Study on the Idiopathic Cardiomyopathy Diagnostic Value of the Apexcardiogram, ^{131}Cs Scintiscanning of the Heart and Plasma Hydroxyproline

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THE development of the diagnostic procedure of the idiopathic cardiomyopathy (ICM) is one of the most challenging problem in clinical cardiology. Although many authors¹ reported it's clinical features recently, diagnostic criteria is not still established and practically the diagnosis is made by excluding other known heart disease. In order to develop the diagnostic method, application of apexcardiogram, scintigram of the heart using ^{131}Cs and the measurement of plasma hydroxyproline containing collagen-like protein on the ICM have been evaluated.

SUBJECTS

Seventy patients diagnosed by careful exclusion of other known heart disease were subjected on this study, and these cases were also limited in only younger patients than 35 years old to exclude the arteriosclerotic heart disease.

Subjects were divided into 4 groups. Twenty cases from 8 families diagnosed as familial heart disease in group 1, 8 cases of hypertrophic obstructive cardiomyopathy (HOCM) in group 2, 3 cases of heart disease due to collagen disease in group 3 and 39 cases of other obscure heart disease in group 4 were studied respectively. Twenty one cases of coronary heart disease were also examined on this study to compare with ICM to the coronary heart disease. The results of examination by electrocardiogram, X-ray finding of chest and phonocardiogram (PCG) in these subjects were almost same as previously reported by other authors.

ECG revealed changes of ST segment and T

wave, abnormal Q and arrhythmia with premature contraction and disorder of conduction system. Cardiac silhouette in chest X-ray was enlarged. Systolic murmur and ventricular and atrial gallop were frequently observed in PCG.

RESULTS

Apexcardiogram (ACG)

In apexcardiogram abnormal prominent "a" wave and bulging wave in systolic and diastolic phase are studied. "A" wave ratio was calculated as "a" wave height divided by total deflection of ACG and its normal limit was within 10% as reported previously by author.

Fig.1. Various pattern of apexcardiogram with phonocardiogram.

- A: normal ACG with small "a" wave and no bulging wave,
- B: sustained type of systolic bulge,
- C: midsystolic bulge,
- D: prominent "a" wave with late systolic bulge,
- E: diastolic bulge.

Key Words: Idiopathic Cardiomyopathy
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Fig.2. "A" wave ratio in various type of cardiomyopathy and coronary heart disease. Closed circle is with bulge, and dotted line shows the upper limit of normal "a" wave ratio. Number of cases with "a" wave ratio over or less than 10% was shown on each column.

As shown in Fig.1 and Fig.2, 24 in 46 cases tested revealed prominent "a" wave over 10%, especially in the group of severe cases of ICM and in HOCM. Bulging wave are also frequently observed (22 in 46 cases) especially in the group of HOCM (6 cases in 7 cases).

Bulging waves are classified into 4 types such as sustained type of systolic bulge, mid-systolic bulge, late systolic bulge and diastolic bulge. Mid-systolic bulge was observed most frequently in every group. There was no difference in incidence and type of bulge among each group of cardiomyopathy and coronary heart disease.

Effect of the drugs on ACG

Effect of the amyl nitrite inhalation and iso-

proterenol infusion on the ACG was observed on the patients who did not show the prominent "a" wave and bulge at rest.

After amyl nitrite inhalation 3 in 17 cases revealed prominent "a" wave and 10 in 17 cases revealed bulging wave in a group of ICM. In the group of coronary heart disease some cases revealed prominent "a" wave and bulge after amyl nitrite inhalation.

Results of isoproterenol infusion were almost same as amyl nitrite inhalation in both groups of ICM and coronary heart disease as shown in Fig.3.

In summary positive incidence in ACG test are as following, 80% at rest, 100% by drug test in severe cases of ICM group 4, 35% at rest 75% by drug test in mild cases of ICM group 4, 55% at rest 82% by drug test in familiar cardiomyopathy, 100% at rest in HOCM and 67% at rest, 86% by drug test in coronary heart disease respectively. Any abnormal "a" and bulge wave was not observed by drug test in 10 normal subjects. In order to differentiate ICM and coronary heart disease by ACG test, effect of nitroglycerin on abnormal wave was studied. On a group of coronary heart disease 7 of 8 cases with prominent "a" wave and 4 of 5 cases with bulge wave showed improvement by nitroglycerin. On a contrary almost no effect on a group of ICM was observed. This nitroglycerin test is useful for differential diagnosis of ICM and coronary heart disease.

¹³¹Cs-Scintiscanning of the heart

Cs is taken into heart muscle as K and it is

Fig.3. Results of pharmacological loading by each drug on ACG.

Upper figure shows the change of "a" wave ratio on the case with prominent "a" (right) and without (left) before drug test.

Lower table shows the change of incidence with bulge.

Fig.4. ^{131}Cs scintigram of the heart

A: normal B: myocardial infarction showing marked defect. C: ICM showing sparse, D: ICM showing sparse and defect, E: HOCM with no defect.

Number shown lower is uptake index of each case.

considered that Cs uptake will be decreased in damaged area of heart muscle as K release from that area. After intravenous administration of 18 micro curie of ^{131}Cs per kg of body weight scintiscanning of anterior chest wall was performed. Normal subjects did not show any defect of heart area but anterior wall infarction showed defect area as shown (Fig.4). Fig.4-C is the scintigram of heart of 12 years old female who had been suffered from intractable congestive heart failure since 4 years and frequent Stokes-Adams attacks with heart block and multifocal ventricular premature beat in ECG and diastolic bulge in ACG. As shown in Fig.4-C diffuse and sparse defect in heart scintigram is observed. After 1 month later of the heart scintigram she had died suddenly and marked and diffuse fibrosis of heart was found. (Fig. 5) Fig. 4-D shows sparse and massive defect of heart scintigram of 20 years old female who is hospitalized for Stokes-Adams attack.

Scintigram of the patient of the HOCM with 70 mmHg of pressure gradient between left ventricular cavity and outflow tract showed dense uptake of ^{131}Cs into heart muscle and no defect as shown in Fig.4-E.

As summarized in Fig. 6, 68% in a group 4 of ICM showed sparse defect. Distribution of fib-

Fig.5. Marked fibrosis of the myocardium seen in the case of ICM whose scintigram was sparse as shown in Fig. 4-C.

Fig. 6. Pattern of scintigram (left) and uptake index (right)
(IHD: Classification of ischemic heart disease by WHO.)

Fig. 7. Distribution of fibrosis in myocardium shown in average of 6 autopsied ICM, 6 valvular disease and 6 myocardial infarction respectively.

rosis in heart muscle of 6 autopsied cases in group 4 of ICM was examined. The specimens of heart tissue were prepared from 8 areas of autopsied heart as shown (Fig. 7). Incidence of fibrotic lesion was induced as follows that using screen with cross mark on which the specimen was projected microscopically, the incidence of fibrosis was calculated by the number of fibrotic lesion on the 200 cross marks.

The heart examined in the group 4 of ICM showed 20% of fibrosis in average and its incidence in each area of heart muscle is almost same degree which means fibrosis in the heart of ICM is diffuse over the heart, while fibrotic lesions in the heart of rheumatic disease is mainly localized in the area of internal layer of left ventricle. This histopathological findings showing diffuse scattered fibrotic lesion over the entire heart in ICM is concomitant with the result of heart

scintigram that revealed the diffuse and sparse defect of heart area. The degree of ^{131}Cs uptake into the heart is calculated as following, the area of triangle figured by the count rate on the recording paper of the rate meter was calculated by the formula shown in Fig. 8.

The sum up of the area of triangles over the heart means total counts of the heart. And from it the grade of uptake of ^{131}Cs into the heart was expressed as an index. As Fig. 6, the uptake index of normal subjects, valvular and congenital heart disease is between 1.2 to 1.9. The majority of ICM showed lower index than 1.2 means low uptake, while 4 cases in 6 HOCM showed high uptake over 2.0 of index.

The measurement of plasma hydroxyproline containing collagen-like protein

On a recovery process from inflammation or damage of tissue fibroblast appeared in the granulation excrete the hydroxyproline and produce collagen. Marked fibrosis of the heart of ICM is well recognized by many reports and authors. While this fibrosis means healing process of the damaged heart tissue, it also disturbs the heart function by decreasing the compliance of the heart chamber. Author attempted to evaluate the process of fibrosis of the heart by measuring the plasma hydroxyproline containing collagen-like protein (HOP) by the method of Udenfriend^{2,3} As shown in Fig. 9 normal value of HOP in the plasma was less than $7\text{ }\mu\text{g/ml}$ and the recent myocardial infarction after 2 weeks of attack showed high level of $9.4\text{ }\mu\text{g/ml}$.

In the myocardial infarction, the period showing high level of HOP is concomitant with the phase of existence of fibroblast in the heart tissue (from Lodge-Patch 1951).

Fig. 8. Schematic representation of the curve of the count rate on the recording paper of the rate meter and formula calculating uptake index. Dotted line shows the level of count from the lung meaning background to the heart area.

Fig. 9. The level of the hydroxyproline containing collagen-like protein in the plasma. Fibroblast appearing period in the tissue on myocardial infarction (from Lodge-Patch 1951) is shown in the upper part.

On the ICM 6 of 11 measured cases revealed high level of HOP. These results suggest that in these cases of ICM, fibroplastic process is still continuing in the heart as active as seen in the heart of fresh myocardial infarction, although any positive sign suggesting active inflammatory process or tissue destruction was not observed by the other routine serological and enzymatic test.

DISCUSSION

Although reports concerning about ICM is increasing in recent year, clinical diagnosis of ICM is still difficult and made by exclusion of other known heart disease, and differential diagnosis to coronary heart disease is also difficult especially to the older case of ICM. ECG, chest X-ray and PCG findings are of course useful for the diagnosis of ICM, but these are non-specific.

Even the exercise test of ECG (Master's two step test) can not be helpful to differentiate the coronary heart disease because 50% positive in ICM was shown in this report.

Biopsy of the heart muscle was performed by authors themselves and many reports evaluate its reliability on the diagnosis of ICM, however, this technique should be limited for its dangerous complication especially on the severe case. Study presented on this paper is attempted to develop the method for the diagnosis of ICM, especially routinely applicable even for the severe case.

1. Apexcardiogram

Dominant "a" wave in ACG is known as a sign of decreased compliance of left ventricle. According to author's own study on normal subjects "a" wave ratio of over 10% is considered abnormally prominent. Bulging wave of systolic phase is also observed frequently, that is suggesting dissynergism⁴ of ventricular contraction caused by myocardial damage. These changes were augmented by pharmacological loading on the heart such as amyl nitrite inhalation and isoproterenol infusion, and by such loading abnormal wave in ACG was evoked in high incidence on the patient without abnormal wave before loading. By adding the results of loading test, positive sign was observed in high incidence, at 93% in severe cases and 75% in mild cases of group 4 respectively. On the cases of HOCM, positive finding were obtained at 100%. ACG test with pharmacological loading is useful as routine test for such diseases, however in coronary heart disease it also revealed same finding at 86%.

By using nitroglycerin elimination of abnormal sign of ACG in the majority of coronary heart disease was observed, while not in the ICM, and this fact was used for the differential diagnosis between these two diseases.

2. ¹³¹Cs Scintiscanning

Using radioactive substances several trial has been reported to demonstrate the infarcted area of the heart⁵. Scintigram of the heart can reveal myocardial lesion as a localized defective cold area. However, the lesions of posterior wall of left ventricle and right ventricular wall can not be detected due to low energy of ¹³¹Cs.

In the case of ICM examined on this study sparse and diffuse defect of the scintigram from left ventricular anterior wall was observed and uptake index of the ¹³¹Cs originally reported in this paper was low. Positive incidence of ¹³¹Cs

scintiscanning test in ICM was 78% in severe cases and 33% in mild cases respectively. High uptake of ^{131}Cs without defective cold area in HOCM is suggesting the thickness of the left ventricular wall. By this method the localization and the area of the lesion can be observed and uptake index suggests the grade of damage of the heart muscle.

3. Plasma hydroxyproline containing collagen-like protein (HOP)

As known in the healing process of myocardial infarction, it is considered that terminal point of the healing of damaged myocardium in ICM is also fibrotic change. Diffuse and high grade fibrosis of myocardium in ICM was shown by histopathological examination in this report. Although this fibrosis is a result of healing, the disturbance on the myocardial function by the fibrosis is important.

Sjoerdsma⁶ reported elevated level of plasma HOP on various disease developing fibrotic process. In this study without any positive sign of serological and enzymatic test about half of ICM showed as high level of plasma HOP as fresh myocardial infarction.

It is considered that the degree of the plasma HOP suggests the active process of the fibrosis in the myocardium of ICM. It is interesting that elevated plasma HOP was observed even on the old cases that course of the disease has been for several years since the beginning of it. This fact suggests that whatever the etiology of ICM is, such as viral infection or metabolic disorder, in some case of ICM fibrosing process can be continuing for a long period such as seen on the hepatic cirrhosis. In such mean, the study on the preventive trial for the fibrosing process in the myocardium is expected.

4. By combining the test of ^{131}Cs scintigram and measurement of the plasma HOP, the ICM can be classified in such as localized or diffuse type of damaged area and active or inactive type in fibrosing process. These examination is also clinically useful because it is frequently repeatable without loading on the patient.

SUMMARY

Seventy cases of ICM including 8 HOCM, 20 familial cardiomyopathies and 3 heart diseases with collagen disease were examined by ACG, Scintigram of the heart using ^{131}Cs and the measurement of the plasma hydroxyproline contain-

ing collagen-like protein comparing with coronary heart disease. The results were evaluated as a useful technique for the diagnosis of ICM.

1. Prominent "a" wave and bulging in ACG is observed in ICM frequently and its utility as a routine test was emphasized, especially with pharmacological test with amyl nitrite for the mild case, and with nitroglycerin for the differential diagnosis to the coronary heart disease, because nitroglycerin improves ACG findings in coronary heart disease while not in ICM.

2. On ICM scintigram of the heart showed sparse defect and low uptake of ^{131}Cs into the heart which is reported as an uptake index in this study.

3. Some of the cases of ICM including old case showed high level of plasma hydroxyproline containing collagen-like protein over $8.0\text{ }\mu\text{g/ml}$ such as seen in fresh myocardial infarction, while normal value was less than $7.0\text{ }\mu\text{g/ml}$ in this study.

The elevated level of plasma HOP suggests the active process of the fibrosis in the heart of ICM and of continuous fibroplastic mechanism in the heart of ICM was discussed.

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