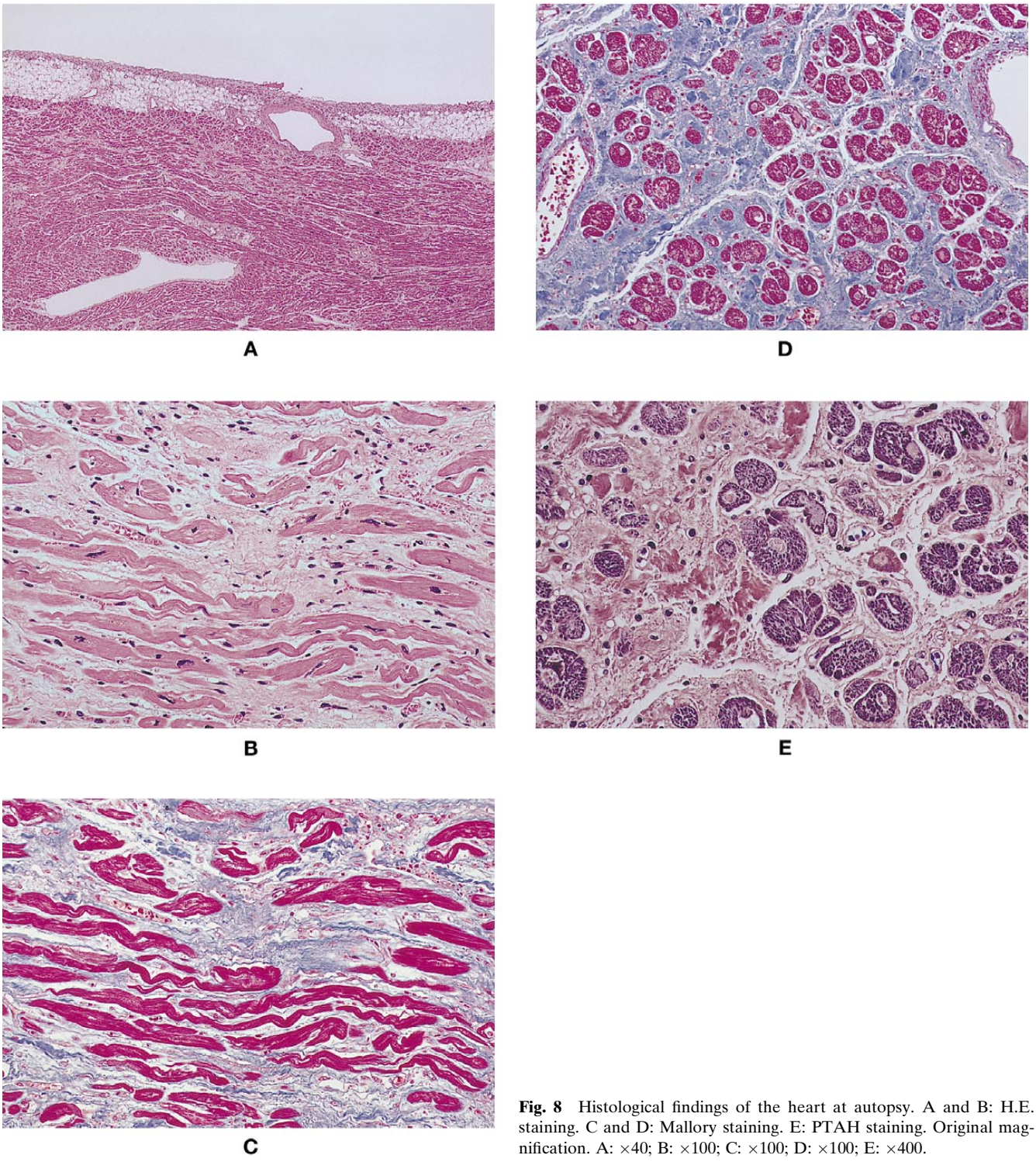


Fig. 8 Histological findings of the heart at autopsy. A and B: H.E. staining. C and D: Mallory staining. E: PTAH staining. Original magnification. A: ×40; B: ×100; C: ×100; D: ×100; E: ×400.

to ask is whether there is any basis for considering DCM as an autoimmune disease. It is possible that both the right and left ventricles are affected when autoantibodies directed against the myocardium are present.

Dr. Yoshikawa: No specific description has been made in terms of the clinical features of hereditary DCM. Many cases of hereditary hypertrophic cardiomyopathy have been reported, with a variety of gene mutations. As for the genetic mechanism responsible for the development of DCM, however, only a limited number of cases have been reported. Several proteins which support the contractile elements, including titin, are responsible for the development of DCM.

Basically, autoimmune cardiomyopathy in animal experiments shows the following pattern: the right ventricle is dilated and cardiomyopathy mimicking arrhythmogenic right ventricular cardiomyopathy (ARVC) develops. It remains unknown whether or not autoimmunity was involved in the present patient, but it would have been of interest to study this aspect.

Dr. Umezawa: There was no morphological evidence of viral infection. I wonder whether viruses are related to autoimmunity.

Dr. Yoshikawa: It has generally been considered that viral infection causes acute myocarditis, in which cellular immune mechanisms are activated. When the cellular membrane becomes disrupted, various proteins are exposed. If some proteins are presented persistently on antigen presenting cells, some antibodies will be produced, causing chronic and persistent damage to the myocardium.

Dr. Ogawa: Could you please give your concluding comments on the case, Dr. Mitamura?

Dr. Mitamura: Of the many patients who die of heart failure, about half die a sudden death, and the remaining die of progressive heart failure. The present patient followed a fairly atypical course; the heart function was considerably poor; even as far back as in 1997, the patient had already reached the level where patients are generally expected to survive for only 1 or 2 years. Of the various treatment methods introduced recently, the use of a β-blocker was initiated in this patient, but unfortunately, it proved to be ineffective. However, pimobendan, a PDE inhibitor, also known as a calcium sensitizer, exerted some beneficial effect, and the patient himself felt significant improvement in his condition. The heart function was very poor, but it remained stable for some time. Death in cases of heart failure is frequently associated with infection, but we often encounter patients, like the present patient, in whom death occurs as a consequence of rapid deterioration of renal function.

One remarkable characteristic in this patient was that the changes in the right ventricle were also marked. The arrhythmia recorded in his case could easily explained by this finding. The serum BNP level was also markedly increased. These findings suggest widespread lesions in the myocardium. The elevation of the BUN level was believed to be influenced by the use of a diuretic, and it is known to be very difficult to use diuretics in the presence of right heart failure. These patients easily slip into dehydration. This also seems to have made the treatment of this patient more difficult.

In conclusion, heart transplantation could have been considered, but my impression is that transplantation would have been a difficult proposition in this case, because his pulmonary function was also compromised as a result of his traffic accident.

Dr. Ogawa: Thank you very much for your comments.

The patient discussed in today's CPC had refractory heart failure. According to the text book, 50% of heart failure patients die within 5 years of the diagnosis. Thus, it is a very serious disease; patients usually die within 2 to 3 years, on average, after the onset of heart failure. Despite this bleak prognosis, owing to the currently available methods of treatment, our patient lived for 8 years after the diagnosis of heart failure. If heart transplantation were introduced more aggressively in clinical cases, it could be lifesaving.