Acute myocarditis
A follow-up study

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Forty-five patients, aged 14-46 years, with an electrocardiographic diagnosis of myocarditis while in hospital for acute infectious disease, were subjected to a follow-up control 6-68 months later. All patients had returned to their ordinary occupation. Moderate 'cardiac' symptoms were reported by 35 per cent. Residual repolarization disturbances corresponding to the location of the acute myocardial lesion were seen in 2 patients at rest and could be provoked by standing and/or exercise in another 14 patients. Ectopic beats were recorded in 6 patients. The physical working capacity (W_{170}) as related to total Hb was within normal limits in all patients and there was invariably a normal correlation between heart volume and physical working capacity. The results are considered to illustrate the good prognosis for cardiac function in uncomplicated post-infectious myocarditis.

The changing concept of myocarditis during the past century with respect to its pathogenesis has been elucidated in an excellent historical review by Mattingly (1965). Necropsy studies with microscopical, serological, and cultivating techniques indicate, however, that myocarditis is a common complication in a great number of acute infectious diseases (Saphir, 1953; Bell and Murphy, 1967; Burch et al., 1967). There are also many clinical reports on the incidence and course of acute myocarditis but, as far as we know, very few follow-up studies.

In a reinvestigation of 174 patients with a pathological electrocardiogram and/or an increased heart size in connexion with diseases known to cause non-ischaemic myocardial lesions, Levander-Lindgren (1965) found a high frequency of persisting symptoms, electrocardiographic changes, and cardiac enlargement, an average of 7 years after the supposed myocarditis. However, this diagnosis was used in a wide sense to include not only infectious but also metabolic, nutritional, and collagenous diseases. A follow-up study with more strictly selected material has been published by Bengtsson and Lamberger (1966). This study comprised 90 cases with clinical and electrocardiographic evidence of myocarditis during treatment for acute infectious disease 5 years earlier. The primary in-

fection had been due to haemolytic streptococci in 50 per cent of the patients. At the time of the follow-up, 26 per cent of the patients still had subjective cardiac symptoms. Abnormalities in the resting, orthostatic, and/or exercise electrocardiogram were seen in 49 per cent, while the incidences of low working capacity and increased heart volume were 41 and 20 per cent, respectively. Recently, Bergström et al. (1970) published a thorough follow-up investigation of 15 patients who had had a non-rheumatic acute perimyocarditis 1 to 4 years earlier. In this series the frequency of persisting electrocardiographic changes was as high as 73 per cent, whereas the correlation between working capacity and heart volume was within normal limits in 13 out of 15 patients.

In view of the small number of controlled follow-up studies and the somewhat conflicting results, the present investigation was designed to elucidate further the long-term prognosis after myocarditis complicating acute infectious disease.

Subjects

The patients participating in the present investigation had been admitted to the Clinic of Infectious Diseases at Danderyd's Hospital during the years 1964-1969 for treatment of acute infections of various aetiology. The selection was based on a simultaneous development of electrocardiographic changes suggestive of acute myocarditis.

The electrocardiographic criteria consisted of transitory, localized repolarization disturbances defined as a T wave inversion of 0·2 mV or more in at least two leads, where T normally is positive. In addition, many patients had initial more or less extensive ST rises. To be included in the study the patient had to have at least 3 consecutive electrocardiograms with a progress followed by a regress or occasionally a regress only of these repolarization disturbances.

Patients below 14 or above 46 years of age were excluded from the study in an attempt to escape juvenile electrocardiogram changes and those caused by ischaemic heart disease.

In the primary selection 57 patients were found to fulfil our electrocardiographic criteria. However, 8 could not accept or were not reached by the invitation to the follow-up investigation. Three patients were excluded due to suspicion of collagenous disease and one due to the diagnosis of a persistent ductus arteriosus. The final subjects comprised 32 male and 13 female patients with a mean age of 25 years for both groups. The follow-up control was performed 5 to 68 months after the acute myocarditis, the mean observation time being 36 months.

Methods and procedures

The follow-up control comprised an interview on anamnestic data, electrocardiograms, a standardized exercise test with an estimation of working capacity, as well as determinations of total amount of haemoglobin and heart volume. For each patient, all examinations were made on the same occasion.

Electrocardiography The recordings were performed on direct ink-writing 6-channel recorders (Mingograph 81, Elema-Schönander AB, Stockholm). Standard extremity and chest leads (CR1, 2, 3, 4, 5, 7) were used under resting conditions. During exercise the CR leads were substituted by corresponding CH leads with the indifferent electrode on the forehead. The electrocardiogram was recorded for at least two minutes at supine rest and continuously during an 8-minute orthostatic test as well during the exercise test up to 10 minutes afterwards. Electrocardiograms intended for detailed analysis were run at a paper speed of 50 mm/sec. The amplification was 1 mV/cm.

Exercise test The patients were exercised in the sitting position on an electrically braked bicycle ergometer (Holmgren and Mattsson, 1954) starting at a load of 300 kpm/min for men and 200 kpm/min for women. The work intensity was increased stepwise every 6 minutes by a further load of 300 or 200 kpm/min, respectively, until the patient was exhausted. The work capacity at a heart frequency of 170/min (W_{170}) was calculated by intrapolation or occasionally a small extrapolation from the relation of heart frequency on work load (Sjöstrand, 1947; Wahlund, 1948). A heart frequency of at least 160/min was reached by 38 patients. One patient had a highest rate of only 125/min, probably due to dysfunction of the sinus node. In this case, the highest work intensity performed during 6 minutes was used instead of W_{170}.

Total Hb The total amount of haemoglobin was determined by an alveolar rebreathing CO method (Sjöstrand, 1948). The correlations between work capacity and total Hb in the individual patients were compared with those of controls from Karolinska Sjukhuset (to be published). These controls consist of 174 men, aged 16–50 (mean 28) years, and 52 women, aged 16–52 (mean 34) years.

Heart volume The radiological determination of heart volume during the acute stage was performed in the conventional way with the patient in the upright position, using the formula presented by Jonsell (1939). At the follow-up control, heart volume was determined with the patient in a prone position as well (Larsson and Kjellberg, 1948) in order to avoid the influence of orthostatic reactions. The controls already mentioned were utilized also in the evaluation of the individual relation between work capacity and supine heart volume. In these subjects a modified frontal projection had been utilized (Kjellberg, Rudhe, and Sjöstrand, 1949) but this is not of significant importance for heart volume determinations (Bergström, Erikson, and Gustafsson, 1969).

Observations at the acute stage

Aetiology The probable aetiological agents of the myocarditis are listed in the Table. The acute infectious disease was of bacterial origin in 12 patients. Pneumonia due to mycoplasma or psittacosis was the primary infection in 3, while in 7 patients the underlying disease proved to be of viral origin. The aetiological agent remained unknown in 23 patients even though attempts were made in most cases to isolate enterovirus from the stools. On the other hand, no attempts had been made to test paired sera for rising antibodies against Coxsackie B virus.

Clinical observations Moderate cardiac symptoms, mostly praecordial pain or oppression, were presented by 26 patients. Obvious tachycardia and dyspnoea were seen in 1 patient, and another developed symptoms of acute heart failure with cyanosis, dyspnoea, and hepatic enlargement in connexion with a pericardial effusion. The physical examination on admission revealed pericardial friction rubs in 11 patients. This was confirmed by phonocardiography in all 8 patients investigated. No patients had signs of valvular lesions.

All but 8 patients had fever, a temperature of at least 38·5°C being noted in 30; 11 patients were febrile for more than a week in hospital. The ESR exceeded 50 mm in 30

TABLE *Diagnosis and type of infection associated with the acute myocarditis*

Clinical diagnosis	Probable aetiology	Evidence of infection	No. of cases
Acute pharyngotonsillitis	β-haemolytic streptococcus	Bacteria cultured from throat and/ or rising titre in antistreptolysin	6
Septicaemia	*Staphylococcus aureus*	Bacteria cultured from blood	1
Septicaemia	*E. meningitis*	Bacteria cultured from blood	2
Enteritis	Salmonella	Bacteria cultured from stool	2
Prostatitis	*Esch. coli*	Bacteria cultured from urine	1
Pneumonia	*Mycoplasma pneumoniae*	Rising titre in complement-fixation test	2
Pneumonia	Bedsonia agent	Rising titre in complement-fixation test	1
Infectious mononucleosis	Epstein-Barr virus	Positive heterophil agglutination test	2
Mumps	Mumps virus	Rising titre in complement-fixation test	3
Aseptic meningitis	Tick-borne virus (Russian spring-summer encephalitis)	Rising titre in complement-fixation test	1
Vaccinia	Vaccinia virus	Rising titre in complement-fixation test	1
Nonspecified infectious disease	—	—	23

patients and was above 100 mm in 11. A serum-GOT of more than 100 Karmen units was observed in 3 of 26 patients tested, the highest value being 308 Karmen units. The mean duration in hospital was 3·7 weeks; it exceeded 5 weeks in 3 patients only. Besides the treatment directed towards the infectious disease, prednisolone was given to patients with cardiac enlargement and friction rubs, but no cardiotropic drugs were administered. Pericardiocentesis was undertaken in one case and resulted in the withdrawal of 400 ml fluid.

Electrocardiograms An electrocardiogram was recorded on admission and thereafter at least once a week. Fifteen patients showed initial ST rises exceeding 0·2 mV in two leads or more. The T changes were mainly localized to leads CR4–7 in 25 patients, while in 12 patients they were most conspicuous in CR1–3; 8 patients finally had their deepest T waves in leads II, III, and aVF. Ectopic beats were recorded in only a few patients, 2 patients having scattered supraventricular and 4 others unifocal ventricular extrasystoles. One patient had transient atrial fibrillation and afterwards a slow sinus rhythm. AV blocks, major intraventricular conduction disturbances, and changes in QRS vectors were not seen.

Heart volume Heart volume was determined in all patients, usually the day after admission and therefore as indicated by the clinical condition. Heart volume (Fig. 1) was judged to be pathologically increased in 3 women (>400 ml/m²) and 4 men (>450 ml/m²). Pleural effusion was observed in 7 patients, none of whom required thoracocenteses.

Observations after discharge and before follow-up control
On being discharged from hospital the patients were usually informed of their myocardial lesion, always with the assurance of a good prognosis. They were, moreover, positively encouraged to increase their physical activity gradually. The period of convalescence averaged 6 weeks and all but 7 patients returned to their ordinary occupation less than 12 weeks after admission. Apart from recurrent urinary tract infections in one case, there were no major infections or diseases during the observation time to the follow-up control.

Electrocardiograms A typical individual pattern during the acute phase and early convalescence is shown in Fig. 2. In 35 patients electrocardiography was performed frequently enough to allow a fairly accurate establishment of the time of normalization. Among these patients 17 had a normal resting electrocardiogram within 6 months after discharge and there were only 3 patients who after a year still had repolarization disturbances corresponding to the location of the acute infectious myocardial lesion (Fig. 3).

Exercise test Several patients with residual cardiac symptoms or electrocardiogram changes at rest were subjected to repeated function
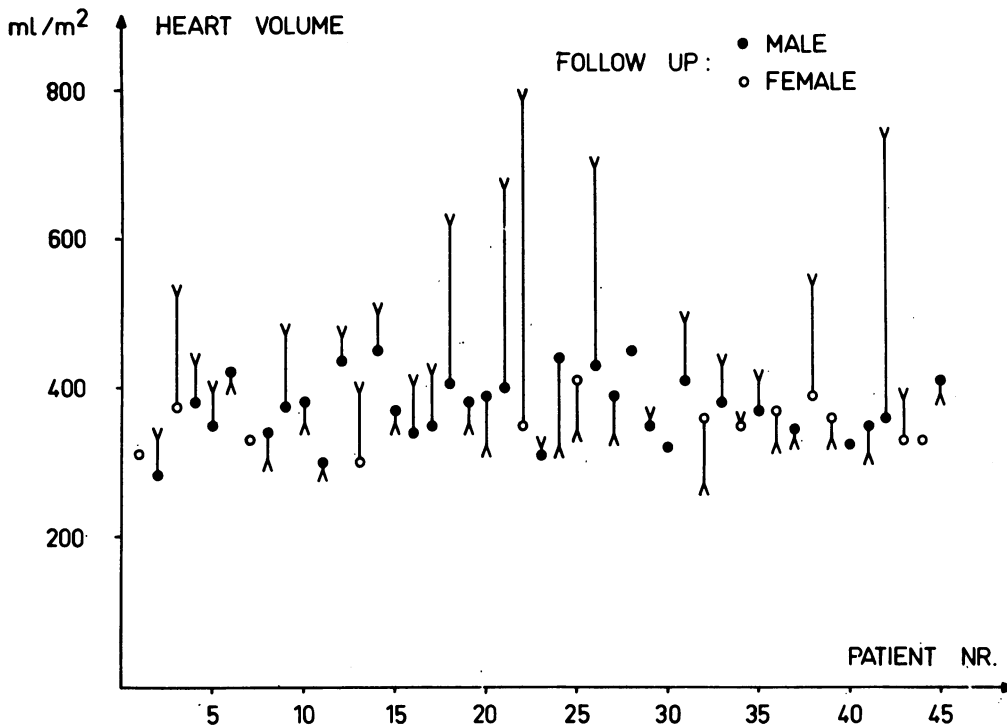
FIG. I   *The heart volume in upright position at the follow-up control in the female (○) and male (●) patients as compared with that obtained at the acute stage (∧ or ∨) of the infectious disease.*

tests during the first years after discharge from hospital. These patients offered an opportunity to estimate the normalization rate for working capacity. The regression of working capacity on total Hb derived from the controls was utilized for predicting the normal working capacity of each individual. The total Hb values obtained at follow-up formed the basis for these estimations on the assumption that total Hb had not changed significantly during the observation time. Patients younger than 19 years at the acute stage were excluded to avoid a possible influence from normal growth; none of the others increased their body weight more than 5 kg or their height more than 2 cm. Values of working capacity above the lower 1 SD limit of the predicted level were regarded as normal.

Of 28 patients tested during the first 4 months after discharge, 21 (75%) were found to have a normal working capacity according to the above criteria. At controls 4 to 16 months after discharge working capacity was normal in 95 per cent of the patients tested. Moreover, the mean value at this second control was 22 per cent higher than at the first one (P < 0·05).

Results of follow-up control

Symptoms   On being asked about residual cardiac symptoms at the follow-up control, 6 patients reported palpitations during exercise while one complained of substernal oppression. Fatigue was admitted by 5 patients and 3 patients had sensations suggestive of recurrent cardiac arrhythmias. However, only 2 patients worried about the heart as a consequence of residual symptoms. Moreover, all of the 11 patients who had taken an active part in some form of athletics before admission to hospital returned to this activity once they had recovered.

Electrocardiograms   Only 3 patients had residual pathological electrocardiographic changes at rest. One patient without earlier apparent arrhythmias showed scattered ectopic beats of supraventricular origin. Two patients had localized repolarization disturbances consisting of flat and biphasic T waves. Both of them had had conspicuous T inversions in corresponding leads during the acute stage, amounting to 1·0 and 0·4 mV, respectively.

A pathological orthostatic electrocardiographic reaction was recorded in 13 patients, all of whom showed abnormal T waves with a location consistent with the most prominent repolarization disturbances in the acute stage (Fig. 4). The acute electrocardiographic changes could thus be provoked by the orthostatic test an average of 36 months later in about one-quarter of the patients. The 2 patients who had pathological T waves even at rest belonged to this group but their T changes were more pronounced at the orthostatic test. The mean increase in heart rate at the transition from supine to standing position amounted to 17 beats/min.

During exercise Arrhythmias were recorded in 5 patients, 1 of whom showed sporadic supraventricular ectopic beats. The other 4 patients showed ventricular ectopic beats, one of them quite frequently throughout the exercise test, the others more sparsely and only at the highest load. One of these patients had had ectopic beats of the same type at the acute stage. Abnormal T waves with a location corresponding to the acute myocardial lesion were seen during exercise in 8 patients, but in 6 of these the T changes had already been disclosed by the orthostatic test.

During the electrocardiogram recording up to 10 minutes after exercise one patient showed a few ventricular ectopic beats as he had done during exercise. Localized abnormal T waves after exercise only were seen in one patient.

To summarize, there were in this series 6 patients with arrhythmias at rest or in connexion with the function test at the follow-up control. Circumscribed repolarization disturbances corresponding to the location of the acute myocardial lesion were seen in 16 patients, 2 of them having arrhythmias as well. Thus, a total of 20 of the 45 patients (44%) had some type of electrocardiographic abnormality at the follow-up control. The T abnormalities were reproduced most frequently by the orthostatic test and particularly in patients where the acute myocarditis had been localized to the diaphragmatic wall (6 out of 8 patients).

Working capacity This was at least 900 kpm/min in 27 of the 32 male patients, 14 of them having a working capacity of 1200 kpm/min or more. Among the women, working capacity amounted to at least 600 kpm/min in 12 of the 13 patients, being over 800 kpm/min in 3 cases.

In relation to their total Hb, all patients had a working capacity within the normal
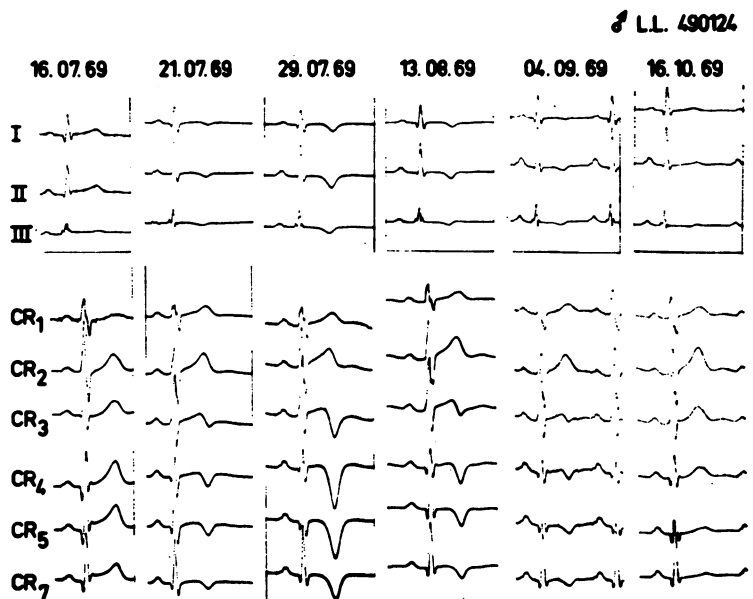

FIG. 2 *A representative electrocardiogram development in a patient with transient repolarization disturbances over the left ventricle in connexion with an acute streptococcal infection with a clinical appearance on 15 July 1969.*

range (mean ± 2 SD) as defined by the healthy controls (Fig. 5). Only 4 patients had values below the 1 SD limit.

Heart volume The largest heart volume in the prone position was 490 ml/m² in the men and 455 ml/m² in the women. Corresponding values from determinations in the upright position amounted to 450 and 410 ml/m², respectively. All heart volumes were thus within limits conventionally regarded as normal. The mean difference in heart volume between determination in prone and upright position was 10 per cent.

Physical working capacity is known to be linearly related to heart volume in normals. On the other hand, myocardial lesions of functional importance tend to decrease working capacity and simultaneously increase heart volume. Relating working capacity to heart volume would consequently help in the detection of deviations from normal conditions. In the present series, however, all patients fell within normal limits in this respect as well (Fig. 5).

Discussion

The selection of patients for the present study was based on the development of transitory,
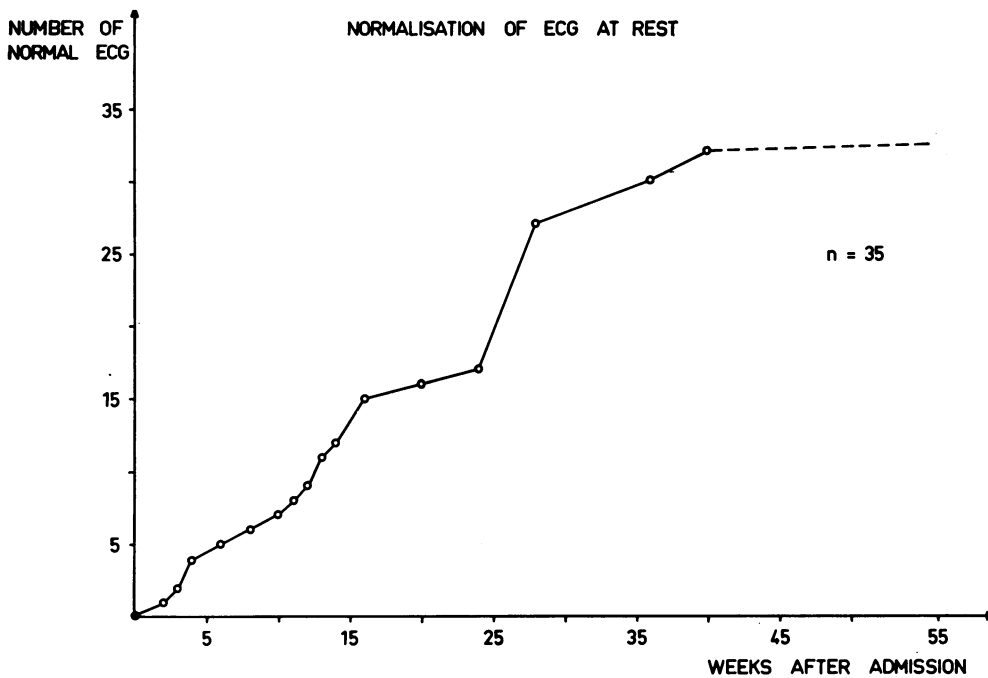
FIG. 3 *The number of normal resting electrocardiograms at different times after discharge from hospital in 35 patients controlled several times during the first year.*

more or less localized repolarization disturbances in close connexion with symptoms of acute infectious disease. The use of stringent electrocardiographic criteria was intended to decrease the risk of including cases with a false diagnosis of myocarditis, but has, on the other hand, probably eliminated a large number of patients with more moderate infectious myocardial lesions. However, these patients are of less prognostic interest in view of the good recovery in the selected, more seriously affected patients. A restriction to patients in a clinic for infectious diseases may further have excluded the most severe cases of acute myocarditis, which may appear as fulminating congestive heart failure and result in primary admission to internal medical wards or occasionally sudden death (Gydell, Biörck, and Winblad, 1955; Bell and Murphy, 1967). The present subjects therefore probably represent an intermediate clinical type of acute myocarditis.

Within such a selection of patients the individual prognosis can be expected to vary with the aetiology and this may at least partly explain the differences between these results and previous follow-up studies with respect to restitution of electrocardiogram, heart size, and physical fitness after acute infectious myocarditis. It is moreover possible that the prognosis of acute myocarditis changes with

FIG. 4 *The electrocardiogram at supine rest, in the standing position as well as during and after work at the follow-up control as compared with the resting electrocardiogram during the acute stage of the infectious disease in a patient observed for 5 years.*
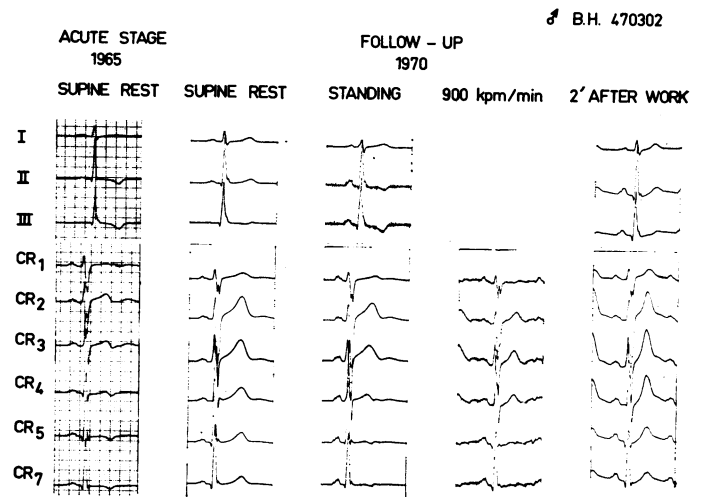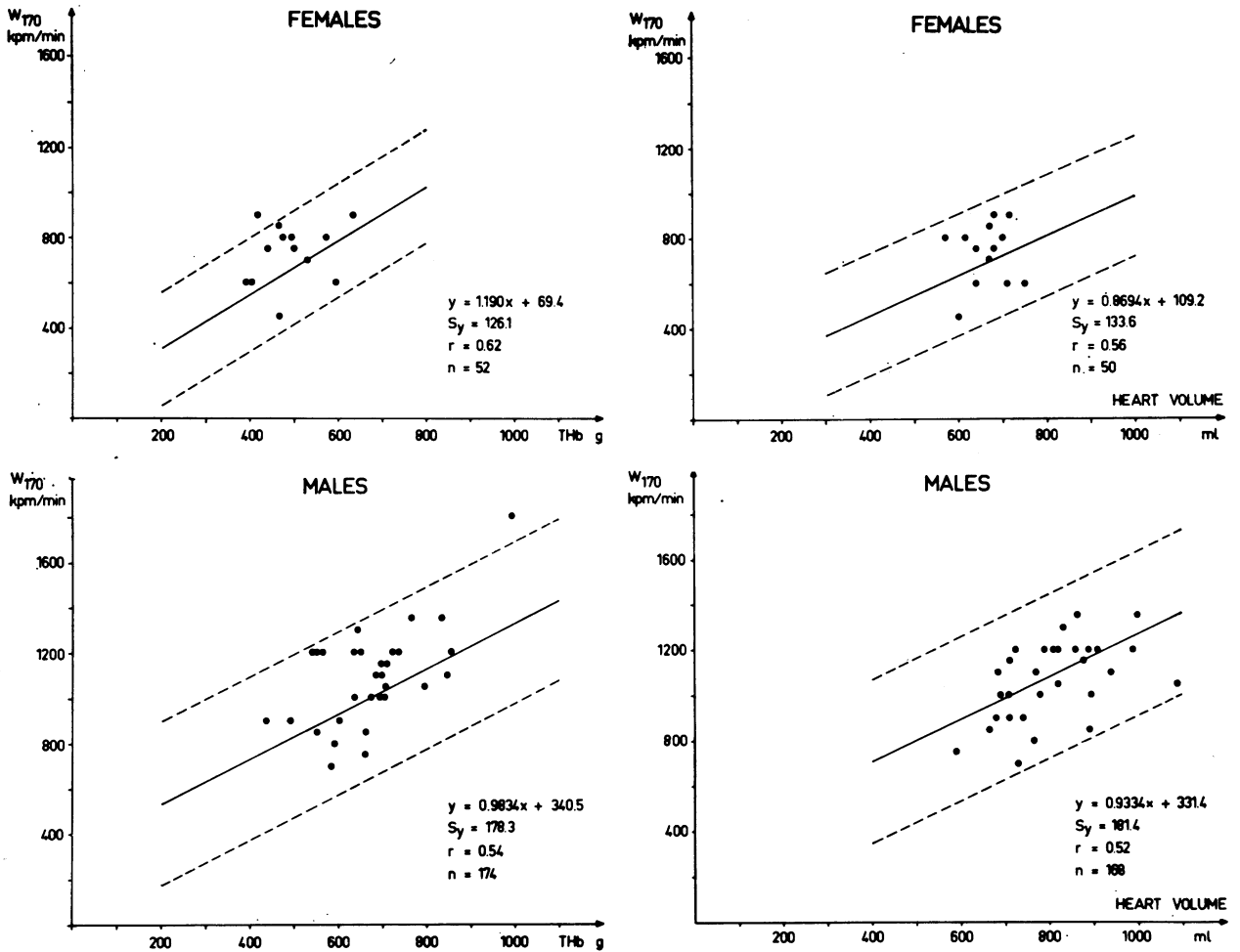
FIG. 5 *The individual relation between working capacity and total Hb as well as between working capacity and the heart volume in prone position as compared with corresponding normal regression lines (± 2 SD).*

time, due to well-known variations in the pattern and characteristics of common infectious diseases. In the patients studied by Bengtsson and Lamberger (1966) the frequency of bacteriological primary infections was probably higher than in our patients. It is interesting to note, however, that these authors found no major difference in prognosis between streptococcal and non-streptococcal myocarditis, including cases connected with aseptic meningitis. The fact that we excluded patients with suspected collagenous disease may have influenced the prognosis favourably as compared to other studies (e.g. Levander-Lindgren, 1965), since such diseases are known to have a recurrent and progressive clinical course. The aetiological pattern of the present series seems to correspond most closely to that investigated by Berg-

ström *et al.* (1970). In both series it was impossible to establish the aetiological diagnosis in about 50 per cent of the cases, but there is reason to believe that there was a high incidence of viral infections, notably Coxsackie B (Helin, Savola, and Lapinleimu, 1968; Smith, 1970). This might have been found if virological diagnostic methods had been used more extensively.

Concerning the clinical picture, there were some patients with obvious clinical manifestations of the myocarditis, including praecordial pain, tachycardia, pericardial effusion, and congestive heart failure. Many patients, however, were completely without symptoms or signs of the myocardial lesion evident from the electrocardiographic development while in hospital. This observation confirms that myocarditis may be a more or less focal myo-

cardial disease without consequences for cardiac function. It also emphasizes the importance of routine electrocardiograms, including complete chest leads, in the course of any major infectious disease (Stapleton, Segal, and Harvey, 1970). Moreover, the sometimes very transient nature of electrocardiographic abnormalities in acute myocarditis makes repeated records important for their detection. The present findings suggest that a complicating perimyocarditis should be suspected in the presence of an unusually high sedimentation rate (cf, Smith, 1970). The fact that serum transaminases were usually within normal limits may differentiate from ischaemic myocardial lesions. However, moderately raised values obviously sometimes occur in acute myocarditis as well, though it remains unknown whether these are due to myocardial or hepatic damage.

The detection of symptomless electrocardiographic abnormalities suggestive of myocarditis in connexion with an infectious disease does not usually change the acute treatment but may of course influence the attitude towards convalescence. Of more importance is the possibility that undetected postinfectious electrocardiographic changes may later be attributed mistakenly to an ischaemic heart disease, with serious implications for the patient. It is true that the resting electrocardiogram became normal within a year in most patients but it is also evident from our and previous follow-up studies that many patients still have residual local repolarization disturbances several years after the acute myocarditis. Bergström et al. (1970) reported a higher incidence of electrocardiographic abnormalities but had a somewhat shorter mean observation time. Like these authors but in contrast to Bengtsson and Lamberger (1966), we found no correlation between residual electrocardiographic abnormalities and persistent cardiac symptoms. Postinfectious repolarization disturbances are often provoked more readily by standing than by exercise (Fig. 4), in contrast to those caused by coronary insufficiency. They can be eliminated temporarily by the administration of β-blocking agents, as shown in Fig. 6. Such a procedure is therefore unfortunately of little help in differentiating from functional repolarization disturbances (cf. Furberg, 1967).

The most important clinical result of the study was the fact that heart volume and physical working capacity were within normal limits in all patients at the follow-up control (Fig. 5) even though electrocardiograms had not always become normal. Bergström et al.
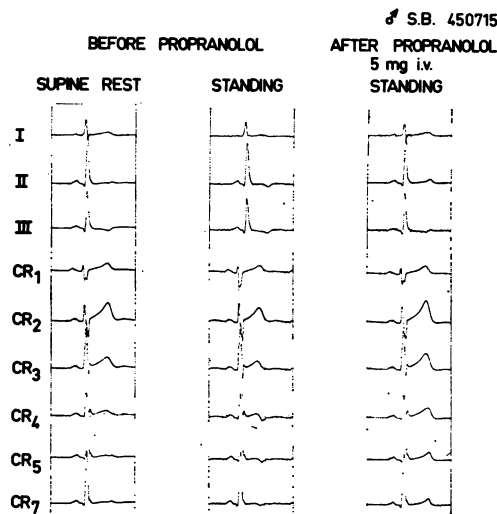

FIG. 6   *The provoking effect of standing on local repolarization disturbances known to originate from an earlier acute myocarditis and the change in orthostatic electrocardiographic reaction after β-receptor blockade.*

(1970) similarly found a normal correlation between heart volume and working capacity in 87 per cent of their patients. These results contrast with the high incidence of low working capacity reported by Bengtsson and Lamberger (1966).

An important error in the evaluation of physical working capacity is the variability in orthostatic reactions. During exercise in the upright position an abnormally increased diversion of blood to the lower limbs may thus result in a higher heart rate than normal in relation to working intensity and consequently involve an underestimation of working capacity. The female patient in the present study who had the lowest working capacity showed a conspicuous orthostatic pulse reaction, her heart rate increasing 35 beats on changing from supine to the standing position. She was therefore reinvestigated later with supine bicycle exercise and reached a working capacity of 650 kpm/min as compared to 450 kpm/min in the upright position. Since orthostatic pulse reactions are known to increase during periods of physical inactivity, this type of follow-up control of working capacity should preferably be performed with the patient in a supine position as with the determination of heart volume. The patients in this study have been encouraged to return to normal physical activity as early as possible, which may have counteracted orthostatic reactions and possibly partly explains the high

proportion with normal working capacity as compared to earlier follow-up studies.

Animal experiments suggest that physical activity is deleterious in the active stage of a myocardial infection (e.g. Tilles *et al.*, 1964). However, there is no clinical evidence for adverse effects of physical activity after myocarditis without signs of myocardial insufficiency or rhythm disturbances. On the contrary, early mobilization and active physical rehabilitation seem to be important components in the treatment of such patients. This may be essential not only for the restitution of physical fitness but also for precluding a neurotic heart disease. It is thus worth noting that in the present study there were very few patients who admitted cardiac symptoms at the follow-up and only two with anxiety about heart disease.

It should be mentioned, however, that one of our patients was later admitted to hospital for a relapse of acute myocarditis with repolarization disturbances of a new location and cardiac enlargement. The risk of recurrent attacks was illustrated also by the fact that another patient obviously had suffered from an acute myocarditis one year before the admission to hospital that led to his inclusion in our series. Further studies following patients for more than a few years after an acute myocarditis might perhaps modify our favourable concept of the long-term prognosis.

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