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Non-Invasive Assessment of the Left Ventricular Response to Exercise Using Praecordial Accelerocardiography and Mitral Valve Echocardiography.

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SUMMARY

The left ventricular responses to isometric and dynamic exercise have been assessed in six normal subjects, twelve patients with aortic stenosis and sixteen patients with myocardial disease, using the non-invasive techniques of praecordial accelerocardiography and mitral valve echocardiography.

Changes in maximum praecordial acceleration have previously been shown to correlate closely with changes in the peak acceleration of blood flow in the ascending aorta during acute manoeuvres in animals, and both have been shown to be highly sensitive to small changes in left ventricular contractile state induced in a variety of ways. In the normal subjects of the present study, isometric handgrip exercise resulted in significant increases in heart rate and systolic and diastolic blood pressure, but a significant decrease in maximum praecordial acceleration. The decrease observed in the maximum amplitude of the accelerocardiogram during handgrip conflicts with previous observations suggesting that the normal left ventricle responds to this stress with an augmentation of contractile state. However, there is some evidence to suggest that this improvement in left ventricular performance is entirely due to the chronotropic effects of handgrip. Maximum praecordial acceleration is not influenced by changes in heart rate per se and it is suggested that this accounts for the failure of maximum praecordial acceleration/

acceleration to increase during handgrip.

In both groups of cardiac patients isometric handgrip caused significant increases in heart rate, blood pressure, left ventricular end-diastolic pressure and left ventricular maximum $\frac{dP}{dt}$ and an insignificant increase in the maximum amplitude of the praecordial accelerocardiogram. There were no significant differences between the normal subjects and the cardiac patients as regards the increases in heart rate or blood pressure during handgrip, but the accelerocardiographic response in both patient groups was significantly different from that in the normal subjects. This abnormal response suggests that some cardiac patients increase left ventricular contractile state during handgrip, independent of the effects of an increase in heart rate. Since the only physiological mechanism known to increase maximum praecordial acceleration is beta adrenergic activation, it seems reasonable to suggest that a significant proportion of cardiac patients, unlike normal subjects, mobilise the beta adrenergic nervous system in response to handgrip. The patients with aortic stenosis who increased praecordial acceleration during handgrip had a significantly higher resting cardiac index than those who did not, and the patients with myocardial disease who responded in this way had a significantly lower resting left ventricular end-diastolic pressure than the remainder, suggesting that the patients who responded abnormally tended to have better left ventricular function at rest than those whose accelerocardiographic/

accelerocardiographic response was "normal". It is therefore suggested that patients with severe left ventricular dysfunction are unable to increase praecordial acceleration during handgrip, despite activation of the beta adrenergic nervous system.

In the normal subjects dynamic exercise caused significant increases in both heart rate and maximum praecordial acceleration, which were significantly impaired by propranolol. These results are in agreement with previous studies showing that the beta adrenergic nervous system contributes significantly to the cardiovascular response to dynamic exercise. In contrast, beta adrenergic blockade had no significant effect on the response to isometric exercise, in terms of heart rate, blood pressure or maximum praecordial acceleration, which is compatible with the results of previous studies indicating that the response to handgrip is relatively independent of the beta adrenergic nervous system. Propranolol also significantly reduced maximum praecordial acceleration in the normal, resting, supine subjects.

In conjunction with the results of previous investigations, the observations made in the present study suggest that an increase in the maximum amplitude of the praecordial accelerocardiogram may specifically signify an increase in left ventricular contractile state due to beta adrenergic activation.

In the present study the time to maximum praecordial acceleration has been shown to correlate significantly with the duration of the pre-ejection period at rest. The time

to/

to maximum praecordial acceleration shortened significantly during both isometric and dynamic exercise in the normal subjects. The shortening during isometric exercise was not impaired by propranolol, unlike the shortening observed during dynamic exercise, which was completely abolished by the drug. These observations again suggest that the response to isometric, unlike dynamic, exercise is relatively independent of the beta adrenergic nervous system. Time to peak acceleration also shortened significantly during handgrip in the patients with myocardial disease but not in the patients with aortic stenosis. However, there were no significant differences between the various groups as regards the shortening of the time to peak acceleration. Furthermore, in the cardiac patients, the response in terms of the time to peak acceleration could not be correlated with any haemodynamic or angiographic indices of left ventricular function. It appears, therefore, that changes in the time to peak acceleration during handgrip are of no value in the assessment of left ventricular function or in the detection of left ventricular disease.

The amplitude of the P wave of the praecordial accelerocardiogram, relative to the maximum systolic deflection, has been shown to correlate with left ventricular end-diastolic pressure at rest in the patients with cardiac disease. The amplitude of the P wave did not change significantly during handgrip in the normal subjects but it increased signficiantly in/

in the cardiac patients. Furthermore, the percentage change in the amplitude of the P wave during handgrip correlated significantly with the percentage change in left ventricular end-diastolic pressure. Since an excessive increase in left ventricular filling pressure during a stress test is a sensitive indicator of the presence of heart disease and since praecordial accelerocardiography possesses important practical advantages over the alternative non-invasive techniques for monitoring changes in left ventricular end-diastolic pressure, these observations suggest a possible clinical role in screening for latent myocardial dysfunction.

The mechanism which underlies the pathological increase in left ventricular filling pressure during the stress of isometric exercise has been investigated, using the echocardiogram of the anterior cusp of the mitral valve to detect changes in the pattern of left ventricular filling. No consistent changes in the echocardiogram occurred either in the normal subjects or the patients with heart disease and no differences between these two groups could be demonstrated. It must therefore be concluded that this technique is unsuitable for detecting acute changes in the diastolic properties of the left ventricle.

CHAPTER 1

Introduction

Until the late 1940s the only techniques available for studying cardiac function were indirect or non-invasive. Interest in such techniques naturally waned following the introduction of cardiac catheterisation, which, for the first time, provided the clinician with direct access to haemodynamic data not only for diagnostic purposes but also for the evaluation of myocardial function. The recent revival of interest in non-invasive techniques may be largely attributed to two factors, the first of which is the need to assess myocardial performance in ill patients, for example those with acute myocardial infarction, in whom catheterisation would constitute an appreciable hazard. The second factor is the possible benefit which might result from the serial evaluation of cardiac performance in patients with various types of heart disease, so that treatment, particularly surgical, can be instituted at the optimum stage in the natural history of the disease. Catheterisation is clearly unsuitable for serial studies, whereas non-invasive tests are, in general, more sensitive at detecting changes within the individual in the course of serial studies than in detecting differences between individuals.

In view of these important potential applications it seems worthwhile at this point to review the literature on some of these non-invasive techniques and, in particular, to discuss/

discuss their usefulness and limitations in the evaluation of cardiac function.

A large amount of work has been directed towards the study of the praecordial pulsations associated with cardiac contraction. Such techniques may be classified according to whether they measure the displacement, velocity or acceleration of praecordial movement.

Displacement:

The apexcardiogram has been shown to be very reliable in reflecting diastolic events within the left ventricle (Dimond and Benchimol, 1963, Gibson et al., 1974; Rios and Massumi, 1965; Tavel et al., 1965; Voigt and Friesinger, 1970; Willems, Kesteloot and de Geest, 1972). The amplitude of the 'a' wave of the apexcardiogram correlates with left ventricular end-diastolic pressure (Dimond and Benchimol, 1963; Gibson et al., 1974; Rios and Massumi, 1965; Tavel et al., 1965; Voigt and Friesinger, 1970; Willems et al., 1972), the height of the left ventricular 'a' wave (Gibson et al., 1974; Voigt and Friesinger, 1970; Willems et al., 1972) and calculated left ventricular end-diastolic compliance (Gibson et al., 1974). An increase in the height of the 'a' wave of the apexcardiogram, relative to the total amplitude of the tracing, is a common finding in patients with heart disease (Benchimol and Dimond, 1962; Gibson et al., 1974; Ginn et al., 1967; Rios and Massumi, 1965; Tavel et al., 1965). Acute changes in the height of the 'a' wave of the apexcardiogram have also been described in association with dynamic/

dynamic exercise (Benchimol and Dimond, 1962; Dimond and Benchimol, 1963; Ginn et al., 1967; Rios and Massumi, 1965), static exercise (Siegel et al., 1972) and the administration of glyceryl trinitrin (Benchimol and Dimond, 1962; Dimond and Benchimol, 1963; Rios and Massumi, 1965; Sawayama et al., 1973). However, although a qualitative relationship has been demonstrated between the contour of the apexcardiogram and left ventricular stroke volume (Sutton, Prewitt and Craige, 1970), recordings of praecordial displacement, in general, provide rather limited information about left ventricular systolic performance (Rios and Massumi, 1965; Willems et al., 1972).

In contrast to the apexcardiogram, which measures the displacement of the apex beat relative to the chest wall, the kinetocardiogram measures displacement of the cardiac apex relative to a fixed point external to the body. The atrial wave of the kinetocardiogram is abnormally prominent in patients with cardiac failure and may increase in amplitude acutely during exercise in some patients with heart disease (Eddleman and Harrison, 1963), but studies correlating events in the kinetocardiogram with circulatory dynamics have not, so far, been reported.

Velocity:

The first time derivative of the apexcardiogram is a measure of the instantaneous velocity of praecordial movement and its maximum amplitude has been shown to correlate/

correlate closely with its haemodynamic counterpart, the maximum rate of rise of left ventricular pressure (maximum left ventricular dP/dt), during beta adrenergic stimulation and blockade and angiotensin infusion (Denef, de Geest and Kesteloot, 1973). However, left ventricular maximum dP/dt, itself, is not a satisfactory index of left ventricular contractile state since it depends largely upon heart rate, pre-load (which is approximated in the intact ventricle by left ventricular end-diastolic volume) and after-load (aortic diastolic blood pressure) (Mason, 1969).

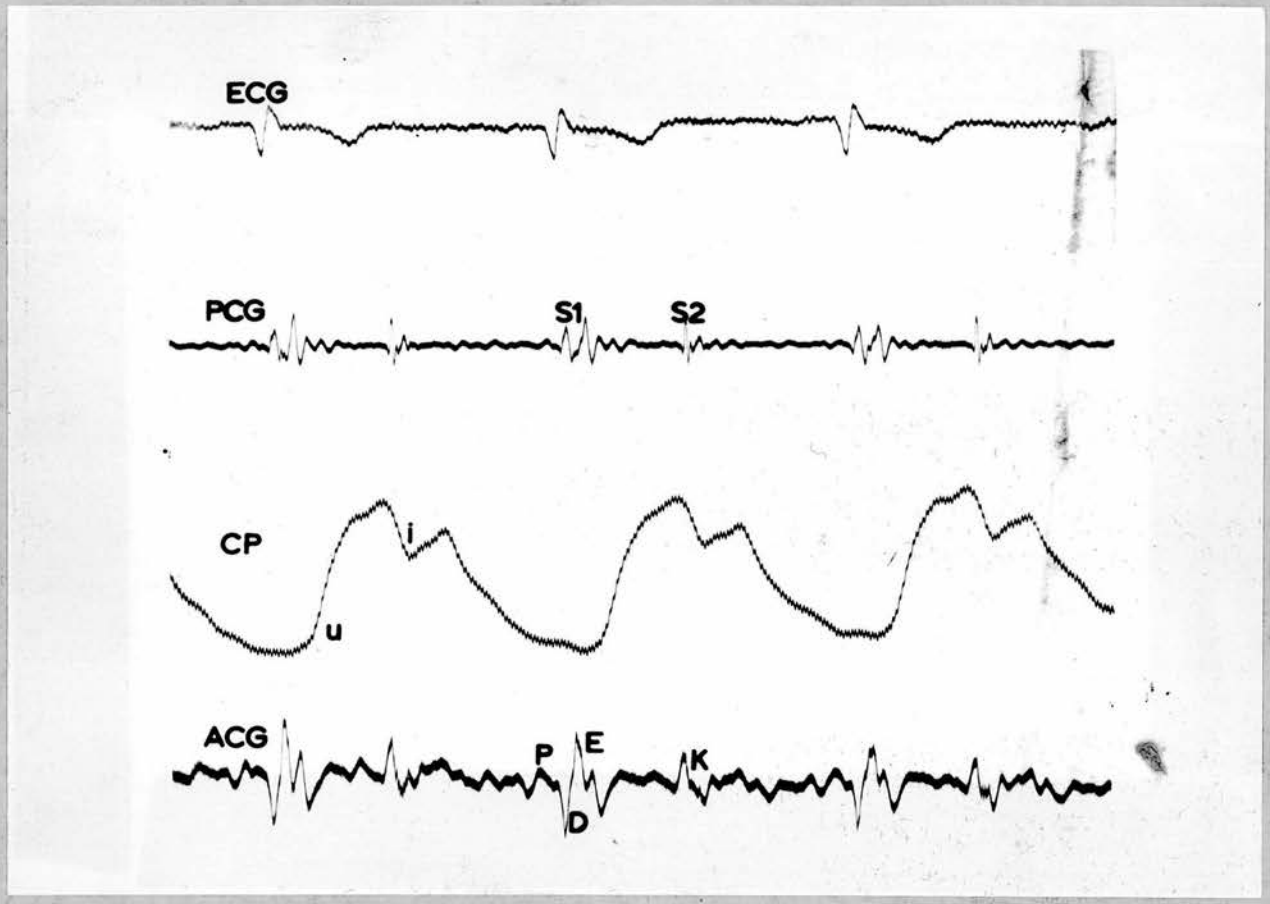
A great deal of work has therefore been devoted to finding a measure of contractility which is independent of the conditions of ventricular loading. Theoretical considerations suggested that such a measure was provided by the derived isovolumetric indices of left ventricular performance, V_{max} and the peak velocity of contractile element shortening (Mason, Spann and Zelis, 1970; Sonnenblick et al., 1970). These are calculated from high-fidelity left ventricular pressure recordings and correlate closely with the equivalent indices calculated from the calibrated apexcardiogram (Denef et al., 1973; Mirsky, Pasternac and Ellison, 1972). However, there are major problems attached to the routine clinical use of the derived isovolumetric indices of contractility, the most important being the complexity of the calculations which, in the case of V_{max}, involves extrapolation of a pressure-velocity curve to "zero/

"zero load." Indeed, one group of workers found that the shapes of their pressure-velocity curves were so variable that no single mathematical expression could be used with confidence to extrapolate back to V_{max} in all cases (van den Bos et al., 1973). They concluded that V_{max} was totally unacceptable as an index of contractility because of its marked dependency on the nature of the mathematical manipulations used in its calculation. Furthermore, some of the many theoretical assumptions which underlie the calculation of the derived isovolumetric indices of contractility have now been shown to be incorrect (Hamer, 1973; van den Bos et al., 1973). Recent work has even cast doubt on whether these indices are, in fact, independent of the conditions of ventricular loading (Hamer, 1973; van den Bos et al., 1973).

Acceleration:

The configuration and timing of the praecordial accelerocardiogram are illustrated in figure 1, which is labelled according to previous workers (Luisada, 1962; Rosa and Kaplan, 1960a; Rose et al., 1961). Double differentiation of the apexcardiogram yields a tracing which is indistinguishable from the praecordial accelerocardiogram and, conversely, double integration of the accelerocardiogram yields a displacement record (Luisada, 1962; Reuben and Littler, 1973). The accelerocardiogram also resembles the second time derivative of the pulmonary arterial pressure tracing (Luisada, 1962; Rosa et al., 1961). These observations/

Figure 1 Configuration and Timing of the Accelerocardiogram.



From above ECG = electrocardiogram
PCG = phonocardiogram
CP = carotid pulse
ACG = praecordial accelerocardiogram
(labelled according to Luisada, 1962; Rosa and Kaplan, 1960; Rosa et al., 1961).

S1 = first heart sound
S2 = second heart sound
u = upstroke of carotid pulse
i = incisura of carotid pulse

observations furnish evidence that the accelerocardiogram does, in fact, record praecordial acceleration.

Praecordial accelerocardiography possesses certain important practical advantages over the alternative techniques for recording praecordial pulsations. Since the transducer is directly sensitive to acceleration, and does not depend on double differentiation of a displacement signal, the baseline is stable and the tracing is relatively uninfluenced by respiratory movement (Luisada, 1962; Reuben and Littler, 1973; Rosa and Kaplan, 1960a). Another advantage of accelerocardiography is that the contour of the tracing is not greatly affected by changes in either the position of the transducer or the patient (Luisada, 1962; Reuben and Littler, 1973; Rosa et al., 1961). Consequently, accurate localisation of the apex beat is not essential. Furthermore, the pattern of the accelerocardiogram recorded from the chest wall is identical to that recorded internally from the surface of the left ventricle in dogs and is unaffected even by the application of a plaster cast between the transducer and the skin, suggesting that the pressure with which the transducer is applied to the chest wall is not as critical as it is with displacement tracings(Luisada, 1962; Reuben and Littler, 1973).

Qualitative changes in the accelerocardiogram, such as splintering of the peaks and alterations in the relative heights of various peaks, have been described in the presence of/

of heart disease and following the administration of cardiotoxic drugs (Luisada, 1962; Mounsey, 1957; Rosa and Kaplan, 1960a, b). Between 60 and 90 per cent of patients with coronary heart disease and 40 per cent of hypertensive patients present abnormalities in the systolic complex of the praecordial accelerocardiogram (Luisada, 1962). Ischaemic heart disease is also associated with excessive prominence of the diastolic waves (Mounsey, 1957). These abnormalities tend to be accentuated by exercise and also following acute myocardial infarction (Luisada, 1962).

While the qualitative aspects of praecordial accelerocardiography have been extensively documented, little information exists in the literature regarding the quantitative aspects of the relationship between the accelerocardiogram and circulatory dynamics. In the only study of this kind so far reported, changes in the maximum amplitude of the praecordial accelerocardiogram, which occurs at the onset of left ventricular ejection (DE - Figure 1), were found to correlate closely with changes in peak aortic acceleration during a wide range of manoeuvres in dogs (Reuben and Littler, 1973). Peak acceleration of blood flow in the ascending aorta had previously been shown to be highly sensitive to small changes in left ventricular contractile state induced in dogs in a variety of ways (Chung, Chamberlain and Seed, 1974; Noble, Trenchard and Gus, 1966a; Noble et al., 1972; Reuben and Littler, 1973; Winter et al., 1967). Furthermore, both peak aortic acceleration and the maximum amplitude/

amplitude of the praecordial accelerocardiogram are relatively independent of increases in heart rate induced by atrial pacing (Noble, Trenchard and Guz, 1966c; Noble et al., 1972; Reuben and Littler, 1973) and, therefore, reflect changes in left ventricular inotropic state independent of any associated chronotropic effects. In the intact animal peak aortic acceleration is also independent of changes in left ventricular filling pressure or pre-load (Noble, Trenchard and Guz, 1966a; b; Noble et al., 1972; Reuben and Littler, 1973; van den Bos et al., 1973), but this does not appear to be true in the open-chest preparation (Chung et al., 1974; van den Bos et al., 1973). The amplitude of the maximum systolic deflection of the praecordial accelerocardiogram has also been shown to be independent of changes in pre-load in the intact animal (Reuben and Littler, 1973). It appears, therefore, that maximum praecordial and aortic acceleration are insensitive to changes in left ventricular performance occurring as a result of the Starling mechanism, at least in the intact animal, and consequently that increases in these parameters reflect true increases in left ventricular contractile state as defined by Sonnenblick and his colleagues (Sonnenblick et al., 1970).

Ballistocardiography:

An obvious similarity exists between the contours of the praecordial accelerocardiogram and the ultra-low frequency ballistocardiogram (Luisada, 1962; Reuben and Littler, 1973; Rosa and Kaplan, 1960a, b; Rosa et al., 1961). This/

This observation is not surprising since the ultra-low frequency ballistocardiogram measures the acceleration of the body in the longitudinal plane (Harrison et al., 1969; Starr, 1965; Starr and Noordergraaf, 1962; Winter et al., 1967). Qualitative abnormalities in the shape of the ballistocardiogram, similar to those described with the praecordial accelerocardiogram, have been observed following acute myocardial infarction, in acute myocarditis, during attacks of angina pectoris and during mild exercise in some patients with ischaemic heart disease (Starr, 1965). Conversely, glyceryl trinitrin frequently restores the pattern of the ballistocardiogram towards normal in patients with coronary heart disease, even between attacks of angina pectoris (Starr, Pederson and Corbascio, 1955). An improvement in the pattern of the ballistocardiogram may also follow the administration of digitalis (Starr, 1965).

The amplitude of the early systolic waves of the ultra-low frequency ballistocardiogram, like the maximum amplitude of the praecordial accelerocardiogram, correlates with peak aortic acceleration in dogs (Winter et al., 1967). These systolic waves are thought to be generated by the elastic recoil of the great arteries during left ventricular ejection. The correlation between these waves and peak aortic acceleration has been attributed to the equal but opposite reactionary force which is produced in the great vessels in response to the acceleratory force imparted to the/

the blood by left ventricular contraction (Deuchar, 1967; Starr, 1965). Perhaps similar principles account for the correlation observed between the maximum amplitude of the praecordial accelerocardiogram and peak aortic acceleration.

There is no doubt that changes in the rate of left ventricular ejection exert a profound influence on the systolic waves of the ballistocardiogram. Slow ejection, whether induced by coronary artery ligation, by the administration of myocardial depressant agents or simulated during experiments on cadavers, is associated with a reduction in the amplitude of the major systolic waves of the ballistocardiogram (Deuchar, 1967; Starr, 1965; Winter et al., 1967). Clinically this situation occurs in aortic stenosis (Deuchar, 1967; Starr, 1965). Conversely, rapid ejection simulated in cadavers, or induced by cardiac stimulants, or occurring clinically in aortic regurgitation and hypertrophic cardiomyopathy, is associated with an increase in the amplitude of the systolic waves of the ballistocardiogram (Darby et al., 1957; Deuchar, 1967; Starr, 1965; Winter et al., 1967). To account for the pronounced effects of changes in the rate of left ventricular ejection on the early systolic waves of the ballistocardiogram, Starr (1965) has suggested that active shortening is largely confined to the period of early ejection. Active shortening of the muscle fibres stretches the in-series elastic elements in the myocardium. The later phase of slower ejection is then due to/

to the elastic recoil of these elements. Thus, active shortening provides the force for the rapid achievement of peak acceleration and flow. During the later phase of ejection acceleration is directed towards the ventricle, forward flow being maintained solely by inertia. Myocardial contractility is, therefore, expressed early during ejection (Deuchar, 1967; Starr, 1965) at the time when peak aortic acceleration is occurring.

Although it is clear from the foregoing discussion that changes in the ballistocardiogram accompany changes in left ventricular performance during acute interventions, the cumbersome nature of the apparatus limits its potential application in clinical practise.

Systolic Time Intervals:

Quantitative analysis of the praecordial pulsations has not generally found application in clinical practice because of difficulties in standardisation and, consequently, the lack of comparability between different individuals. The amplitude of the vibrations recorded at the praecordium depends not only upon the magnitude of the intra-cardiac forces and movements which produce the vibrations, but also on the coupling properties of the chest wall which, of course, can not be quantified. Measurement of the duration of the various phases of the cardiac cycle overcomes the problems of standardisation and allows of direct comparison between different individuals.

The duration of the pre-ejection period, measured by non-invasive techniques, has been particularly intensively studied and has been shown to correlate closely with the pre-ejection period measured by transducer-tipped catheters during cardiac catheterisation (Metzger et al., 1970; Talley, Meyer and McNay, 1971). Theoretically, changes in the duration of the pre-ejection period could be due to changes in either of its two components, the electromechanical delay and the isovolumetric contraction time but, in practice, the electromechanical delay is constant (Harris, Schoenfeld and Weissler, 1967a; Martin, Shaver and Leonard, 1972). Consequently, changes in the pre-ejection period reflect changes in isovolumetric contraction time (Martin et al., 1972; Metzger et al., 1970), which, by definition, is the time required for the myocardium to increase left ventricular end-diastolic pressure to aortic diastolic pressure, at which point ejection begins. The determinants of the duration of isovolumetric contraction time and, hence, pre-ejection period are

1. Left ventricular end-diastolic pressure and volume (Flessas et al., 1971; Martin et al., 1972; Talley et al., 1971). Only very large increases in end-diastolic pressure influence the pre-ejection period (Metzger et al., 1970), tending to shorten it both by the Starling mechanism and by reducing the total pressure required to open the aortic valve (Harris, Aytan and Pouget, 1973; Martin et al., 1972; Pouget et al., 1971).

2. Aortic diastolic blood pressure (Aronow, 1970; Aronow, Bowyer and Kaplan, 1971a; Flessas et al., 1971; Harris et al., 1967a; Harris, Weissler and Brooks, 1967b; Martin et al., 1972, 1974; Metzer et al., 1970; Shaver et al., 1968; Talley et al., 1971). An increase in aortic diastolic pressure tends to prolong the pre-ejection period by increasing the total pressure which the left ventricle must generate in order to open the aortic valve and, possibly, by activating baroreceptor reflexes which depress myocardial contractility (Harris et al., 1967a, b; Metzger et al., 1970; Sawayama et al., 1969; Shaver et al., 1968).

3. Left ventricular mean dP/dt. An increase in left ventricular dP/dt will clearly shorten the pre-ejection period (Aronow, 1970; Aronow et al., 1971a; Harris et al., 1973; Leighton et al., 1969; Maher et al., 1974; Martin et al., 1972; Metzger et al., 1970; Pouget et al., 1971; Sawayama et al., 1969; Talley et al., 1971). In turn, left ventricular dp/dt is influenced by changes in heart rate, contractility, left ventricular end-diastolic volume and, to some extent, aortic diastolic blood pressure (Aronow, 1970; Aronow et al., 1971a; Harris et al., 1973; Leighton et al., 1969; Martin et al., 1972; Metzger et al., 1970; Pigott et al., 1971; Pouget et al., 1971; Talley et al., 1971; Whitsett and Naughton, 1971).

Tachycardia, induced by atrial pacing or atropine, has no effect on the pre-ejection period (Harris et al., 1967b; Leighton/

Leighton et al., 1969; Martin et al., 1974; Talley et al., 1971), unlike the tachycardia associated with beta adrenergic stimulation which profoundly shortens the pre-ejection period (Ahmed et al., 1972; Harris et al., 1966, 1967b, 1973; Maher et al., 1974; Martin et al., 1972; Pigott et al., 1971; Pouget et al., 1971; Whitsett and Naughton, 1971). On the other hand, tachycardia produces a pronounced increase in left ventricular dP/dt which would be expected to shorten the pre-ejection period (Leighton et al., 1969; Mason, 1969). The explanation for this apparent paradox probably lies in the fact that atrial pacing increases the total pressure generated during isovolumetric contraction by reducing left ventricular end-diastolic pressure, while aortic diastolic pressure increases (Leighton et al., 1969). This tends to obscure any trend towards shortening of the pre-ejection period with increasing heart rate. In fact, an inverse correlation between the duration of the pre-ejection period and heart rate, which could not be explained on the basis of changes in ventricular filling, was inferred by Harley and his colleagues (1969) who studied beat-to-beat variation in the systolic time intervals in patients with atrio-ventricular dissociation.

It is clear from the foregoing discussion that the relationship between the pre-ejection period and left ventricular contractility is a complex one and that it may be difficult, under certain circumstances, to interpret the significance of changes in the duration of the pre-ejection period./

period. Although correlations have been established, in resting subjects, between pre-ejection period and various indices of myocardial performance, such as cardiac output and stroke volume (Ahmed et al., 1972; Weissler, Harris and Schoenfeld, 1969), ejection fraction (Ahmed et al., 1972; Flessas et al., 1971; Garrard, Weissler and Dodge, 1970; Martin et al., 1972), mean velocity of circumferential fibre shortening (Flessas et al., 1971) and the derived isovolumetric indices of contractility (Ahmed et al., 1972; Talley et al., 1971), these correlations have not, in general, been sufficiently close to enable any direct prediction of left ventricular contractile state to be made. The observation that the degree of prolongation of the pre-ejection period in cardiac patients is proportional to the severity of the cardiac disease assessed on clinical criteria (Ahmed et al., 1972; Weissler, Harris and Schoenfeld, 1968, 1969) is not helpful, since it would be equally justifiable to conclude from this data that measurement of the pre-ejection period provides no more information than a careful history and clinical examination. However, in acute experiments, pre-ejection period shortens when left ventricular contractility is augmented by dynamic exercise (Ahmed et al., 1972; Aronow, 1970; Aronow et al., 1971a; Cardus, 1973; Frank and Haberern, 1971; Harris et al., 1973; Leon et al., 1972; Lindqvist, Spangler and Blount, 1973; Maher et al., 1974; Martin et al., 1972; Miller et al., 1970; Pigott/

Pigott et al., 1971; Pouget et al., 1971; Whitsett and Naughton, 1971), digitalis (Harris et al., 1967a; Weissler and Schoenfeld, 1970; Weissler et al., 1965) and sympathomimetic amines (Ahmed et al., 1972; Harris et al., 1966, 1967a; Hunt et al., 1970; Leon et al., 1972; Martin et al., 1972; Metzger et al., 1970).

The conventional technique for calculating the systolic time intervals involves simultaneous recordings of electrocardiogram, phonocardiogram and carotid pulse, which, in practice, is rather cumbersome. As a result, some investigators have attempted to measure the systolic time intervals from the apexcardiogram and its first derivative. It appears, however, that no event in the apexcardiogram corresponds reliably enough with the onset of left ventricular ejection, so that accurate measurement of systolic time intervals from the apexcardiogram is impossible (Gabor, Porubszky and Kalman, 1972; Tavel et al., 1965; Willems, de Geest and Kesteloot, 1971). The interval between the onset of the QRS complex of the electrocardiogram and the maximum amplitude of the first derivative of the apexcardiogram has been shown to correlate closely with its haemodynamic counterpart, the time to maximum left ventricular dP/dt, which is a useful index of myocardial contractility (Mason, 1969), during beta adrenergic stimulation and blockade and vagal stimulation (Reale, 1967; Vetter, Sullivan and Hyall, 1972; Willems et al., 1971). Since maximum dP/dt normally occurs at the onset of left ventricular/

ventricular ejection (Metzger et al., 1970), the time to maximum dP/dt is also closely related to pre-ejection period. Estimates of the pre-ejection period measured from the first derivative of the apexcardiogram have been shown to correlate with estimates made using conventional techniques (Gabor et al., 1972).

Although the temporal relationships between the waves of the praecordial accelerocardiogram and the events of the cardiac cycle are well documented (Luisada, 1962; Rosa and Kaplan, 1960a; Rosa et al., 1961), no attempt has previously been made to measure systolic time intervals from the accelerocardiogram.

Echocardiography:

The introduction of ultrasound cardiography by Edler and his associates in the early 1950s (Edler et al., 1961) evoked little interest among cardiologists in general for over ten years. However, the past decade has seen such intensive investigation that, in many centres, echocardiography has developed into a routine procedure in the assessment of a variety of cardiac diseases. Over the years different intra-cardiac structures have been identified, their characteristic movement patterns documented and anatomical confirmation established by autopsy studies and by injection of contrast medium at cardiac catherterisation (Edler et al., 1961; Feigenbaum, 1972; Gramiak, Shah and Kramer, 1969). Apart from its value in cardiac diagnosis, echocardiography, in common with/

with other non-invasive techniques, is potentially valuable in the serial assessment of myocardial function. In this context the validity of the method depends to a large extent on its reproducibility within the individual, which has been repeatedly examined and confirmed (Cooper et al., 1972; Feigenbaum, 1972; McDonald, Feigenbaum and Chang, 1972; Pombo et al., 1971a).

It is possible to measure the diameter of a minor axis of the left ventricle throughout the cardiac cycle by simultaneously displaying the endocardial surfaces of the interventricular septum and posterior left ventricular wall (Belenkie et al., 1972; Fortuin et al., 1971; Fortuin, Hood and Craige, 1972; Grossman et al., 1973b; McCans and Parker, 1973; McDonald et al., 1972; Pombo, Troy and Russell, 1971b; Bopp and Harrison, 1970; Popp et al., 1969; Troy, Pombo and Rackley, 1972). These diameters can be converted to the corresponding volumes at end-systole and end-diastole by various manoeuvres based on the assumption that the left ventricular cavity can be represented as an ellipse whose major axis equals twice the length of its minor axis (Belenkie et al., 1973; Fortuin et al., 1971, 1972; Ludbrook et al., 1973; Murray, Johnston and Reid, 1972; Pombo et al., 1971 a, b; Troy et al., 1972). From these volumes it is clearly possible to calculate stroke volume and ejection fraction (Belenkie et al., 1973; Cooper et al., 1972; Fortuin et al., 1971, 1972; Murray et al., 1972; Pombo et al., 1971 a, b). Excellent correlations have been established between

between ultrasound estimates of left ventricular volumes and estimates obtained by left ventricular angiography and by dye dilution techniques in patients with myocardial and valvular disease (Belenkie et al., 1973; Cooper et al., 1972; Feigenbaum et al., 1972; Fortuin et al., 1971, 1972; Gibson, 1973; Ludbrook et al., 1973; McDonald et al., 1972; Millward, McLaurin and Craige, 1973; Murray et al., 1972; Pombo et al., 1971 a, b; Popp and Harrison, 1970; Ratshin et al., 1974; Teicholz et al., 1972; Troy et al., 1972).

Using this technique, it has been possible to demonstrate characteristic abnormalities in left ventricular volumes in patients with heart disease but normal haemodynamics (Belenkie et al., 1973), patients with clinical or haemodynamic evidence of cardiac failure (Belenkie et al., 1972; Danford et al., 1973; Fortuin et al., 1972; McDonald, et al., 1972) and patients with left ventricular volume overload (Burgess et al., 1973; Danford et al., 1973; Fortuin et al., 1972; Millward et al., 1973; Popp et al., 1969), as compared with normal subjects.

The mean velocity of circumferential fibre shortening may be calculated from ultrasound data and has been shown to correlate with estimates made by left ventricular cine-angiography (Cooper et al., 1972; Ludbrook et al., 1973; Paraskos et al., 1971). Mean velocity of circumferential fibre shortening appears to be a most sensitive indicator of the presence of heart disease (Cooper et al., 1972; McDonald et/

et al., 1972; Paraskos et al., 1971) and is reduced both in overt cardiac failure (Fortuin et al., 1972) and in the presence of sub-clinical left ventricular dysfunction (Ludbrook et al., 1973).

More recently it has become apparent that left ventricular echocardiography is sufficiently sensitive to detect small changes in left ventricular volumes induced acutely by changes in posture (Redwood, Henry and Epstein, 1974), by the administration of propranolol (Frishman et al., 1974) and glyceryl trinitrin (Burggraf and Parker, 1974; Redwood et al., 1974), or occurring spontaneously with variations in diastolic filling time in atrial fibrillation (Redwood et al., 1974).

In summary, left ventricular echocardiography is extremely useful in detecting changes in left ventricular volumes in the presence of heart disease and during acute manoeuvres. Unfortunately, technically satisfactory left ventricular echocardiograms may be difficult to obtain in a significant proportion of patients and some workers have therefore attempted to quantitate the movement of the posterior left ventricular wall alone, which is a simpler technique. Abnormalities have been described in posterior wall movement in patients with left ventricular failure (Belenkie et al., 1973; Carson and Kanter, 1971), acute myocardial infarction (Inoue et al., 1971; Jacobs et al., 1973; Kerber and Abbound, 1973; Stefan and Bing, 1972; Wharton, Smithen and Sowton, 1971) and left ventricular volume overload/

overload (Danford et al., 1973). Furthermore, changes in the velocity of posterior wall movement have been shown during acute manoeuvres such as beta adrenergic stimulation (Kraunz and Ryan, 1971) and blockade (Frishman et al., 1974) and dynamic exercise (Fogelman et al., 1972; Kraunz and Kennedy, 1970; Smithen, Wharton and Sowton, 1972). Although the echocardiogram of the posterior left ventricular wall is technically much easier to study than the echocardiogram of the left ventricular cavity, some doubt has recently been cast upon the resproducibility of measurements made from the posterior wall echo alone (Ludbrook et al., 1974a). The data obtained from echocardiograms of the posterior left ventricular wall does not correlate with other indices of left ventricular performance (Belenkie et al., 1973; Cooper et al., 1972; Kerber and Abboud, 1973; Ludbrook et al., 1974a) or with the clinical condition of the patients (Corya et al., 1974). Indeed, widely varying estimates of the normal range for posterior wall excursion and velocity have been published (Carson and Kanter, 1971; Cooper et al., 1972; Fogelman et al., 1972; Inoue et al., 1971; Jacobs et al., 1973; Ludbrook et al., 1974a).

The evaluation of left ventricular function from ultrasound studies of left ventricular wall movement poses problems in some patients. The assumptions about left ventricular geometry necessary for the conversion of echocardiographic dimensions to volumes may not hold true in patients with a dilated/

dilated left ventricle (Feigenbaum et al., 1972; Fortuin et al., 1971, 1972; Gibson, 1973; Ludbrook et al., 1973; McDonald et al., 1972; Popp et al., 1969, 1973; Teicholz et al., 1972). Furthermore, there is some evidence to suggest that the relative lengths of the major andminor axes of the ventricle alter throughout the cardiac cycle (Popp et al., 1973), thus invalidating one of the assumptions. Another problem is that patients with myocardial disease commonly have a degree of associated mitral regurgitation (Cheng, 1969; Heikilla, 1967) which, in itself, may influence left ventricular volumes independent of the effects of the primary disease (Belenkie et al., 1973; Burgess et al., 1973; Millward et al., 1973; Popp and Harrison, 1970). However, the major problem arises in patients with localised areas of dyskinesis, in whom the movement pattern of the visualised segments of the left ventricular wall may not be representative of overall left ventricular contraction (Belenkie et al., 1973; Feigenbaum et al., 1972; Fortuin et al., 1971; Grossman et al., 1973b; McLaurin et al., 1973a; Popp et al., 1973; Ratshin et al., 1974; Teicholz et al., 1973). In this situation it appears that echnocardiographic volumes continue to correlate with angiographic estimates overall but, on an individual basis, ultrasound becomes unreliable in predicting left ventricular volumes (Ludbrook et al., 1973; Popp et al., 1973). Indeed, it has been suggested that echocardiography might be useful diagnostically in the detection of areas of dyskinesis/

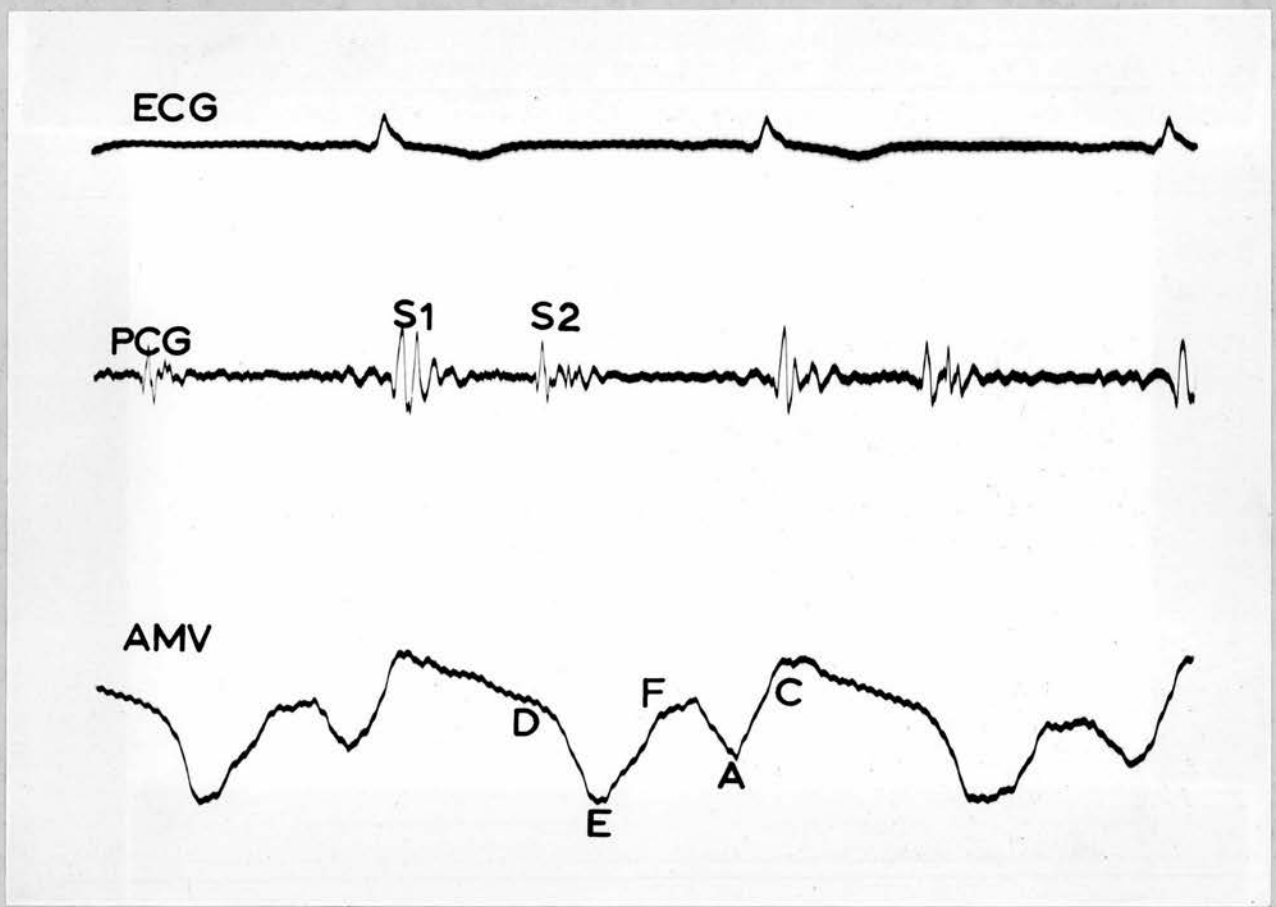
dyskinesis (Jacobs et al., 1973; Kerber and Abboud, 1973; Stefan and Bing, 1972).

The echo arising from the anterior cusp of the mitral valve was among the first to be described and, on account of its distinctive movement pattern, it constitutes a landmark for all ultrasound studies (Feigenbaum, 1972; Gramisk et al., 1969; Layton et al., 1973; Popp and Harrison, 1969; Pridie, Benham and Oakley, 1971; Shah et al., 1968a; Shah, Gramiak and Kramer, 1969; Zaky, Grabhorn and Feigenbaum, 1967; Zaky, Steimetz and Feigenbaum, 1969). The normal pattern of movement of the anterior cusp is illustrated in figure 2. In early diastole the cusp abruptly moves anteriorly to the open position (DE - figure 2). It then moves posteriorly in mid-diastole to a semi-closed position (EF - figure 2), followed by a reopening movement in response to atrial contraction (A - figure 2). A rapid movement then takes the cusp to its most posterior position by the end of isometric contraction (AC - figure 2) and finally, during left ventricular ejection, the cusp appears to move slowly anteriorly (CD - figure 2). This apparent opening movement during ejection is attributable to the fact that the pattern of the anterior cusp echo is, in fact, a composite of the movement of the cusp itself and movement of the mitral valve ring and, with it, the entire mitral valve apparatus (Chakorn et al., 1972; Layton et al., 1973; Zaky et al., 1967). During left ventricular ejection, shortening of the myocardial/

myocardial fibres results in the mitral valve ring and the entire mitral valve apparatus being drawn anteriorly, thus producing an apparent opening movement of the anterior cusp. Movement of the valve ring also accounts for some of the posterior movement in mid-diastole during left ventricular filling (Charkorn et al., 1972; Laniado et al., 1975).

The earliest abnormality to be recognised in the field of echocardiography was a reduction in the initial valve closure rate in mid-diastole (EF - figure 2) in patients with mitral stenosis (Pridie et al., 1971; Wharton and Lopez Bescos, 1970; Zaky, Nasser and Feigenbaum, 1968). It was soon appreciated that this abnormality was not specific to mitral stenosis but could also be found in the presence of aortic valve disease and in patients with other forms of left ventricular disease (Duchak, Chang and Feigenbaum, 1972; Layton et al., 1973; Pridie et al., 1971; Shah et al., 1968a, 1969). Early work suggested, and recent work has confirmed, that the initial valve closure rate really reflects the rate of left ventricular filling, being reduced in any patient in whom filling is slow, as it is in mitral stenosis (Duchak et al., 1972; Laniado et al., 1975; Layton, et al., 1973; Pridie et al., 1971; Shah et al., 1968a, 1969; Ziady et al., 1973). In the absence of mitral valve disease the rate of left ventricular filling depends upon the filling pressure and on the compliance of the left ventricle, an impairment of compliance producing slower mitral valve closure/

Figure 2 Configuration of the Mitral Valve Echocardiogram.



From above ECG = electrocardiogram
PCG = phonocardiogram
AMV = echocardiogram of the anterior cusp of the mitral valve (labelled according to previous workers). A downward movement signifies anterior movement of the cusp)

S1 = first heart sound
S2 = second heart sound
Note DE in early diastole
BF in mid-diastole
AC with atrial systole

closure at any given filling pressure (Duchak et al., 1972; Layton et al., 1973; Shah et al., 1968a, Ziady et al., 1973).

The pattern of complete mitral valve closure following atrial contraction (AC - Figure 2) has also been investigated. The first indication that this might provide information about the diastolic properties of the left ventricle occurred in the course of ultrasound studies in patients with complete heart block. In beats with a short PR interval mitral valve closure occurs exclusively during ventricular systole (Shah, Kramer and Gramiak, 1970) because ventricular contraction begins immediately after the mitral valve has opened in response to atrial systole. Following a normal PR interval the mitral valve is partially closed by the time left ventricular contraction begins (Pohost et al., 1975; Rubenstein et al., 1975; Shah, Kramer and Gramiak, 1968b; 1970; Zaky et al., 1968, 1969). In this situation left ventricular pressure exceeds left atrial pressure prior to the onset of ventricular systole, creating a reverse gradient across the valve which tends to close it (Zaky et al., 1969). However, two patterns were observed in beats with a prolonged PR interval. In patients with no haemodynamic evidence of left ventricular failure mitral valve closure was complete before ventricular contraction and the first heart sound was soft (Burggraf and Craige, 1974; Shah et al., 1970; Zaky et al., 1969). In these patients also, a reverse gradient from left ventricle to left atrium was present before the onset/

onset of left ventricular contraction (Zaky et al., 1969). In patients with left ventricular failure mitral valve closure was only partially complete before left ventricular systole and the first heart sound was normal or loud (Shah et al., 1968b, 1970; Zaky et al., 1969). In this group atrial and ventricular pressures both rose and fell rapidly in association with atrial systole, such that no pressure gradient from left ventricle to left atrium existed until left ventricular contraction had begun (Zaky et al., 1969). It appears that, at normal left heart pressures, the increase in atrial pressure due to atrial contraction is transmitted to the ventricle after a short delay, so that the pressure in the ventricle is rising while atrial pressure is falling. This creates a reverse gradient across the valve and closes it before left ventricular systole. When left heart pressures are elevated, this delay in the transmission of the pressure wave from left atrium to left ventricle is abolished, left atrial and left ventricular pressures rise and fall together and a reverse gradient across the mitral valve does not occur until the left ventricular pressure is increased by ventricular contraction (Zaky et al., 1969).

These observations have since been extended to patients with normal atrio-ventricular conduction. The normal time interval between the peak of the 'A' wave of the echocardiogram and the assumption of its most posterior position (AC - figure 2) is prolonged in cardiac patients with/

with an elevated left ventricular end-diastolic pressure. In a small series of patients, those in whom this interval was 200 milliseconds or less had an end-diastolic pressure of 5 to 16 millimetres mercury with an 'a' wave of less than 5 millimetres, in contrast to those in whom the interval was greater than 400 milliseconds, who had an end-diastolic pressure of 27 to 42 millimetres mercury and an 'a' wave greater than 12 millimetres. Furthermore, glyceryl trinitrin caused reductions in both the AC interval and left ventricular end-diastolic pressure (Feigenbaum et al., 1970). In extreme cases the closing movement is not merely prolonged but occurs in two distinct phases separated by a plateau. It appears that, in patients with increased left heart pressures, the rapid transmission of the atrial pressure wave to the left ventricle leads to the early onset of mitral valve closure. However, the pressures across the valve also equalise rapidly, interrupting valve closure, which is finally completed by left ventricular systole (Konecke et al., 1973).

It is possible to summarise these observations by saying that the duration of the final closing movement depends on whether the valve is closed before or after the onset of left ventricular systole (Shah et al., 1970). In turn, the timing of the closing movement of the mitral valve relative to the onset of ventricular contraction depends upon the PR interval (Shah et al., 1970; Zaky et al., 1969) and on the effectiveness of atrial contraction (Zaky et al., 1969).

The/

The PR interval influences the timing of mitral valve closure by determining the degree of separation of the valve cusps at the onset of ventricular systole (Burggraf and Craige, 1974; Parisi and Milton, 1973). Since the duration of the closing movement depends on the PR interval, one group of workers have corrected for this by subtracting the AC interval from the PR interval and have shown that when the calculation works out at less than 60 milliseconds left ventricular end-diastolic pressure exceeds 20 millimetres mercury with an 'a' wave greater than 8 millimetres, but when it exceeds 60 milliseconds the 'a' wave is less than 8 millimetres, irrespective of the level of end-diastolic pressure (Konecke et al., 1973). This parameter has been shown to be capable of distinguishing normal subjects from patients with myocardial disease and also patients with cardiac failure from those without (Corya et al., 1974). The second factor which determines the timing of mitral valve closure relative to the onset of ventricular systole is the effectiveness of left atrial contraction, which is reduced in mitral stenosis and in the presence of increased left heart pressures. Inneffective atrial contraction mitigates against the development of a reverse gradient across the valve until ventricular contraction begins (Chakorn et al., 1972; Shah et al., 1970; Zaky et al., 1969). Consequently the valve cusps remain open until the onset of left ventricular systole.

These, then, are some of the non-invasive techniques which/

which have been used in the past to evaluate left ventricular function. This thesis is concerned with the information which can be obtained from two of these techniques, the praecordial accelerocardiogram and the mitral valve echocardiogram.

Stress tests:

Continuing advances in the techniques of cardiac surgery have made this form of treatment available to an ever widening range of patients. However, cardiopulmonary by-pass continues to be a hazardous procedure, particularly in patients with impaired myocardial function pre-operatively. Consequently the pre-operative assessment of myocardial function is of considerable importance in selecting patients for surgical treatment and in evaluating new forms of treatment. A more precise evaluation of left ventricular performance is possible if a stress test is employed, since this will reveal abnormalities of cardiac reserve in a particular sub-group of patients with normal haemodynamics at rest. A variety of stress tests have been used in cardiac laboratories, including dynamic exercise (Dwyer, Wiener and Cox, 1968; Parker, di Giorgi and West, 1966; Parker, West and di Giorgi, 1967; Wiener, Dwyer and Cox, 1968, 1969), static or isometric exercise (Amende et al., 1972; Fisher et al., 1973; Grossman et al., 1973a; Helfant, de Villa and Meister, 1971; Mivowitz et al, 1971; Payne, Horwitz and Mullins, 1973; Quinones et al., 1974b), rapid atrial pacing (Barry et al., 1974; Conti et al., 1970;/

1970; Dwyer, 1970; Kasparian and Wiener, 1969; Parker et al, 1969), infusion of radiographic contrast medium (Brown et al., 1969; Cohn et al., 1973a) and administration of vasoactive drugs (Herman et al., 1967; Payne et al., 1973).

Like the more familiar, dynamic exercise, isometric exercise is a physiological stress encountered in everyday activities, such as lifting, carrying and pushing (Donald, et al., 1967; Krayenbuehl and Rutishauser, 1973; Lind, 1970). However, isometric exercise, in the form of sustained handgrip is more convenient to perform during diagnostic cardiac catheterisation than is dynamic exercise. The stressful effects of sustained handgrip on the left ventricle are due to a combination of tachycardia and an acute increase in blood pressure (Donald et al., 1967; Lind, 1970; Lind et al., 1964; McDonald et al., 1966) both of which tend to cause an increase in left ventricular work and oxygen consumption. An increase in myocardial oxygen consumption has been confirmed directly by coronary sinus catheterisation studies (Kivowitz et al., 1971; Lowe et al., 1975; Nelson et al., 1974). The magnitude of the pressor response depends upon the percentage of the maximum tension achieved in the active muscles and not on the absolute muscle bulk involved (Donald et al., 1967; Krayenbuehl and Rutishauser, 1973), which means that it is faily simple to arrange for a comparable cardiovascular stress in different individuals. Up to a level of twenty percent of maximum tension a steady haemodynamic state is achieved, but at higher work loads there is a continuing increase in heart rate and blood/

blood pressure throughout the test period (Donald et al., 1967, Krayenbuehl and Rutishauser, 1973; Lind, 1970; Lind et al., 1964). The cardiovascular effects of handgrip are interpreted as an attempt to compensate for local obstruction to blood flow in the exercising muscles by increasing the perfusion pressure (Donald et al., 1967; Helfant et al., 1971; Kivowitz et al., 1971; Lind, 1970; Lind et al., 1964; McDonald et al., 1966).

Aims of this Thesis:

The principal aim of this thesis is to investigate the left ventricular response to isometric handgrip, using the non-invasive techniques of praecordial accelerocardiography and mitral valve echocardiography.

The systolic response of the left ventricle has been assessed by measuring the maximum systolic amplitude of the praecordial accelerocardiogram and the time to maximum praecordial acceleration. The maximum systolic deflection of the accelerocardiogram was used as an index of left ventricular systolic function on the basis of its previously demonstrated correlation with peak aortic acceleration (Reuben and Littler, 1973). In theory, time to maximum praecordial acceleration (E - Figure 1) should be closely related to the duration of the pre-ejection period because the E point occurs at the onset of left ventricular ejection (Luisada, 1962; Rosa and Kaplan, 1960a). However, this has not previously been demonstrated quantitatively and it was necessary first to do this before proceeding to study the effects of exercise on this measurement. The changes which occurred in both of these parameters during handgrip have been compared in normal subjects and patients studied during cardiac catheterisation and, in the latter group, the accelero-cardiographic response has been related to central circulatory dynamics. Unfortunately in this study it was not feasible to measure the exact haemodynamic equivalent of maximum praecordial acceleration, peak aortic acceleration and it was, consequently, necessary to compare the changes in the praecordial accelerocardiogram with haemodynamic variables to which the accelerocardiogram is not directly related. In addition the praecordial accelerocardiogram has been used to compare the response to isometric and dynamic exercise in the normal subjects/...

subjects before and after beta adrenergic blockade, in order to shed further light on the autonomic mechanisms which mediate the responses to these different forms of exercise.

The diastolic behaviour of the left ventricle during handgrip has been investigated in the normal subjects and the cardiac patients by measuring the amplitude of the P wave of the praecordial accelerocardiogram and also by ultrasound studies of the anterior cusp of the mitral valve. The P wave of the accelerocardiogram, like the 'a' wave of the apexcardiogram, coincides with atrial systole (Luisada, 1962; Mounsey, 1959; Rosa and Kaplan, 1960a; Rose et al, 1961). A correlation between the amplitude of the 'a' wave of the apexcardiogram and left ventricular diastolic pressure has previously been established (Diamond and Benchimol, 1963; Rios and Massumi, 1965; Voigt and Friesinger, 1970) but there have been no reports in the literature of any attempts to correlate the P wave of the accelerocardiogram with left ventricular pressure. Consequently in this thesis it was first necessary to establish such a correlation and then to compare the response in normal subjects and cardiac patients. The ultrasound section of the study was undertaken in an attempt to detect changes in the pattern of left ventricular filling accompanying the changes in left ventricular diastolic pressure during isometric exercise.

CHAPTER 2

Methods

EQUIPMENT:

Accelerocardiogram Transducer

The accelerometer consists of a light aluminium cylinder, 2 centimetres in diameter, incorporating a piezzo-electric strain gauge (Pixie transducer, Endevco Laboratories Ltd., U.K.) mounted as a cantilever spring, the free end of which is a 420 mg. lead bob (Figure 3). When an acceleration is applied towards the base of the transducer, the magnitude of the movement of the lead bob relative to the base depends upon the mass of the bob, the stiffness of the spring and the acceleration applied. Since the mass of the bob and the stiffness of the spring are constant, the displacement of the lead bob is proportional to the acceleration applied. Any movement of the bob relative to the base deforms the strain gauge, whose resistance is 1 K Ohm and whose resonant frequency is 1 K Hz. The output of the strain gauge is fed to an amplification system containing a filter network which limits the frequency response so that it is uniform from D.C. to 25 Hz. The output of the instrument has been shown to be linear up to 0.5g. and is unaffected by changes in the pressure with which the accelerometer is applied to the chest wall. Full details of the instrument have previously been published (Bew et al., 1971; Reuben and Littler, 1973).

Echocardiography

Mitral valve echocardiograms were recorded using a Hewlett-Packard ultrasonoscope (HP 7214 A) and a 2.5 megaHertz transducer. The transducer was placed in the fourth or fifth left intercostal space adjacent to the left sternal edge and directed posteriorly until the characteristic movement pattern of the anterior cusp of the mitral valve was identified. The echo from the anterior cusp was isolated by means of an analogue gate system and displayed on a UV recorder. The analogue gate system works on the principle that only the dominant (i.e. highest amplitude) echo within the gate is recorded, all other echoes within the gate, and any echo outwith the gate, being discarded.

The/...

The electronic gate is adjusted to the depth (i.e. distance from the surface) of the structure to be studied and its width is adjusted according to the amplitude of the excursion of that structure. With suitable adjustment the movement pattern of a single structure may be recorded, in isolation, throughout the cardiac cycle on a conventional recorder, in contrast to the more recently developed strip-chart recorder, using which it is possible to record echoes from many intracardiac structures simulutaneously.

Dynanometer

The dynanometer which was used in the handgrip studies in the normal subjects included a miniature linear displacement transducer whose electrical output is measured on a voltmeter scale calibrated from 0 to 50kilogram. A 50 kilogram thrust produces a 5 millimetre displacement. Full details have already been published (Ewing et al., 1973).

SUBJECTS:

The normal subjects were six healthy, volunteer members of staff aged between 26 and 33 years. These subjects did not undergo cardiac catheterisation. The patients, who were studied during diagnostic cardiac catheterisation, comprised twelve with dominant aortic stenosis, three of whom had mild aortic regurgitation and two of whom had co-existent coronary artery disease, and sixteen with myocardial disease due to coronary atherosclerosis in thirteen and idiopathic congestive cardiomyopathy in three. All patients were in sinus rhythm at the time of the study and none had clinical or haemodynamic evidence of mitral valve disease. Ten of the patients with aortic stenosis had electrocardiographic evidence of left ventricular hypertrophy. Resting haemodynamic and cine-angiographic data is summarised in table I. Left ventricular cine-angiography was performed with the patients in the right anterior oblique position and showed a dyskinetic area in four patients with coronary heart disease. Of the patients with coronary artery disease, eight had sustained a previous myocardial infarction and one was in clinical cardiac failure, controlled by medical treatment, at the time of/...

Figure 3 Diagram of the Accelerometer.

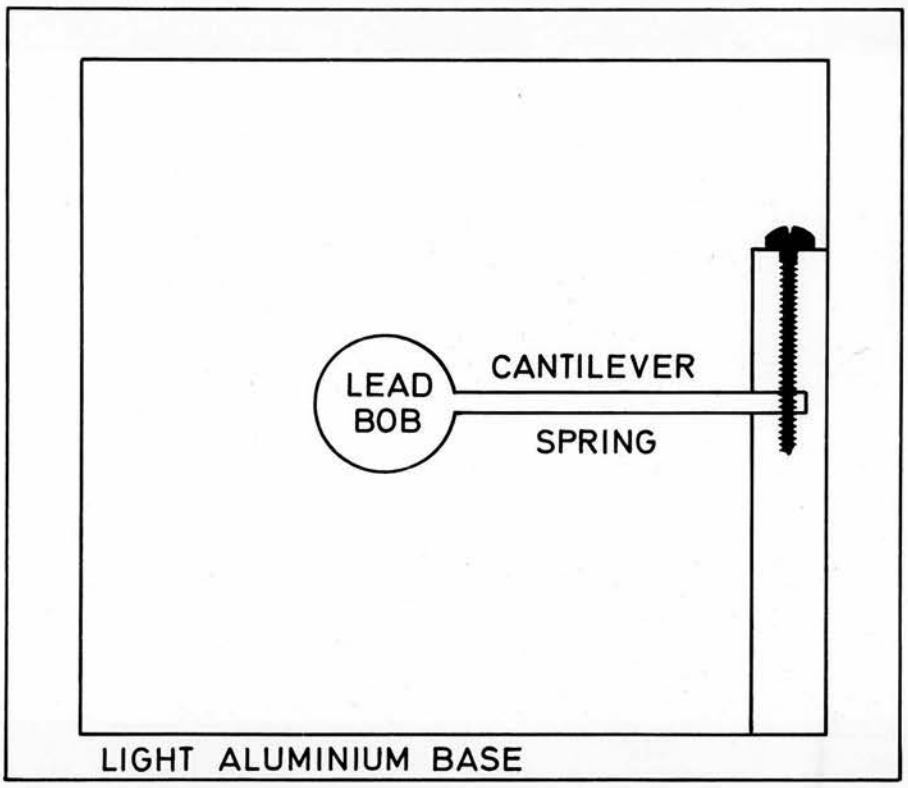


Table 1. RESTING CATHETERISATION DATA IN CARDIAC PATIENTS

Case	Patients with Aortic Stenosis			Case	Patients with Myocardial Disease	
	Aortic Valve Gradient (mm Hg)	Aortic Valve Area (cm^2)	Cardiac Index ($L/m^2/min$		Coronary Angiography	LV Angiography
1	35	0.43	1.72	13	3 vessel disease	Poor
2	34	1.13	2.72	14	3 vessel disease	Good
3	38	0.65	1.87	15	3 vessel disease	Good
4	79	0.72	4.18	16	Normal	Good
5	10	-	3.80	17	3 vessel disease	Poor
6	76	0.60	2.90	18	3 vessel disease	Good
7	77	1.10	3.10	19	3 vessel disease	Good
8	60	0.53	2.40	20	Normal	Good
9	43	0.90	2.30	21	1 vessel disease	Anterior Aneurysm
10	85	0.40	2.16	22	3 vessel disease	Poor
11	87	0.52	2.40	23	2 vessel disease	Apical Aneurysm
12	49	0.95	3.49	24	3 vessel disease	Anterior Hypokinesis
				25	Normal	Poor
Group Mean	56	0.72	2.92	26	1 vessel disease	Good
SEM	7	0.08	0.22	27	3 vessel disease	Good
				28	2 vessel disease	Inferior Hypokinesis

of the study. The mean age (± one standard deviation) in the patients with aortic stenosis was 56 ± 10 years and in the patients with myocardial disease, 48 ± 9 years.

Three patients with aortic stenosis (Cases 2, 6, 8) and five patients with myocardial disease (Cases 17, 19, 23, 25, 28) had been excluded from the part of the study concerned with the time to peak acceleration because of difficulties in identifying the onset of the QRS complex of the electrocardiogram. Two patients with aortic stenosis (Cases 3, 12) and three with myocardial disease (Cases 14, 24, 25) had to be excluded from the studies of the P wave of the accelerocardiogram because of the gain setting on the instrument was insufficient to enable accurate measurement of the amplitude of the P wave. Two patients with aortic stenosis (Cases 7, 9) had also to be excluded from this part of the study because the standardisation of the left ventricular pressure measurements did not permit accurate measurement of left ventricular end-diastolic pressure. Echocardiographic studies were only performed on ten patients, three with aortic stenosis (Cases 2, 5, 10) and seven with myocardial disease (Cases 13, 16, 17, 18, 19, 23, 28). One patient with aortic stenosis (Case 9) was excluded because of inadequacy of left ventricular diastolic pressure recordings and another patient with aortic stenosis (Case3) because of his echocardiogram was not of sufficiently high quality.

Protocol:

The accelerocardiogram transducer was attached to the chest wall overlying the fifth rib, internal to the mid-clavicular line by means of an adhesive disc. An electrocardiogram, recorded from praecordial leads, was displayed simultaneously with the accelerocardiogram on an ultra-violet recorded (Honeywell Recording Oscillograph, Type 1185, Mark 2). All recordings were made during uninhibited respiration with the subjects supine. The normal subjects gripped the strain gauge dynanometer while the patients gripped a partially inflated sphygmomanometer cuff. Each patient's maximum grip strength (maximum voluntary contraction - MVC) was initially determined

and/...

and he was then instructed to maintain 30 percent MVC for three minutes, a level of isometric exercise which has been repeatedly shown to elicit significant increases in heart rate and blood pressure (Fisher et al., 1973; Kivowitz et al., 1971; Payne et al., 1973; Quinones et al., 1974b). Care was taken to ensure that no subjects performed a Valsalva manoeuvre, as has been emphasised previously (Fisher et al., 1973; Helfant et al., 1971; Krayenbuehl et al., 1973).

The protocol in the normal subjects was as follows. After a thirty minute rest period, control readings were taken and the supine subject then performed sustained isometric handgrip using his right hand. Further readings were taken during the final thirty seconds of handgrip and again four minutes later. After resting for twenty minutes, control observations were repeated, following which the subjects exercised, in the erect posture, on a bicycle ergometer at an initial load of 600 kilopond metres (kpm) while maintaining a pedal speed of 50 to 60 r.p.m. The load was increased by 150 kpm every minute until a heart rate of 170 beats per minute was attained. The subject dismounted and lay supine again, further recordings being made one and a half minutes after the end of exercise and again twenty minutes later. This level of exercise has been shown to approximate to 70 percent of maximum oxygen comsumption (Astrand and Radahl, 1970). Thirty minutes after the end of exercise a control reading was taken and propranolol (Inderal - I.C.I.) was administered intravenously in a dose of 0.2 milligram per kilogram body weight over a period of five minutes, delivered in a total volume of approximately thiry millilitres. This dose has been shown to produce a potent beta adrenergic blocking effect (Jose, 1966). Five minutes after the completion of the injectinn the above sequence of manoeuvres and recordings was repeated. The positions of the electrocardiogram leads and accelerocardiogram transducer were not altered throughout the study.

The patients were studied during diagnostic cardiac catheterisation after the collection of resting haemodynamic data but before angiography. On the day before catheterisation/...

catheterisation each subject was familiarised with the handgrip procedure. Beta adrenergic blocking drugs were discontinued over the 72 hours preceding catheterisation but all other medication was administered as usual up to the time of the studies. One hour prior to catheterisation the patients were sedated with five milligrams of diazepam (Valium - Roche) orally. The timing of the readings was identical to that in the normal subjects. The patients did not perform dynamic exercise.

Measurements

Heart rate was calculated from the mean of 10 consecutive RR intervals measured at a paper speed of 100 millimetres per second and the maximum amplitude of the accelerocardiogram (DE - Figure 1), was averaged over 20 consecutive beats at a paper speed of 25 millimetres per second. The amplitude of the P wave of the accelerocardiogram (Figure 1) was averaged over 10 consecutive cardiac cycles at a paper speed of 25 millimetres per second. It must be recognised that variations in chest wall thickness and transducer coupling make it impractical to compare the absolute value of the amplitude of a praecordial pulsation either between different subjects or with any haemodynamic variable. In acute studies, such as handgrip, this problem is overcome by considering the change from resting control values which occurs during the intervention. However, one of the aims of the study was to determine if there was a relationship between the amplitude of the P wave and left ventricular end-diastolic pressure at rest in the cardiac patients. An elevated left ventricular end-diastolic pressure is associated with a prominent atrial systolic wave ('a' wave) in the apexcardiogram i.e. the amplitude of the 'a' wave is increased relative to the total excursion of the apexcardiogram (Dimond and Benchimol, 1963; Rios and Massumi, 1965). For quantitative work with the apexcardiogram, therefore, the amplitude of the 'a' wave is expressed as a percentage of the total amplitude of the tracing (Gibson et al., 1974; Ginn et al., 1967; Voigt and Friesinger, 1970). Using this principle, the amplitude of the P wave of the accelerocardiogram in the present study was expressed as a percentage of the total excursion of the tracing (i.e. the amplitude of the maximum deflection, DE) for the resting data./...

resting data.

For those parts of the study concerning the effects of exercise on the accelerocardiogram the accelerocardiographic data was expressed in microvolts (uV) using a 0.5 millivolt square wave as a standard. It is possible to calibrate the amplitude of the various waves of the accelerocardiogram in units of accerlation (g) by attaching the transducer to the arm of a pendulum which is then set at various angles from the vertical (θ). On releasing the pendulum arm the initial acceleration is $g \sin \theta$ and this calculated value can be plotted against the amplitude of the initial accelerocardiogram deflection for a variety of angles at any fixed gain setting. However, this calibration is tedious to perform for each patient examined (i.e. each gain setting) and the absolute value for praecordial acceleration at any point during the cardiac cycle is not meaningful for comparison with haemodynamic data at rest or for comparisons between different subjects, as discussed above.

However, the principal aim of this study was to assess the response to acute interventions, each subject serving as his own control. Time to peak acceleration was measured from the onset of the QRS complex of the electrocardiogram to the maximum systolic peak of the accelerocardiogram (E - figure 1). This was averaged over ten consecutive cardiac cycles at a paper speed of 100 millimetres per second.

Recordings of the anterior cusp echocardiogram were made simultaneously with the electrocardiogram and accelerocardiogram before, during and after handgrip. The slope of the opening movement of the mitral valve in early diastole (DE - figure 2), the initial valve closure rate in mid-diastole (EF - figure 2) and the duration of the closing movement at end-diastole (AC - figure 2) were each averaged over ten cardiac cycles at a paper speed of 100 millimetres per second. Between recordings, the transducer was held in place and the anterior cusp echo continuously monitored.

In the normal subjects arterial blood pressure in the non-exercising arm was measured by sphygmomanometry before, during and after handgrip. In the patients with aortic stenosis left ventricular pressure was measured by means of a Brockenbrough catheter/...

catheter, following trans-septal catheterisation of the left atrium, and central aortic pressure was measured by means of a polyethylene catheter 100 centimetres in length with an interval diameter of 0.066 centimetres (Formocath, Becton-Dickson Ltd.), introduced into the right femoral artery by the Seldinger technique. The frequency response of the catheter-manometer system was flat to 20 Hertz. Left ventricular maximum dP/dt was obtained by electronic differentiation of the pressure signal, using an R.C. filter network whose response was uniform to 50 Hertz. Resting cardiac output was measured by the indicator dilution method, using indocyanine green as the indicator and a Waters X 300 cuvette densitometer. Mean simultaneous aortic valve gradient was measured at rest and the valve area was calculated from Gorlin's formula (Gorlin and Gorlin, 1951). In the patients with myocardial disease only left ventricular pressure was measured after the Formocath had been manipulated across the aortic valve. Peak left ventricular systolic pressure, post 'a' wave left ventricular end-diastolic pressure and the height of the 'a' wave, aortic systolic and diastolic pressure (in the patients with aortic stenosis) and left ventricular maximum dP/dt were recorded on an ultra-violet recorder (Shandon Southern Instruments Ltd., U.K.) before, during the final thirty seconds of, and four minutes after handgrip. For the echocardiographic studies left ventricular maximum negative dP/dt during isovolumetric relaxation and the minimum ventricular pressure during early diastole were also measured at these times.

STATISTICAL METHODS

The results for the individual are expressed as the mean $\pm$ one standard deviation and for the groups as the mean $\pm$ one standard error of the mean. Individual and group means, standard deviations and standard errors of the mean were calculated on a Burroughs desk top computer (C 3660). In the studies on the normal subjects, statistical analysis was performed on the Burroughs desk top computer using student's paired t test. For comparisons between the groups of normal subjects and patients, student's unpaired t test w used,/...

used, calculations being performed on a PDP 11/10 computer (Digital Equipment Corporation, Maynard, Massachussets). Regression data was also calculated on the PDP 11/10 computer.

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CHAPTER 3

Results

The Maximum Amplitude of the Praecordial Accelerocardiogram

The results of this part of the study are summarised in tables 2 to 8 and figures 4 to 10.

A) Effects of Handgrip.

In the normal subjects group mean heart rate increased from 69 to 79 beats per minute, an increase of 15 $\pm$ 3% ($p < 0.005$) (Table 2; Figures 4, 5). Systolic and diastolic blood pressure increased by 23 $\pm$ 2%, from 114 to 138 mm Hg. ($p < 0.001$), and by 17 $\pm$ 4%, from 78 to 91 mm Hg. ($p < 0.001$), respectively, for the group as a whole (Table 2; Figures 4,6). The group mean value for the maximum amplitude of the accelerocardiogram decreased significantly by 11 $\pm$ 4% from 671 to 597 microvolts ($p < 0.05$) (Table 2; Figures 4, 7). Although the number of subjects was small, there was no correlation between the individual changes in the amplitude of the accelerocardiogram and the changes in heart rate or blood pressure.

After propranolol, handgrip increased group mean heart rate from 67 to 74 beats per minute, a change of 10 $\pm$ 2% ($p < 0.005$) (Table 2; Figures 4, 5). Average systolic blood pressure increased from 107 to 120 mm Hg., a change of 12 $\pm$ 5% ($p < 0.05$) and average diastolic blood pressure increased from 75 to 93 mm Hg., a change of 24 $\pm$ 5% ($p < 0.001$) (Table 2; Figures 4, 6). Following the drug, handgrip resulted/

TABLE 2. EFFECTS OF HANDGRIP ON HEART RATE, BLOOD PRESSURE AND DE, BEFORE AND AFTER PROPRANOLOL, IN THE NORMAL SUBJECTS.

Subject		Before Propranolol					After Propranolol			
		Heart Rate (beats/min)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	DE (microvolts)		Heart Rate (beats/min)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	DE (microvolts)
AM	CONTROL	82	118	74	655 (52)	CONTROL	75	98	60	480 (52)
	GRIP	85	130	90	565 (67)	GRIP	78	110	80	370 (36)
RT	CONTROL	71	130	95	835 (98)	CONTROL	69	125	85	400 (52)
	GRIP	85	160	95	610 (85)	GRIP	82	120	95	430 (94)
SS	CONTROL	69	90	55	885 (80)	CONTROL	66	90	60	545 (63)
	GRIP	71	110	70	805 (103)	GRIP	71	95	75	535 (71)
LH	CONTROL	64	118	75	648 (94)	CONTROL	64	110	70	597 (89)
	GRIP	75	150	90	660 (85)	GRIP	67	145	100	739 (98)
SR	CONTROL	59	115	90	355 (40)	CONTROL	60	110	90	295 (27)
	GRIP	75	145	105	345 (36)	GRIP	67	120	105	355 (49)
JI	CONTROL	66	110	80	650 (52)	CONTROL	67	110	85	545 (40)
	GRIP	82	130	95	595 (98)	GRIP	78	130	100	455 (67)
GROUP	CONTROL	69 (3)	114 (5)	78 (6)	671	CONTROL	67 (2)	107 (5)	75 (5)	477
	GRIP	79 (2)	138 (7)	91 (5)	597	GRIP	74 (3)	120 (7)	93 (5)	481
% CHANGE		+15 (3)	+23 (2)	+17 (4)	-11 (4)		+10 (2)	+12 (5)	+24 (5)	+1 (8)
P		<0.005	<0.001	<0.001	<0.05		<0.005	<0.05	<0.001	>0.90 NS

FIGURES IN PARENTHESES REPRESENT 1 STANDARD ERROR OF THE MEAN VALUE FOR THE GROUP DATA AND 1 STANDARD DEVIATION FOR THE INDIVIDUAL DATA.

resulted in an insignificant increase in the maximum amplitude of the accelerocardiogram, from 477 to 481 microvolts ($p > 0.90$) (Table 2; Figures 4, 7). The absolute values for maximum praecordial acceleration during handgrip were considerably lower after propranolol (Table 2; Figure 4). Propranolol had no significant effect on the response to handgrip in terms of heart rate ($p > 0.10$), systolic blood pressure ($p > 0.10$), diastolic blood pressure ($p > 0.10$) or the maximum amplitude of the praecordial accelerocardiogram ($p > 0.10$).

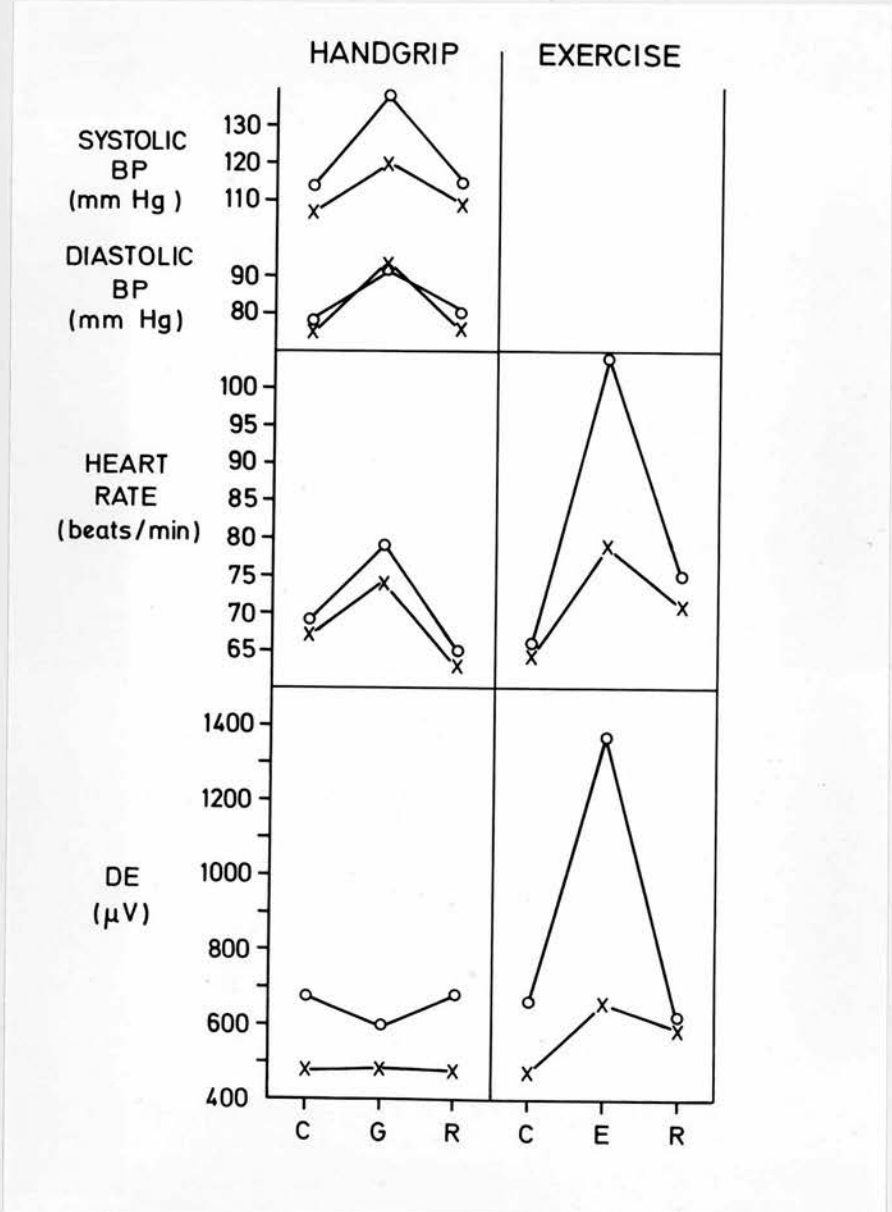
In the patients with aortic stenosis handgrip increased group mean heart rate from 75 to 83 beats per minute, a change of 11 $\pm$ 2% ($p < 0.001$) (Table 3; Figure 8). Average left ventricular systolic pressure increased from 201 to 231 mm Hg., a change of 15 $\pm$ 4% ($p < 0.001$) (Table 3; Figure 8) and mean aortic diastolic pressure increased from 79 to 93 mm Hg., a change of 18 $\pm$ 3% ($p < 0.001$) (Table 3; Figure 8). The group mean value for left ventricular maximum dP/dt increased from 1670 to 2100 mm Hg. per second, a change of 25 $\pm$ 5% ($p < 0.001$) and mean left ventricular end-diastolic pressure increased from 18 to 24 mm Hg., a change of 35 $\pm$ 9% ($p < 0.01$) (Table 3). In contrast to the normal subjects, the maximum amplitude of the accelerocardiogram increased, but insignificantly, from 650 to 705 microvolts, a change of 8.5 $\pm$ 6% ($p > 0.50$) (Table 3; Figure 8). The response in the patients with aortic stenosis did not differ significantly from that in the normal subjects as regards the increases in heart rate ($p > 0.60$), left ventricular systolic pressure ($p > 0.20$)/

TABLE 3. EFFECTS OF HANDGRIP ON HAEMODYNAMICS AND DE IN PATIENTS WITH AORTIC STENOSIS.

Case	Heart Rate (beats/min)		LV Syst Press (mm Hg)		Ao Diast Press (mm Hg)		LV End-Diast Press (mm Hg)		LV Max dP/dt (mm Hg/sec)		DE (microvolts)	
	Control	Grip	Control	Grip	Control	Grip	Control	Grip	Control	Grip	Control	Grip
1	76	82	163	182	86	92	20	23	1870	2540	1100 (91)	1005 (92)
2	60	79	210	240	95	120	24	45	1890	3040	380 (38)	450 (67)
3	50	68	210	265	80	95	14	19	1780	2400	705 (101)	710 (78)
4	94	98	203	215	75	85	18	20	1600	1800	342 (16)	480 (54)
5	65	73	120	160	70	87	11.5	19	1330	1550	785 (111)	1000 (78)
6	109	110	210	215	80	97	21	32	1560	1900	860 (320)	1020 (88)
7	62	76	230	320	72	98	-	-	2150	3180	763 (231)	763 (199)
8	72	81	220	258	65	75	11.5	18.5	500	620	470 (37)	551 (132)
9	94	101	150	172	61	72	-	-	2500	2620	1195 (71)	885 (132)
10	63	68	233	250	78	84	21	26	1450	1650	450 (31)	350 (46)
11	81	83	240	250	90	100	15	15	1820	1960	689 (92)	826 (86)
12	70	78	219	240	100	111	24	24	1580	1950	245 (14)	280 (50)
Group Mean	75	83	201	231	79	93	18	24	1670	2100	650	705
SEM	5	4	11	13	4	4	2	3	140	205	-	-
% Change	+ 11 (2)		+ 15 (4)		+ 18 (3)		+ 35 (9)		+ 25 (5)		+ 8.5 (6)	
P	<0.001		<0.001		<0.001		<0.01		<0.001		>0.50 NS	

Figures in parentheses represent 1 standard error of the mean value for the group data and 1 standard deviation for the individual data.

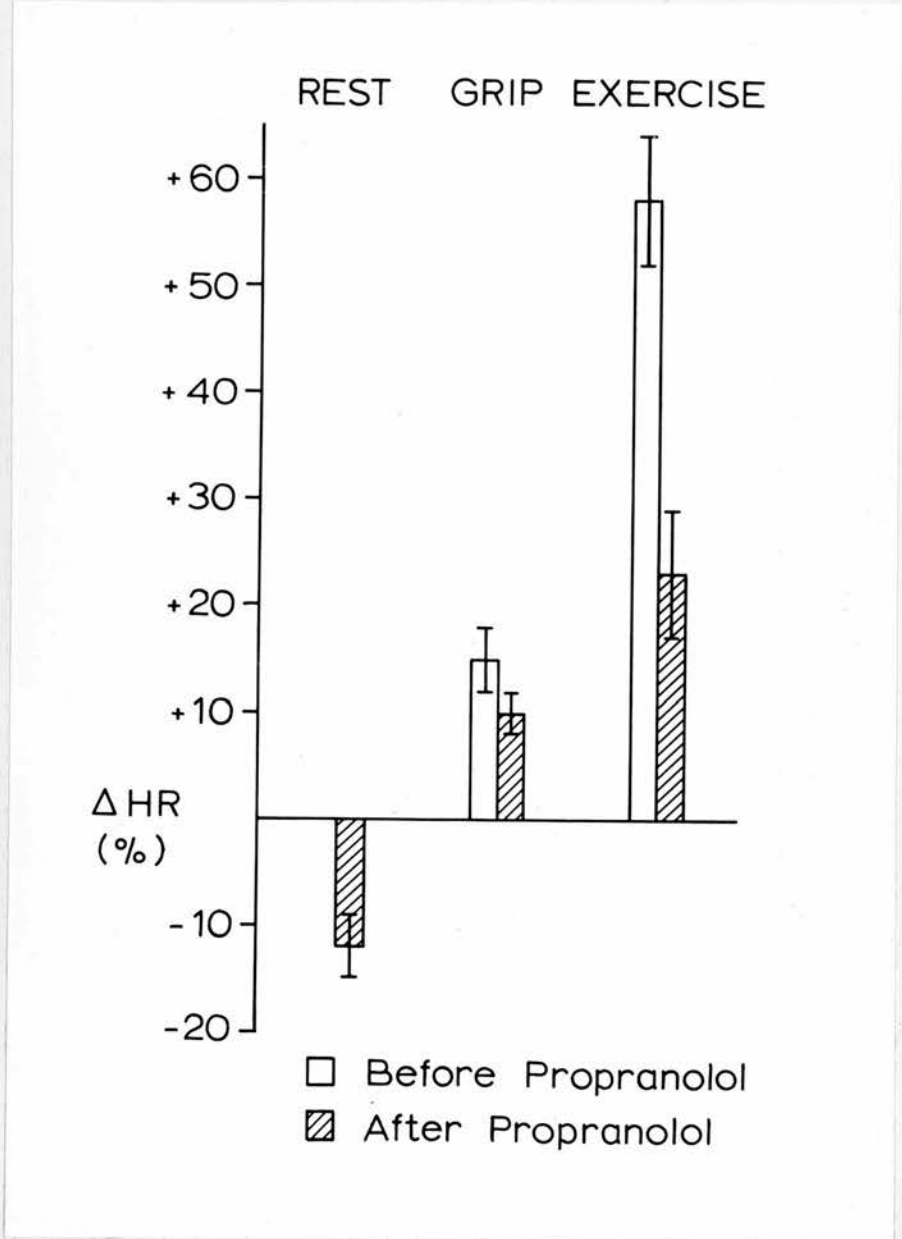
Figure 4 Effects of Handgrip and Dynamic Exercise on Heart Rate, Blood Pressure and DE in the Normal Subjects, Before and After Propranolol.



Effects of handgrip are shown on the left and of dynamic exercise on the right. Each point represents the mean value for the group of normal subjects

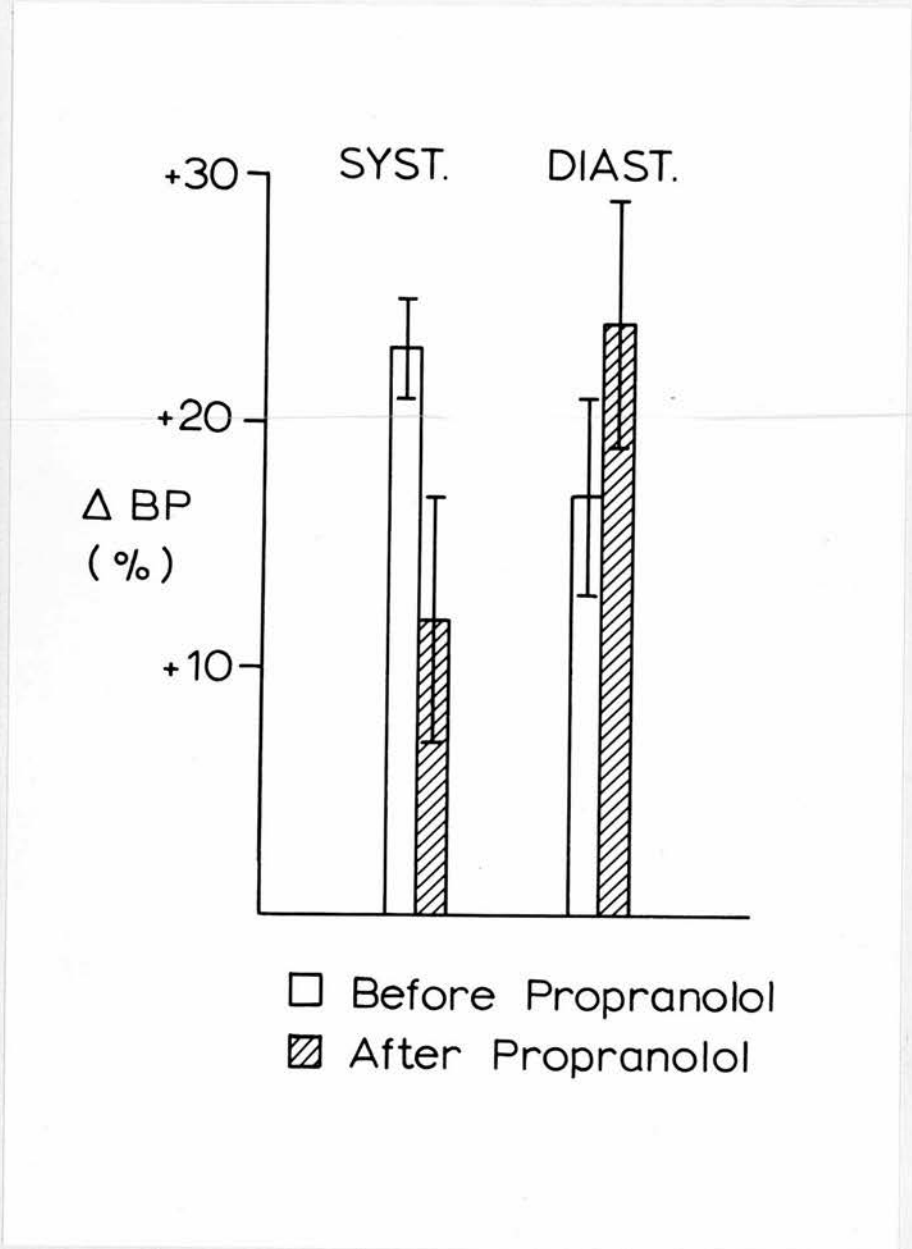
Open circles = before propranolol
Crosses = after propranolol
C, G, R = control, handgrip, recovery
C, E, R = control, exercise, recovery
DE = maximum amplitude of the accelerocardiogram.

Figure 5 Effects of Handgrip and Dynamic Exercise on Heart Rate in the Normal Subjects.



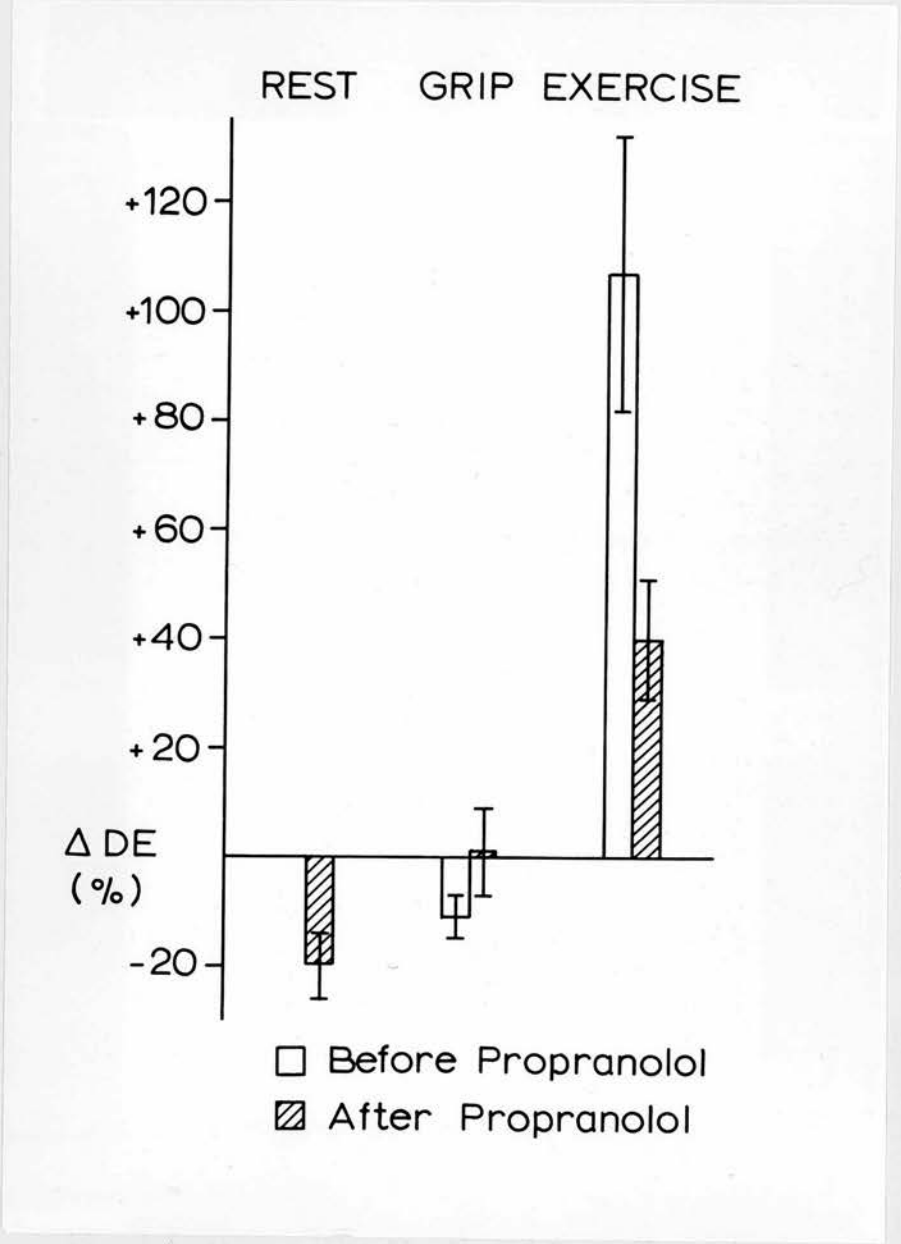
Blocks represent group mean value for the normal subjects.
Bars represent one standard error of the mean.
ΔHR = percentage change in heart rate.
Note suppression of tachycardia of dynamic exercise by propranolol in contrast to the lack of effect of the drug on the tachycardia of handgrip.

Figure 6 Effects of Handgrip on Blood Pressure in the Normal Subjects.



Blocks represent group mean value for the normal subjects.
Bars represent one standard error of the mean.
Δ BP = percentage change in blood pressure.
Syst = systolic blood pressure.
Diast = Diastolic blood pressure.

Figure 7 Effects of Handgrip and Dynamic Exercise on DE in the Normal Subjects.



Blocks represent group mean value for the normal subjects.
Bars represent one standard error of the mean.
Δ DE = percentage change in the maximum amplitude of the accelerocardiogram.
Note the marked effect of propranolol on the response to dynamic exercise, in contrast to the lack of effect on the response to isometric exercise.
Note also the effect of propranolol at rest.

($p > 0.20$) or aortic diastolic blood pressure ($p > 0.80$) (Figure 8). However, the accelerocardiographic response in the patients with aortic stenosis did differ significantly from that in the normal subjects ($p < 0.02$) (Figure 8).

In the patients with myocardial disease handgrip increased mean heart rate from 68 to 77 beats per minute, a change of 11 $\pm$ 2% ($p < 0.001$) (Table 4; Figure 8), and average left ventricular systolic pressure from 128 to 154 mm Hg., a change of 21 $\pm$ 3% ($p < 0.001$) (Table 4; Figure 8). Left ventricular maximum dP/dt increased from a mean of 1450 to 1700 mmHg. per second, a change of 16 $\pm$ 5% ($p < 0.005$) (Table 4) and mean left ventricular end-diastolic pressure increased from 17 to 22 mm Hg., a change of 33 $\pm$ 6% ($p < 0.001$) (Table 4). The maximum amplitude of the praecordial accelerocardiogram increased insignificantly by 4 $\pm$ 4%, from 575 to 595 microvolts ($p > 0.30$) (Table 4; Figure 8). The response in the patients with myocardial disease did not differ significantly from the response in the normal subjects as regards the increases in heart rate ($p > 0.40$) or left ventricular systolic pressure ($p > 0.95$), but did differ significantly as regards the accelerocardiographic response ($p < 0.01$) (Figure 8).

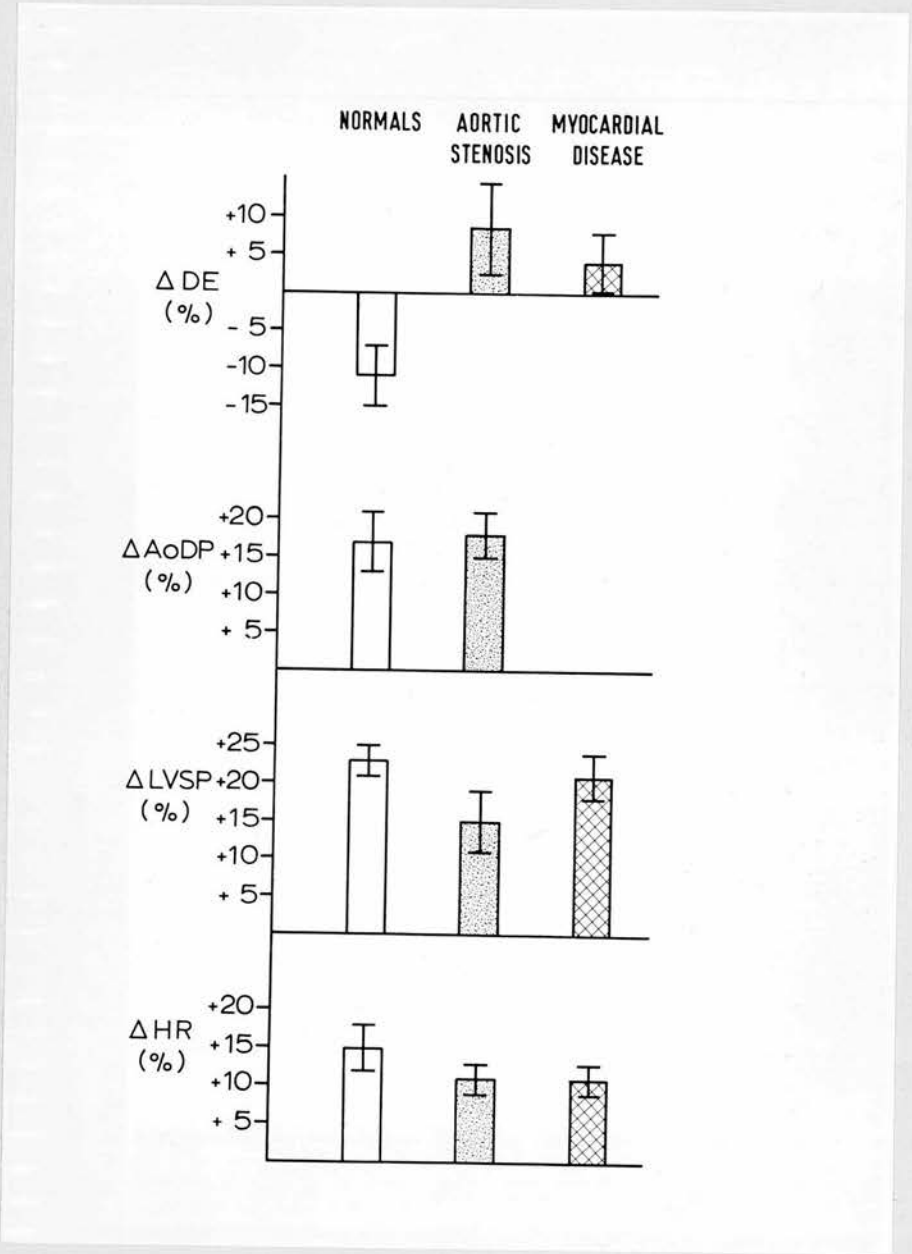
There were no significant differences between the two patient groups as regards the increases in heart rate ($p > 0.80$), left ventricular systolic pressure ($p > 0.10$), left ventricular maximum dP/dt ($p > 0.50$), end-diastolic pressure ($p > 0.80$) or maximum praecordial acceleration ($p > 0.60$) during handgrip.

Table 4. EFFECTS OF HANDGRIP ON HAEMODYNAMICS AND DE IN PATIENTS WITH MYOCARDIAL DISEASE

Case	Heart Rate (beats/min)		LV Syst Press (mm Hg)		LV End-Diast Press (mm Hg)		LV Max dP/dt (mm Hg/sec)		DE (microvolts)	
	Control	Grip	Control	Grip	Control	Grip	Control	Grip	Control	Grip
13	47	58	135	175	20	21	2000	2000	670 (68)	695 (90)
14	63	69	120	155	15	20	1070	1130	823 (126)	795 (156)
15	60	62	190	215	15	20	1780	1930	613 (109)	527 (69)
16	81	88	160	180	18.5	25	960	1060	790 (88)	630 (99)
17	65	90	125	168	15	29.5	1820	2180	600 (65)	670 (81)
18	53	57	125	140	16	20	1120	1250	372 (67)	453 (89)
19	76	82	125	148	18	21	2360	2800	660 (48)	670 (95)
20	61	71	120	157	11	18.5	2150	3170	685 (24)	820 (84)
21	76	80	120	130	22	28	870	1000	475 (48)	434 (43)
22	110	113	-	-	31	40	1100	1150	477 (36)	425 (61)
23	81	85	117	137	13.5	15.5	1390	1530	490 (63)	565 (81)
24	59	76	115	143	18	22	850	820	680 (56)	670 (96)
25	60	72	100	145	12	21	845	1040	397 (29)	426 (46)
26	67	68	130	135	20	25	1850	1790	632 (95)	794 (105)
27	70	78	112	140	12	14	1190	1300	562 (36)	585 (27)
28	76	87	120	140	12	13	1840	2780	370 (51)	430 (53)
Group Mean	68	77	128	154	17	22	1450	1700	575	595
SEM	4	4	6	6	1	2	130	180	-	-
% Change	+ 11 (2)		+ 21 (3)		+ 33 (6)		+ 16 (5)		+ 4 (4)	
P	< 0.001		< 0.001		< 0.001		< 0.005		> 0.30 NS	

Figures in parentheses represent 1 standard error of the mean value for the group data and 1 standard deviation for the individual data.

Figure 8 Effects of Handgrip on Heart Rate, Blood Pressure and DE in the Normal Subjects and Cardiac Patients.



Blocks represent group mean value for the normal subjects (left), the patients with aortic stenosis (centre) and patients with myocardial disease (right).
Bars represent one standard error of the mean.
Δ HR = percentage change in heart rate.
ΔLVSP = percentage change in left ventricular systolic pressure.
ΔAoDP = percentage change in aortic diastolic blood pressure.
Δ DE = percentage change in the maximum amplitude of the accelerocardiogram.

Fifty percent of the individuals in each of the patient groups responded abnormally to handgrip in that maximum praecordial acceleration increased significantly. The data was therefore examined to see if any haemodynamic differences existed between these patients with an abnormal response and those with a normal response. These two sub-groups did not differ significantly from one another as regards the changes in heart rate, left ventricular systolic pressure, aortic diastolic pressure or left ventricular end-diastolic pressure during handgrip, in either the patients with aortic stenosis or those with myocardial disease (Tables 5, 6). Although the patients with myocardial disease who increased maximum praecordial acceleration significantly during handgrip had a 24% increase in left ventricular maximum dP/dt on average, as compared with an average increase of 7.5% in the remainder, this was not statistically significant ($p > 0.30$) (Table 6). There were also no significant differences between the two sub-groups as regards the mean values for resting left ventricular maximum dP/dt, aortic valve gradient or aortic valve area (Tables 5, 6). However, the patients with aortic stenosis who responded to handgrip with a significant increase in praecordial acceleration had a significantly higher resting cardiac index, 3.27 as against 2.59 litres per metre^2 per minute ($p < 0.05$) (Table 5). Furthermore, there was a significant linear correlation between the percentage change in praecordial acceleration during handgrip and resting cardiac index (Figure 9). The patients/

Table 5. HAEMODYNAMIC DATA IN SUB-GROUPS OF PATIENTS WITH AORTIC STENOSIS

Case	Δ Heart Rate (%)	Δ LV Syst Press (%)	Δ Ao Diast. Press (%)	Δ LV Max dP/dt (%)	Δ LVEDP (%)	Resting LV Max dP/dt (mm Hg/sec)	Resting LVEDP (mm Hg)	Resting Card. Index ($L/m^2/min$)	Resting Ao Value Grad (mm Hg)	Ao Value Area (cm^2)
Abnormal Response (Group A)										
2	+ 23.5	+ 14	+ 26	+ 55.5	+ 87	1890	24	2.72	34	1.13
4	+ 4.5	+ 6	+ 13	+ 12.5	+ 11	1600	18	4.18	79	0.72
5	+ 12	+ 33	+ 24	+ 16.5	+ 65	1330	11.5	3.80	10	-
8	+ 12	+ 17	+ 15	+ 24	+ 61	500	11.5	2.40	60	0.53
11	+ 2.5	+ 4	+ 11	+ 8	0	1820	15	3.40	87	0.52
12	+ 11.5	+ 9.5	+ 11	+ 23.5	0	1580	24	3.49	49	0.95
Mean	+ 11	+ 14	+ 18.5	+ 23	+ 37	1450	17	3.27	53	0.77
SEM	3	4	3	7	16	205	2.5	0.26	12	0.11
Normal Response (Group B)										
1	+ 7.5	+ 12	+ 7	+ 36	+ 15	1870	20	1.72	35	0.43
3	+ 27	+ 26	+ 19	+ 35	+ 36	1780	14	1.87	38	0.65
6	+ 1	+ 2	+ 21	+ 22	+ 52	1560	21	2.90	76	0.60
7	+ 19	+ 39	+ 36	+ 48	-	2150	-	3.10	77	1.10
9	+ 7	+ 15	+ 18	+ 5	-	2500	-	2.30	43	0.90
10	+ 8	+ 7	+ 8	+ 14	+ 24	1450	21	2.16	85	0.40
Mean	+ 11.5	+ 17	+ 18	+ 27	+ 32	1885	19	2.59	53	0.68
SEM	4	6	4	6.5	8	160	2	0.25	11	0.11
Group A versus Group B										
P	>0.90 NS	>0.60 NS	>0.80 NS	>0.70 NS	>0.70 NS	>0.10 NS	>0.60 NS	<0.05	>0.90 NS	>0.50 NS

Table 6. HAEMODYNAMIC DATA IN SUB-GROUPS OF PATIENTS WITH MYOCARDIAL DISEASE

Case	ΔHeart Rate (%)	ΔLV Syst. Press (%)	ΔLV Max dP/dt (%)	ΔLVEDP %	Resting LV Max dP/dt (mm Hg/sec)	Resting LVEDP (mm Hg)
Abnormal Response (Group A)						
17	+ 28.5	+ 34	+ 20	+ 97	1820	15
18	+ 6.5	+ 11.5	+ 12	+ 25	1120	16
20	+ 14	+ 31	+ 47.5	+ 68	2150	11
23	+ 4	+ 17	+ 10	+ 15	1390	13.5
25	+ 16.5	+ 45	+ 47	+ 75	845	12
26	+ 2	+ 4	- 3	+ 25	1850	20
27	+ 10.5	+ 25	+ 9	+ 17	1190	12
28	+ 12.5	+ 16.5	+ 51	+ 8	1840	12
Mean	+ 12	+ 23	+ 24	+ 41	1525	14
SEM	3	5	7.5	12	160	1
Normal Response (Group B)						
13	+ 18	+ 30	0	+ 5	2000	20
14	+ 9.5	+ 29	+ 5.5	+ 33	1070	15
15	+ 2	+ 13	+ 8.5	+ 33	1780	15
16	+ 8.5	+ 11	+ 10.5	+ 35	960	18.5
19	+ 7	+ 18.5	+ 18.5	+ 17	2360	18
21	+ 5	+ 8.5	+ 15	+ 27	870	22
22	+ 3	-	+ 4.5	+ 29	1100	31
24	+ 22.5	+ 24	- 3.5	+ 22	850	18
Mean	+ 9.5	+ 19	+ 7.5	+ 25	1375	20
SEM	2.5	3.5	2.5	3.5	205	2
Group A versus Group B						
P	>0.50 NS	>0.50 NS	>0.30 NS	>0.20 NS	>0.50 NS	<0.02

patients with myocardial disease who responded abnormally in terms of maximum praecordial acceleration had a lower mean resting left ventricular end-diastolic pressure, 14 as against 20 mm. Hg ($p < 0.02$ (Table 6).

Patients with a history of myocardial infarction and those with dyskinesis evident on cine-angiography did not differ from the remainder in their accelerocardiographic response to handgrip.

B) Effects of Dynamic Exercise

Immediately after exercise group mean heart rate in the normal subjects was 104 beats per minute as compared with a rate of 66 before exercise (Table 7; Figure 4). This represented an average increase in heart rate of 58 $\pm$ 6% ($p < 0.005$)(Table 7; Figure 5). The mean increase in the maximum amplitude of the praecordial accelerocardiogram was 107 $\pm$ 25%, from 658 to 1365 microvolts ($p < 0.005$) (Table 7; Figures 4, 7). The increase in the standard deviation of the individual values during dynamic exercise (Table 7) was largely due to an increase in the respiratory variation of the measurement consequent upon hyperventilation.

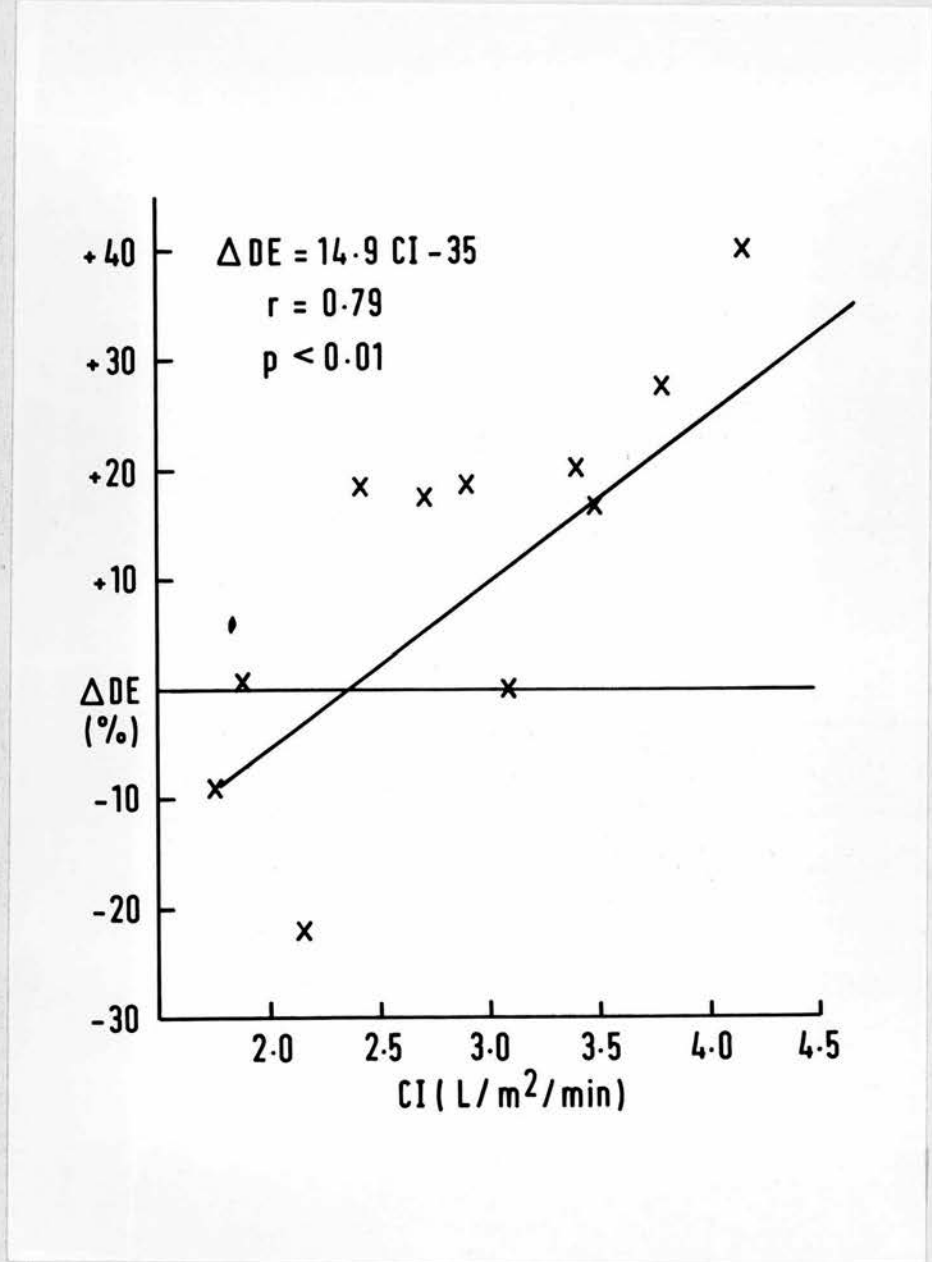
After propranolol, dynamic exercise increased group mean heart rate from 64 to 79 beats per minute, a change of 23 $\pm$ 6% ($p < 0.01$) (Table 7; Figures 4, 7), while maximum praecordial acceleration increased from 473 to 660 microvolts, a change of 40 $\pm$ 11% ($p < 0.005$) (Table 7; Figures 4, 7). Propranolol significantly impaired the heart rate ($p < 0.025$) and accelerocardiographic ($p < 0.025$) responses to exercise (Figures 4, 5, 7). The absolute amplitude of the accelerocardiogram during exercise was much reduced in every case.

Table 7. EFFECTS OF DYNAMIC EXERCISE ON HEART RATE AND DE, BEFORE AND AFTER PROPRANOLOL, IN THE NORMAL SUBJECTS

Subject		Before Propranolol			After Propranolol	
		Heart Rate (beats/min)	DE (microvolts)		Heart Rate (beats/min)	DE (microvolts)
AM	CONTROL	83	600 (52)	CONTROL	73	455 (53)
	EXERCISE	104	1360 (415)	EXERCISE	91	655 (107)
RT	CONTROL	61	755 (71)	CONTROL	66	445 (76)
	EXERCISE	109	2150 (240)	EXERCISE	86	800 (196)
SS	CONTROL	62	905 (52)	CONTROL	63	555 (49)
	EXERCISE	91	1340 (270)	EXERCISE	84	610 (134)
LH	CONTROL	62	735 (111)	CONTROL	60	550 (76)
	EXERCISE	115	1305 (142)	EXERCISE	80	680 (63)
SR	CONTROL	58	375 (46)	CONTROL	56	315 (63)
	EXERCISE	66	525 (46)	EXERCISE	49	540 (67)
JI	CONTROL	71	580 (85)	CONTROL	63	520 (52)
	EXERCISE	139	1510 (205)	EXERCISE	83	675 (76)
GROUP	CONTROL	66 (4)	658	CONTROL	64 (2)	473
	EXERCISE	104 (10)	1365	EXERCISE	79 (6)	660
% Change		+ 58 (6)	+ 107 (25)		+ 23 (6)	+ 40 (11)
P		<0.005	<0.005		<0.01	<0.005

Figures in parentheses represent 1 standard error of the mean value for the group data and 1 standard deviation for the individual data.

Figure 9 Correlation Between the Change in DE During Handgrip and R_{esting} Cardiac Index in the Patients with Aortic Stenosis.



Δ_{DE} = percentage change in the maximum amplitude of the accelerocardiogram.

CI = resting cardiac index (litres per metre^2 per minute).

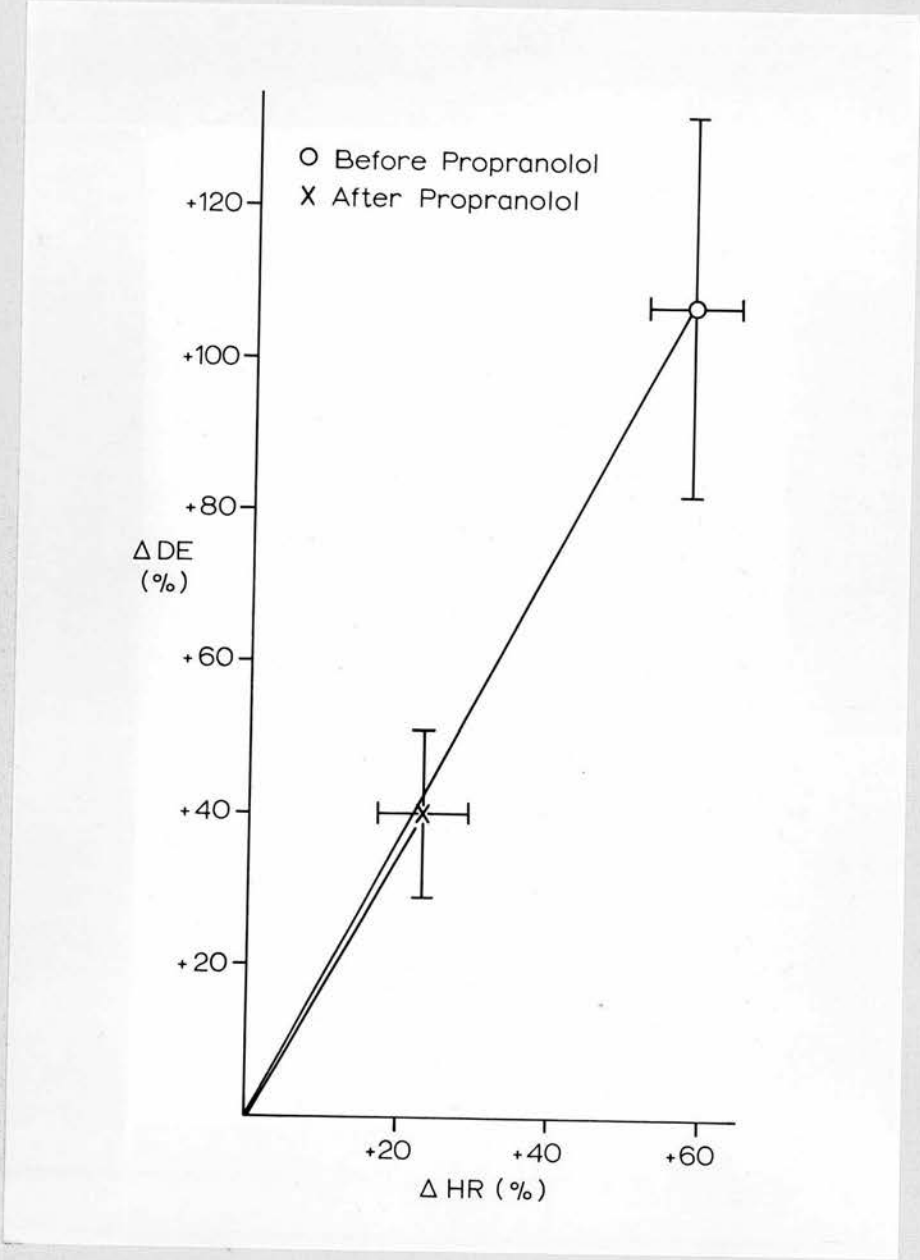
Table 8 EFFECTS OF PROPRANOLOL AT REST ON HEART RATE, BLOOD PRESSURE, DE AND TIME TO MAXIMUM PRAECORDIAL ACCELERATION

Subject	Heart Rate (beats/min)		Systolic BP (mm Hg)		Diastolic BP (mm Hg)		DE (microvolts)		Time to Peak Acceleration (milliseconds)	
	Control	Prop	Control	Prop	Control	Prop	Control	Prop	Control	Prop
AM	85	78	118	98	84	60	580 (58)	480 (58)	99 (5)	83 (5)
RT	85	69	130	125	85	85	675 (71)	400 (58)	114 (7)	112 (4)
SS	74	66	90	90	55	60	725 (67)	545 (63)	102 (4)	98 (7)
LH	73	64	118	110	70	70	624 (103)	597 (89)	99 (4)	93 (8)
SR	60	60	105	110	85	90	395 (36)	295 (31)	124 (9)	145 (7)
JI	79	67	110	110	85	85	585 (45)	545 (40)	88 (9)	90 (6)
Group	76(4)	67(2)	112(6)	107(5)	77(5)	75(5)	597	477	104(5)	104(9)
% Change	-12 (3)		-4 (3)		-3 (6)		-20 (6)		0 (5)	
P	< 0.005		> 0.20 NS		> 0.60 NS		< 0.02		> 0.80 NS	

Figures in parentheses represent 1 standard error of the mean value for the group data and 1 standard deviation for the individual data.

Prop = after propranolol (5 minutes)

Figure 10 Effects of Propranolol on the Response to Dynamic Exercise in the Normal Subjects.



Δ DE = percentage change in the maximum amplitude of the accelerocardiogram.
Δ HR = percentage change in heart rate.
Cross and circle represent group mean value.
Bars represent one standard error of the mean.
Note that the increases in heart rate and DE during dynamic exercise are suppressed proportionately.

CHAPTER 4

Results

The Time to Peak Acceleration

The results of this part of the study are summarised in tables 8 to 12 and figures 11 to 13.

A) Correlation with Pre-Ejection Period.

A close correlation was noted, at rest, between the time to maximum praecordial acceleration and the pre-ejection period, measured in the conventional way from simultaneous recordings of electrocardiogram, phonocardiogram and carotid pulse, in a small group of normal subjects (Figure 11). In fact, peak acceleration consistently followed the onset of ejection.

B) Resting Data.

At rest, time to peak acceleration was 105 $\pm$ 5 milliseconds in the normal subjects, 104 $\pm$ 5 milliseconds in the patients with aortic stenosis and 101 $\pm$ 3 milliseconds in the patients with myocardial disease (Tables 9 - 11). These group mean values were not significantly different.

C) Effects of Handgrip.

The increases in heart rate and blood pressure during handgrip in the normal subjects have already been presented in detail in chapter 3 and are presented again in table 9. In the normal subjects handgrip significantly shortened the time to peak acceleration from 105 to 97 milliseconds ($p < 0.05$) (Table 9;/

TABLE 9. EFFECTS OF HANDGRIP ON TIME TO PEAK ACCELERATION IN NORMAL SUBJECTS, BEFORE AND AFTER PROPRANOLOL.

Subject		Before Propranolol					After Propranolol			
		Heart Rate (beats/min)	Systol BP (mm Hg)	Diastol BP (mm Hg)	Time to peak acceleration (msec)		Heart Rate (beats/min)	Systol BP (mm Hg)	Diastol BP (mm Hg)	Time to peak acceleration (msec)
AM	CONTROL	82	118	74	100 (6)	CONTROL	75	98	60	83 (5)
	GRIP	85	130	90	90 (4)	GRIP	78	110	80	81 (7)
RT	CONTROL	71	130	95	110 (7)	CONTROL	69	125	85	112 (4)
	GRIP	85	160	95	105 (7)	GRIP	82	120	95	104 (10)
SS	CONTROL	69	90	55	95 (5)	CONTROL	66	90	60	98 (7)
	GRIP	71	110	70	90 (4)	GRIP	71	95	75	94 (4)
LH	CONTROL	64	118	75	102 (4)	CONTROL	64	110	70	93 (8)
	GRIP	75	150	90	107 (4)	GRIP	67	145	100	87 (5)
SR	CONTROL	59	115	90	129 (8)	CONTROL	60	110	90	145 (7)
	GRIP	75	145	105	111 (9)	GRIP	67	120	105	134 (9)
JI	CONTROL	66	110	80	95 (5)	CONTROL	67	110	85	90 (6)
	GRIP	82	130	95	79 (10)	GRIP	78	130	100	87 (9)
GROUP	CONTROL	69 (3)	114 (5)	78 (6)	105 (5)	CONTROL	67 (2)	107 (5)	75 (5)	104 (9)
	GRIP	79 (2)	138 (7)	91 (5)	97 (5)	GRIP	74 (3)	120 (7)	93 (5)	98 (8)
% CHANGE		+15 (3)	+23 (2)	+17 (4)	-8 (3)		+10 (2)	+12 (5)	+24 (5)	-5 (1)
P		<0.005	<0.001	<0.001	<0.05		<0.005	<0.05	<0.001	<0.005

FIGURES IN PARENTHESES REPRESENT 1 STANDARD ERROR OF THE MEAN VALUE FOR THE GROUP DATA AND 1 STANDARD DEVIATION FOR THE INDIVIDUAL DATA.

(Table 9; Figure 12). After propranolol, handgrip shortened the time to peak acceleration from 104 to 98 milliseconds ($p < 0.005$) (Table 9; Figure 12), which was not significantly different from the response before the drug ($p > 0.40$).

In the patients with aortic stenosis mean heart rate increased from 72 to 80 beats per minute during handgrip, an increase of 11 $\pm$ 3% ($p < 0.001$), mean left ventricular systolic pressure increased from 196 to 228 mmHg., a change of 16 $\pm$ 4% ($p < 0.005$), and aortic diastolic blood pressure increased by 16 $\pm$ 3%, from an average of 79 to 92 mm Hg. ($p < 0.001$) (Table 10). These were not significantly different from the changes observed in the normal subjects. Left ventricular maximum dP/dt increased, on average, from 1785 to 2185 mm Hg per second ($p < 0.005$) and left ventricular end-diastolic pressure increased from 18 to 21 mm Hg. ($p < 0.02$) (Table 10).

In the patients with myocardial disease, mean heart rate increased from 68 to 75 beats per minute, a change of 9 $\pm$ 2% ($p < 0.001$) and left ventricular systolic pressure increased, on average, by 17 $\pm$ 3%, from 132 to 156 mm Hg. ($p < 0.001$) (Table 11). These were not significantly different from the changes observed in the normal subjects. Left ventricular maximum dP/dt increased, but insignificantly, from 1360 to 1520 mm Hg. per second ($p > 0.05$) and left ventricular end-diastolic pressure increased from 18 to 23 mm Hg ($P < 0.001$) (Table 11). There were no significant differences/

Table 10. EFFECTS OF HANDGRIP ON TIME TO PEAK ACCELERATION IN PATIENTS WITH AORTIC STENOSIS

Case		Heart Rate (beats/min)	LV Syst Press (mm Hg)	Ao Diast BP (mm Hg)	LV End-Diast Press (mm Hg)	LV Max dP/dt (mm Hg/sec)	Time to peak acceleration (milliseconds)
1	CONTROL	76	163	86	20	1870	98 (6)
	GRIP	82	182	92	23	2540	97 (4)
3	CONTROL	50	210	80	14	1780	114 (6)
	GRIP	68	265	95	19	2400	84 (6)
4	CONTROL	94	203	75	18	1600	108 (5)
	GRIP	98	215	85	20	1800	108 (7)
5	CONTROL	65	120	70	11.5	1330	100 (5)
	GRIP	73	160	87	19	1550	109 (7)
7	CONTROL	62	230	72	-	2150	114 (5)
	GRIP	76	320	98	-	3180	103 (6)
9	CONTROL	94	150	61	-	2500	119 (5)
	GRIP	101	172	72	-	2620	115 (8)
10	CONTROL	63	233	78	21	1450	73 (4)
	GRIP	68	250	84	26	1650	78 (4)
11	CONTROL	81	240	90	15	1820	113 (6)
	GRIP	83	250	100	15	1960	112 (5)
12	CONTROL	70	219	100	24	1580	97 (6)
	GRIP	78	240	111	24	1950	94 (7)
Group Mean	CONTROL	72 (5)	196 (14)	79 (4)	18 (4)	1785 (120)	104 (5)
	GRIP	80 (4)	228 (17)	92 (4)	21 (2)	2185 (180)	100 (4)
% Change		+11 (3)	+16 (4)	+16 (3)	+22 (9)	+22 (5)	-3 (4)
P		< 0.001	< 0.005	< 0.001	< 0.02	< 0.005	> 0.30 NS

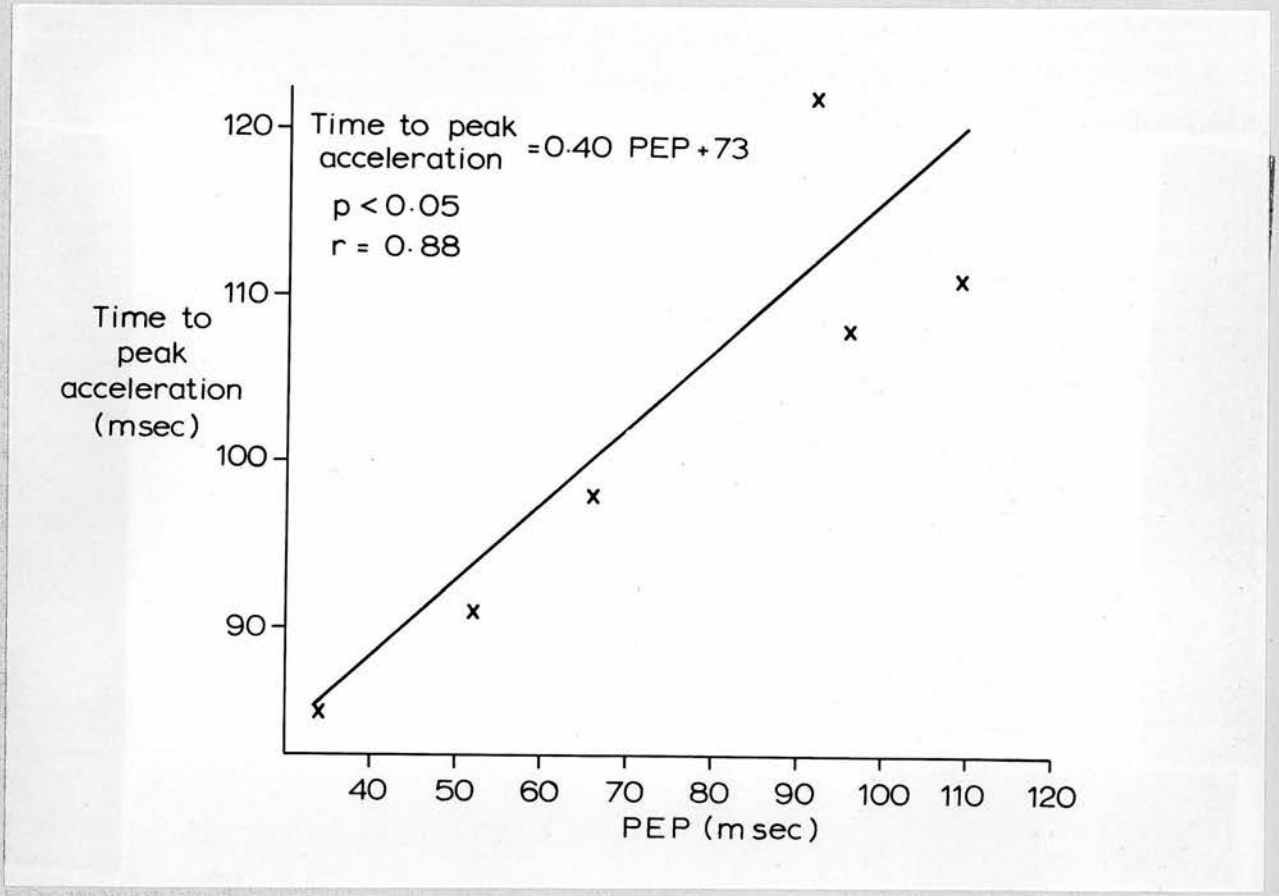
Figures in parentheses represent 1 standard error of the mean value for the group data and 1 standard deviation for the individual data

TABLE 11. EFFECTS OF HANDGRIP ON TIME TO PEAK ACCELERATION PATIENTS WITH MYOCARDIAL DISEASE.

Case		Heart Rate (beats/min)	LV Syst Press (mm Hg)	LV End-Diast Press (mm Hg)	LV Max dP/dt (mm Hg/sec)	Time to peak acceleration (milliseconds)
13	CONTROL	47	135	20	2000	119 (5)
	GRIP	58	175	21	2000	119 (5)
14	CONTROL	63	120	15	1070	112 (7)
	GRIP	69	155	20	1130	104 (7)
15	CONTROL	60	190	15	1780	86 (1)
	GRIP	62	215	20	1930	79 (5)
16	CONTROL	81	160	18.5	960	95 (6)
	GRIP	88	180	25	1060	91 (10)
18	CONTROL	53	125	16	1120	107 (5)
	GRIP	57	140	20	1250	105 (6)
20	CONTROL	61	120	11	2150	110 (7)
	GRIP	71	157	18.5	3170	97 (4)
21	CONTROL	76	120	22	870	99 (7)
	GRIP	80	130	28	1000	102 (5)
22	CONTROL	110	-	31	1100	98 (5)
	GRIP	113	-	40	1150	93 (3)
24	CONTROL	59	115	18	850	102 (9)
	GRIP	76	143	22	820	84 (4)
26	CONTROL	67	130	20	1850	82 (8)
	GRIP	68	135	25	1790	83 (6)
27	CONTROL	70	112	12	1190	105 (4)
	GRIP	78	140	14	1300	98 (4)
ROUP	CONTROL	68 (5)	132 (7)	18 (2)	1360 (145)	101 (3)
	GRIP	75 (5)	156 (8)	23 (2)	1520 (200)	96 (4)
Change		+9 (2)	+17 (3)	+29 (5)	+10 (4)	-5 (2)
P		<0.001	<0.001	<0.001	>0.05 NS	<0.01

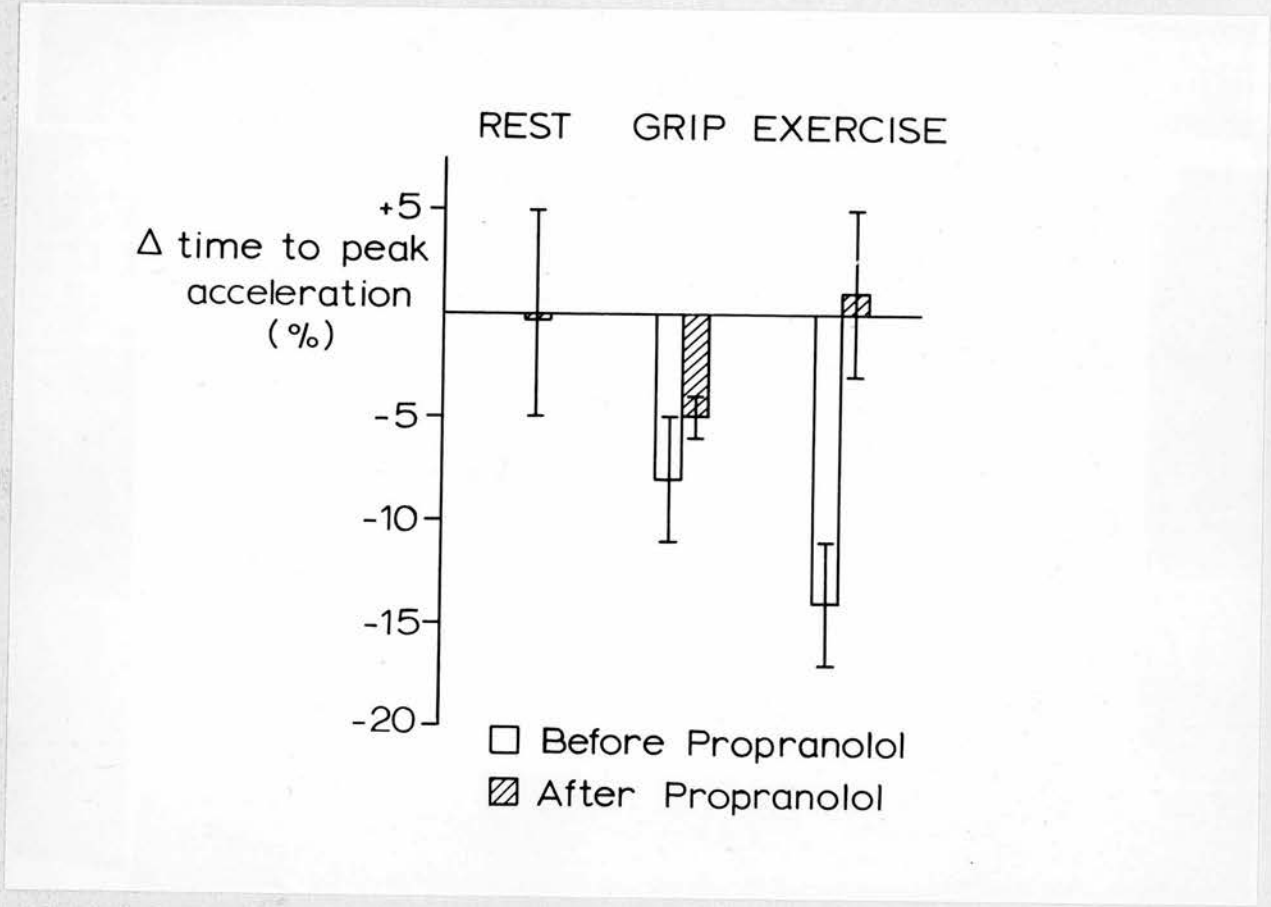
GURES IN PARENTHESES REPRESENT 1 STANDARD ERROR OF THE MEAN VALUE FOR THE GROUP DATA
D 1 STANDARD DEVIATION FOR THE INDIVIDUAL DATA.

Figure 11 Correlation Between Time to Peak Acceleration and Pre-Ejection Period.



PEP = pre-ejection period (milliseconds).

Figure 12 Effects of Handgrip and Dynamic Exercise on Time to Peak Acceleration in the Normal Subjects.



Blocks represent group mean value for the normal subjects.
Bars represent one standard error of the mean.
Note the marked effect of propranolol on the response to dynamic exercise, in contrast to the lack of effect on the response to isometric exercise.

differences between the patients with aortic stenosis and those with myocardial disease, as regards the haemodynamic response to handgrip.

In the patients with myocardial disease time to peak acceleration shortened significantly, from 101 to 96 milliseconds ($p < 0.01$) (Table 11), but in the patients with aortic stenosis the change, from 104 to 100 milliseconds, was not significant ($p > 0.30$) (Table 10). The degree of shortening of the time to peak acceleration in the normal subjects was not significantly different from that in the patients with myocardial disease ($p > 0.40$) or those with aortic stenosis ($p > 0.40$).

In the patient groups, the percentage shortening of the time to peak acceleration during handgrip correlated inversely with the percentage increase in heart rate (Figure 13). However, no other correlations could be established between the change in time to peak acceleration during handgrip and any of the other haemodynamic findings at rest or during handgrip, or with the findings on left ventricular cine-angiography, or with the extent of the coronary artery disease demonstrated on coronary arteriography.

D) Effects of Exercise

In the normal subjects, dynamic exercise caused a significant reduction in time to peak acceleration from 104 to 89 milliseconds ($p < 0.01$) (Table 12; Figure 12). After propranolol, time to peak acceleration failed to shorten/

TABLE 12. EFFECTS OF DYNAMIC EXERCISE ON HEART RATE AND TIME TO PEAK ACCELERATION BEFORE AND AFTER PROPRANOLOL

Subject		Before Propranolol			After Propranolol	
		Heart Rate (beats/min)	Time to peak acceleration (msec)		Heart Rate (beats/min)	Time to peak acceleration (msec)
AM	CONTROL	83	94 (5)	CONTROL	73	80 (6)
	EXERCISE	104	87 (2)	EXERCISE	91	87 (4)
RT	CONTROL	61	112 (5)	CONTROL	66	112 (4)
	EXERCISE	109	96 (6)	EXERCISE	86	109 (7)
SS	CONTROL	62	94 (5)	CONTROL	63	95 (6)
	EXERCISE	91	82 (4)	EXERCISE	84	86 (7)
LH	CONTROL	62	97 (7)	CONTROL	60	93 (4)
	EXERCISE	115	66 (7)	EXERCISE	80	109 (6)
SR	CONTROL	58	124 (13)	CONTROL	56	135 (13)
	EXERCISE	66	112 (8)	EXERCISE	49	116 (5)
JI	CONTROL	71	102 (6)	CONTROL	63	88 (4)
	EXERCISE	139	89 (2)	EXERCISE	83	86 (5)
Group Mean	CONTROL	64 (4)	104 (6)	CONTROL	64 (2)	101 (9)
	EXERCISE	104 (10)	89 (8)	EXERCISE	79 (6)	99 (6)
% Change		58 (6)	-14 (4)		23 (6)	+1 (4)
P		<0.005	<0.01		< 0.01	> 0.80 NS

FIGURES IN PARENTHESE REPRESENT 1 STANDARD ERROR OF THE MEAN VALUE FOR THE GROUP DATA AND 1 STANDARD DEVIATION FOR THE INDIVIDUAL DATA.

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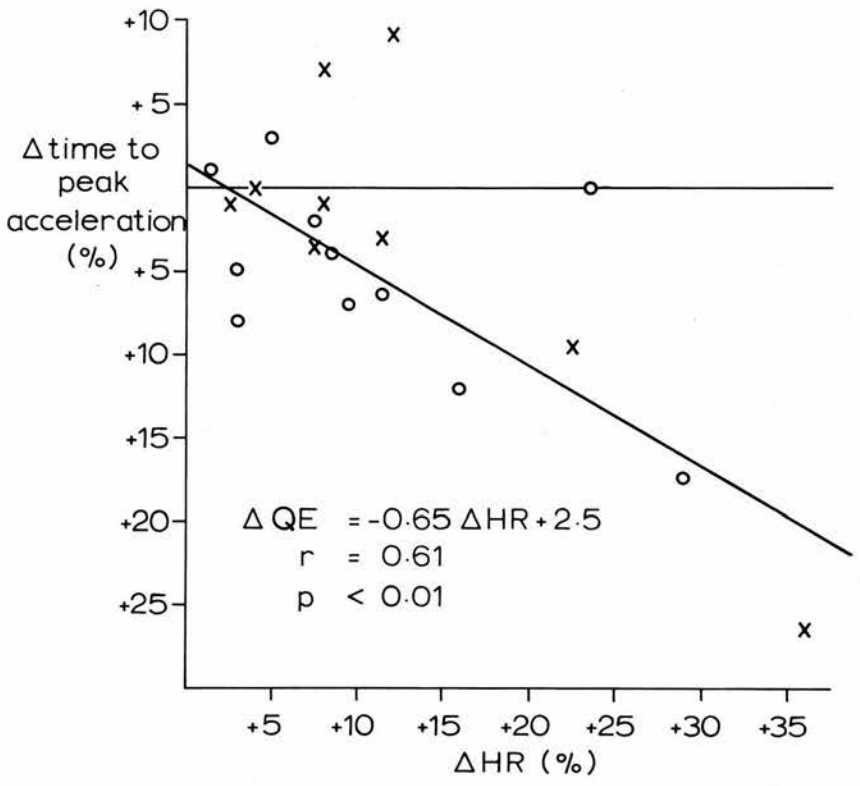
shorten significantly during dynamic exercise ($p > 0.80$) (Table 12; Figure 12). This effect of the drug was significant ($p < 0.05$).

E) Effects of Propranolol at Rest

At rest, propranolol had no significant effect on the time to peak acceleration ($p > 0.80$) (Table 8; Figure 12) in the normal subjects.

Figure 13 Correlation Between the Changes in Time to Peak Acceleration and Heart Rate During Handgrip in the Cardiac Patients.



Crosses represent patients with aortic stenosis.
Circles represent patients with myocardial disease.
ΔHR = percentage change in heart rate.
ΔQE = percentage change in time to peak acceleration.

CHAPTER 5

Results

The P Wave of the Praecordial Accelerocardiogram

The results of this part of the study are summarised in tables 13 to 15 and figures 14 and 15. For the purposes of analysis, the results in the patients with aortic stenosis and myocardial disease have been combined.

A) Correlation with Left Ventricular End-Diastolic Pressure

In the patient groups a significant linear correlation existed, at rest, between the amplitude of the P wave of the accelerocardiogram relative to the maximum systolic deflection (P/DE) and left ventricular end-diastolic pressure (Table 13; Figure 14), this being largely due to an extremely close correlation in the patients with myocardial disease. When the height of the left ventricular 'a' wave was substituted for end-diastolic pressure no improvement in the correlation was observed.

B) Resting Data

Although the average ratio P/DE in the normal subjects was 29 $\pm$ 5% (Table 14), compared with 37 $\pm$ 4% in the cardiac patients (Table 15), these were not significantly different ($p > 0.30$).

C) Effects of Handgrip

The haemodynamic effects of handgrip in the normal subjects have been presented previously and are summarised in table 14. In the cardiac patients mean heart rate increased by 9 $\pm$ 2%, from 74 to 81 beats per minute ($p \ll 0.001$), average/

Table 13. CORRELATION BETWEEN THE ACCELEROCARDIOGRAM AND LEFT VENTRICULAR PRESSURE IN THE CARDIAC PATIENTS

	Regression Equation	Correlation Co-Efficient	p Value
P/DE v LVEDP	P/DE = 2.4 x LVEDP - 5.7	0.60	<0.01
ΔP v LVEDP	ΔP = 0.85 x ΔLVEDP - 9	0.68	<0.01

Table 14. RESTING DATA AND EFFECTS OF HANDGRIP ON THE P WAVE OF THE ACCELEROCARDIOGRAM IN NORMAL SUBJECTS

Subject		Heart Rate (beats/min)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	P (microvolts)	P/DE %
AM	CONTROL	82	118	74	224 (28)	33 (6)
	GRIP	85	130	90	196 (35)	
RT	CONTROL	71	130	95	220 (38)	26 (6)
	GRIP	85	160	95	228 (47)	
SS	CONTROL	69	90	55	169 (35)	19 (3)
	GRIP	71	110	70	200 (35)	
LH	CONTROL	64	118	75	155 (22)	24 (6)
	GRIP	75	150	90	179 (60)	
SR	CONTROL	59	115	90	182 (35)	50 (9)
	GRIP	75	145	105	178 (28)	
JI	CONTROL	66	110	80	148 (13)	23 (3)
	GRIP	82	130	95	216 (32)	
GROUP	CONTROL	69 (3)	114 (5)	78 (6)	183 (13)	29 (5)
	GRIP	79 (2)	138 (7)	91 (5)	200 (8)	
% Change		+15 (3)	+23 (2)	+17 (4)	+9 (8)	
P		< 0.005	< 0.001	< 0.001	> 0.20	

Figures in parentheses represent 1 standard error of the mean value for the group data and 1 standard deviation for the individual data.

RESTING DATA AND EFFECTS OF HANDGRIP ON THE P WAVE OF THE ACCELEROCARDIOGRAM PATIENTS WITH HEART DISEASE

Case		Heart Rate (beats/min)	LV Syst Press (mm Hg)	Ao Diast BP (mm Hg)	LV Max dP/dt (mm Hg/sec	LV End-Diast Press (mm Hg)	P (microvolts)	P/DE (%)
1	CONTROL	76	163	86	1870	20	228 (35)	21 (3)
	GRIP	82	182	92	2540	23	185 (32)	
2	CONTROL	60	210	95	1890	24	158 (19)	44 (9)
	GRIP	79	240	120	3040	45	293 (41)	
4	CONTROL	94	203	75	1600	18	184 (19)	87 (9)
	GRIP	98	215	85	1800	20	200 (51)	
5	CONTROL	65	120	70	1330	11.5	140 (19)	19 (3)
	GRIP	73	160	87	1550	19	167 (41)	
6	CONTROL	109	210	80	1560	21	220 (41)	30 (9)
	GRIP	110	215	97	1900	32	204 (70)	
8	CONTROL	72	220	65	500	11.5	205 (9)	46 (6)
	GRIP	81	258	75	620	18.5	253 (32)	
10	CONTROL	63	233	78	1450	21	183 (16)	40 (3)
	GRIP	68	250	84	1650	26	184 (38)	
11	CONTROL	81	240	90	1820	15	184 (38)	29 (6)
	GRIP	83	250	100	1960	15	187 (38)	
13	CONTROL	47	135	-	2000	20	254 (70)	27 (3)
	GRIP	58	175	-	2000	21	276 (68)	
15	CONTROL	60	190	-	1780	15	143 (22)	29 (3)
	GRIP	62	215	-	1930	20	158 (44)	
16	CONTROL	81	160	-	960	18.5	243 (51)	34 (6)
	GRIP	88	180	-	1060	25	234 (41)	
17	CONTROL	65	125	-	1820	15	121 (9)	21 (3)
	GRIP	90	168	-	2180	29.5	245 (51)	
18	CONTROL	53	125	-	1120	16	110 (9)	30 (6)
	GRIP	57	140	-	1250	20	140 (25)	
19	CONTROL	76	125	-	2360	18	210 (32)	33 (6)
	GRIP	82	148	-	2800	21	242 (54)	
20	CONTROL	61	120	-	2150	11	115 (13)	12 (3)
	GRIP	71	157	-	3170	18.5	202 (70)	
21	CONTROL	76	120	-	870	22	251 (32)	53 (9)
	GRIP	80	130	-	1000	28	234 (35)	
22	CONTROL	110	-	-	1100	31	377 (73)	91 (9)
	GRIP	113	-	-	1150	40	335 (47)	
23	CONTROL	81	117	-	1390	13.5	135 (22)	28 (6)
	GRIP	85	137	-	1530	15.5	210 (92)	
26	CONTROL	67	130	-	1850	20	208 (28)	41 (9)
	GRIP	68	135	-	1790	25	277 (57)	
27	CONTROL	70	112	-	1190	12	153 (16)	27 (3)
	GRIP	78	140	-	1300	14	123 (16)	
28	CONTROL	76	120	-	1840	12	120 (16)	32 (9)
	GRIP	87	140	-	2780	13	145 (25)	
Group	CONTROL	74 (4)	159 (10)	80 (4)	1545 (100)	17 (1)	185 (14)	37 (4)
	GRIP	81 (3)	182 (10)	93 (5)	1855 (155)	23 (2)	214 (12)	
% Change		+9 (2)	+16 (2)	+16 (3)	+19 (4)	+34 (6)	+16 (7)	-
P		<0.001	<0.001	<0.001	<0.001	<0.001	<0.02	

FIGURES IN PARENTHESE REPRESENT 1 STANDARD ERROR OF THE MEAN VALUE FOR THE GROUP DATA AND 1 STANDARD DEVIATION FOR THE INDIVIDUAL DATA.

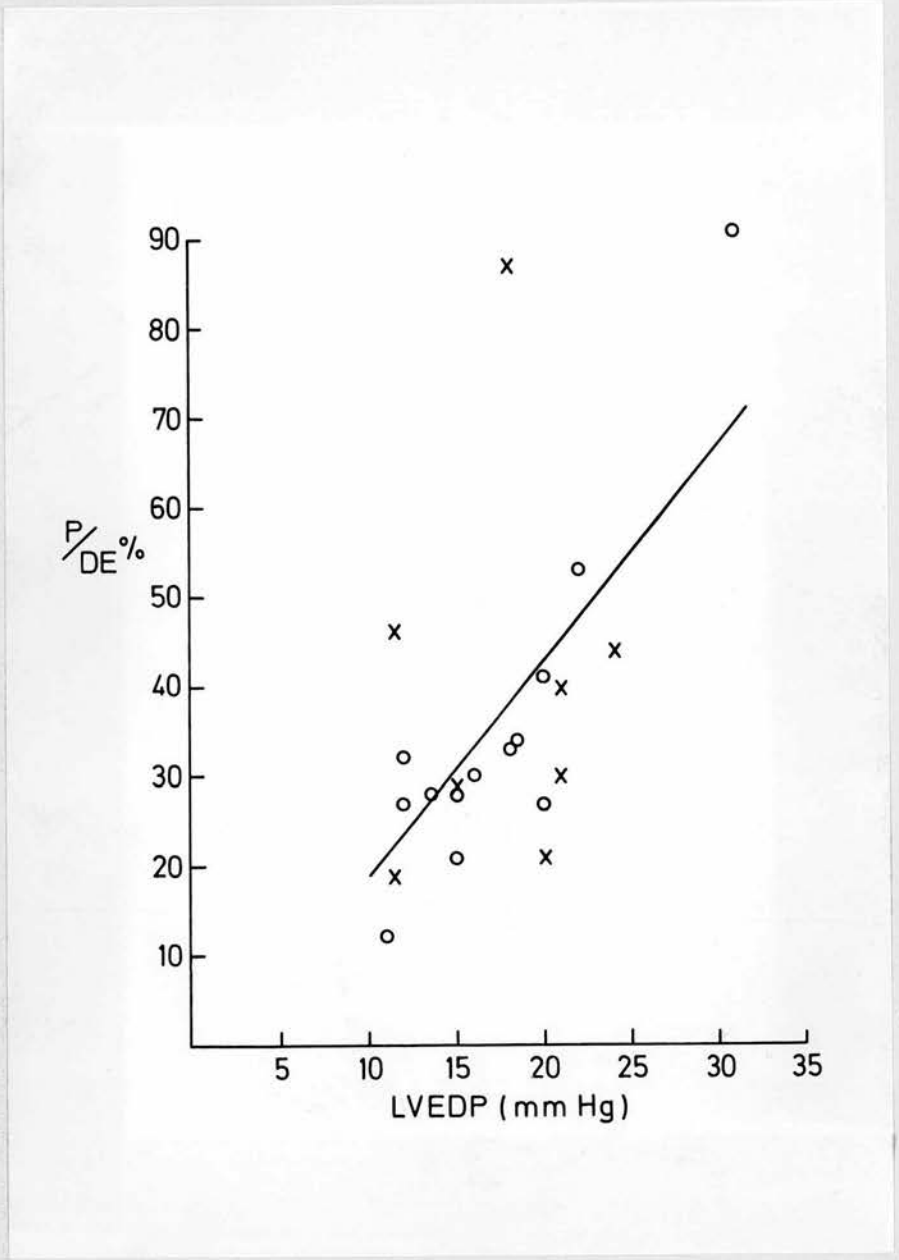
pressure
average left ventricular systolic/increased by 16 ± 2%, from 159 to 182 mm Hg. ($p < 0.001$), and aortic diastolic pressure increased from 80 to 93 mm Hg. ($p < 0.001$) (Table 15). There were no significant differences between the normal subjects and the cardiac patients as regards the changes in heart rate ($p > 0.20$), systolic pressure ($p > 0.30$) or aortic diastolic pressure ($p > 0.80$) during handgrip.

In the cardiac patients the mean left ventricular end-diastolic pressure increased from 17 to 23 mm Hg., a change of 34 ± 6% ($p < 0.001$) (Table 15).

In the normal subjects the mean amplitude of the P wave of the accelerocardiogram increased from 183 to 200 microvolts during handgrip, a change of 9 ± 8% (Table 14), which was not significant ($p > 0.20$). In the cardiac patients the amplitude of the P wave increased from a mean of 185 to 214 microvolts, a change of 16 ± 7% (Table 15), which was significant ($p < 0.02$). However, the difference between the groups, as regards the increase in the amplitude of the P wave during handgrip was not significant ($p > 0.30$).

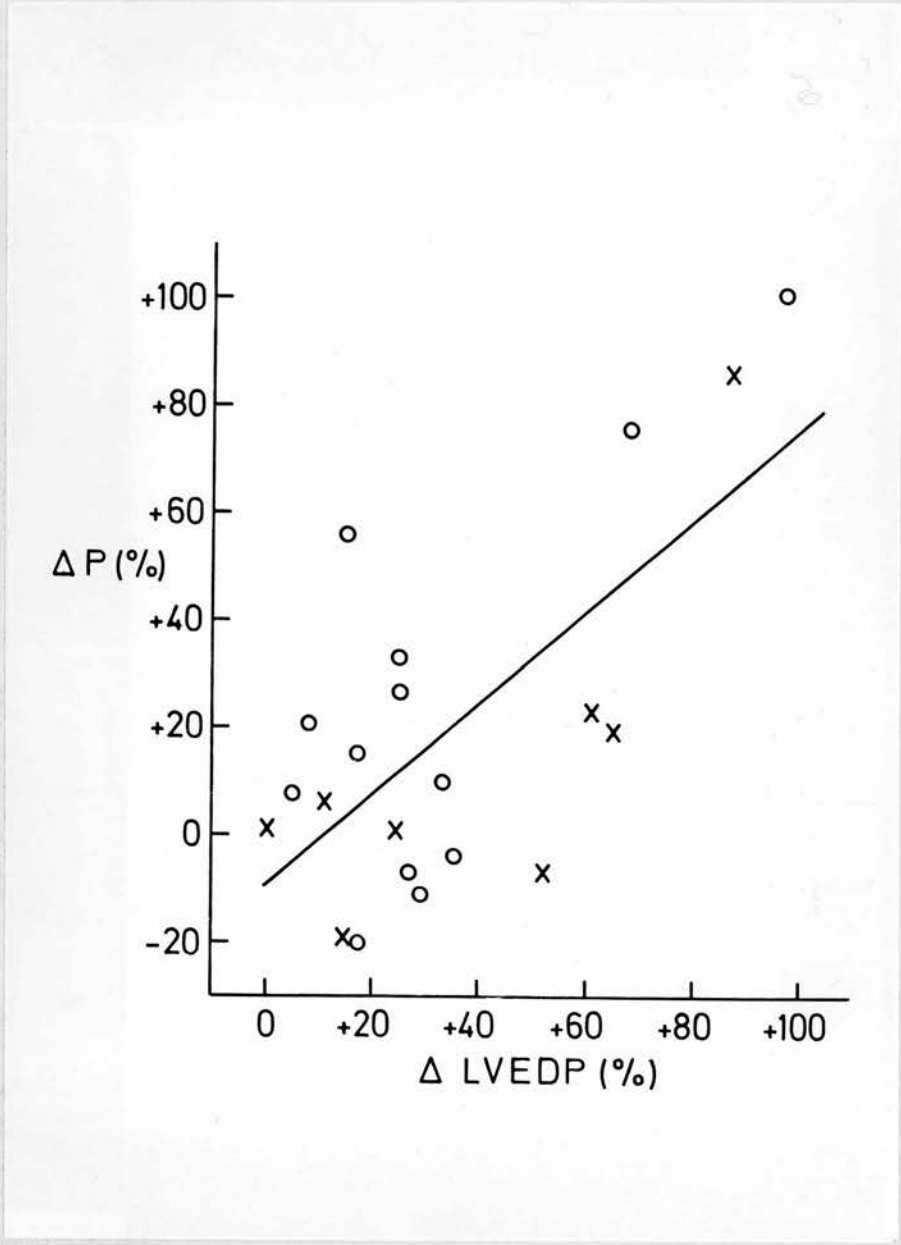
A significant linear correlation existed between the percentage changes in the amplitude of the P wave and end-diastolic pressure during handgrip in the patients with heart disease (Table 13; Figure 15). The correlation was not improved by substituting the percentage change in the height of the left ventricular 'a' wave for the percentage change in end-diastolic pressure.

Figure 14 Correlation Between P/DE and Left Ventricular End-Diastolic Pressure at Rest in the Cardiac Patients.



Crosses represent patients with aortic stenosis.
Circles represent patients with myocardial disease.
P/DE = amplitude of the P wave relative to the maximum systolic deflection of the accelerocardiogram (percent).
LVEDP = left ventricular end-diastolic pressure.
For correlation data see table 13.

Figure 15 Correlation Between the Changes in the Amplitude of the P Wave of the Accelerocardiogram and Left Ventricular End-Diastolic Pressure During Handgrip in the Cardiac Patients.



Crosses represent patients with aortic stenosis.
Circles represent patients with myocardial disease.
ΔP = percentage change in the amplitude of the P wave of the accelerocardiogram.
ΔLVEDP = percentage change in left ventricular end-diastolic pressure.
For correlation data see table 13.

CHAPTER 6

Results

The Echocardiogram of the Anterior Cusp of the Mitral Valve

The results of this part of the study are summarised in tables 16 and 17. Again, the results in the two groups of patients have been combined.

A) Haemodynamic Effects of Handgrip.

The effects of handgrip on heart rate and blood pressure in the normal subjects have already been described (Table 16). In the cardiac patients mean heart rate increased from 67 to 77 beats per minute, a change of 15 $\pm$ 4% ($p < 0.001$), and left ventricular systolic pressure increased from 147 to 174 mm Hg., a mean change of 18 $\pm$ 9% ($p < 0.001$) (Table 17). There were no significant differences between the normal subjects and the cardiac patients as regards the increases in heart rate ($p > 0.70$) or systolic blood pressure ($p > 0.80$) during handgrip. During handgrip the average left ventricular maximum dP/dt increased from 1615 to 1985 mm Hg. per second in the cardiac patients, a change of 23 $\pm$ 6% ($p < 0.01$) (Table 17).

In the patient group, left ventricular end-diastolic pressure increased from 17 to 24 mm Hg., a change of 38 $\pm$ 11% ($p < 0.005$), minimum diastolic pressure increased from 8 to 11 mm Hg., a change of 38 $\pm$ 18% ($p < 0.005$), and the maximum negative left ventricular dP/dt during isovolumetric relaxation increased from 3080 to 3670 mm Hg. per second, a change of 19 $\pm$ 7% ($p < 0.02$) (Table 17).

B)/

Table 16. EFFECTS OF HANDGRIP ON THE MITRAL VALVE ECHOCARDIOGRAM IN NORMAL SUBJECTS

Subject		Heart Rate (beats/min)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	DE Slope (mm/sec)	ICR (mm/sec)	AC Interval (milliseconds)
AM	CONTROL	82	118	74	248 (20)	133 (16)	89 (5)
	GRIP	85	130	90	271 (44)	137 (23)	108 (6)
RT	CONTROL	71	130	95	263 (17)	112 (14)	104 (7)
	GRIP	85	160	95	293 (41)	125 (14)	103 (5)
SS	CONTROL	69	90	55	269 (13)	103 (6)	95 (3)
	GRIP	71	110	70	274 (19)	107 (9)	98 (7)
LH	CONTROL	64	118	75	179 (17)	148 (16)	82 (8)
	GRIP	75	150	90	228 (22)	98 (7)	107 (9)
SR	CONTROL	59	115	90	250 (16)	104 (10)	111 (12)
	GRIP	75	145	105	230 (15)	102 (13)	96 (3)
JI	CONTROL	66	110	80	242 (10)	94 (7)	92 (9)
	GRIP	82	130	95	225 (11)	105 (4)	96 (11)
Group	CONTROL	69 (3)	114 (5)	78 (6)	242 (13)	116 (8)	96 (4)
	GRIP	79 (2)	138 (7)	91 (5)	254 (12)	112 (6)	101 (2)
% Change		+15 (3)	+23 (2)	+17 (4)	+5 (5)	-3 (7)	+5 (6)
P		<0.005	<0.001	<0.001	>0.30 NS	>0.70 NS	>0.30 NS

Figures in parentheses represent 1 standard error of the mean value for the group data and 1 standard deviation for the individual data.

Table 17. EFFECTS OF HANDGRIP ON THE MITRAL VALVE ECHOCARDIOGRAM IN PATIENTS WITH HEART DISEASE

Case		Heart Rate (beats/min)	LV Syst Press (mm Hg)	LV Max dP/dt (mm Hg(sec)	LV End-Diast Press (mm Hg)	LV Max Neg dP/dt (mm Hg/sec)	LV Min Diast Press (mm Hg)	DE Slope (mm/sec)	ICR (mm/sec)	AC Interval (milliseconds)
2	CONTROL	60	210	1890	24	2175	8	98 (9)	41 (7)	83 (12)
	GRIP	79	240	3040	45	2450	20	138 (16)	50 (7)	155 (14)
5	CONTROL	65	120	1330	11.5	2900	7	400 (68)	34 (9)	158 (20)
	GRIP	73	160	1550	19	3330	8	366 (89)	57 (7)	103 (18)
10	CONTROL	63	233	1450	21	2580	11	305 (20)	33 (5)	93 (12)
	GRIP	68	250	1650	26	2820	15	240 (68)	25 (7)	123 (10)
13	CONTROL	47	135	2000	20	3500	11	254 (48)	98 (11)	85 (11)
	GRIP	58	175	2000	21	4750	14	267 (30)	101 (20)	110 (10)
16	CONTROL	81	160	960	18.5	890	3	213 (36)	104 (8)	116 (5)
	GRIP	88	180	1060	25	860	4	252 (42)	103 (5)	94 (15)
17	CONTROL	65	125	1820	15	2550	9	245 (13)	80 (13)	115 (10)
	GRIP	90	168	2180	29.5	4425	21	224 (20)	95 (21)	118 (8)
18	CONTROL	53	125	1120	16	3175	9	151 (12)	84 (9)	109 (6)
	GRIP	57	140	1250	20	3175	9	183 (12)	103 (20)	100 (9)
19	CONTROL	76	125	2360	18	2975	8	229 (24)	105 (14)	92 (9)
	GRIP	82	148	2800	21	3400	7	203 (28)	88 (38)	97 (8)
23	CONTROL	81	117	1390	13.5	4900	9	232 (6)	102 (14)	122 (16)
	GRIP	85	137	1530	15.5	6200	9	207 (17)	91 (9)	138 (13)
28	CONTROL	76	120	1840	12	5150	6	109 (22)	89 (6)	107 (15)
	GRIP	87	140	2780	13	5300	7	154 (17)	77 (5)	114 (13)
Group	CONTROL	67 (4)	147 (13)	1615 (140)	17 (1)	3080 (395)	8 (1)	224 (29)	77 (9)	108 (7)
	GRIP	77 (4)	174 (13)	1985 (220)	24 (3)	3670 (485)	11 (2)	223 (20)	79 (8)	115 (6)
% Change		+15 (4)	+18 (9)	+23 (6)	+38 (11)	+19 (7)	+38 (18)	0 (7)	+3 (9)	+6 (11)
P		<0.001	<0.001	<0.01	<0.005	<0.02	<0.05	>0.98 NS	>0.60 NS	>0.50 NS

Figures in parentheses represent 1 standard error of the mean value for the group data and 1 standard deviation for the individual data

B) Reproducibility of Ultrasound Measurements

In 12 subjects echocardiography of the anterior cusp of the mitral valve was performed after 10 minutes of supine rest on two consecutive days. There were no significant differences in the group mean values for the slope of the opening movement of the mitral valve (DE-Figure 2), the initial valve closure rate (EF-Figure 2) or the duration of the final closing movement (AC-Figure 2) on the two days. The standard deviations of the differences between the two readings were 31 mm per second for the DE slope, 10 mm per second for the EF slope and 9 msec for the AC duration.

C) The Slope of the Opening Movement of the Mitral Valve

At rest, the mean value for the DE slope of the anterior cusp echocardiogram was 242 $\pm$ 13 millimetres per second in the normal subjects (Table 16) and 224 $\pm$ 29 millimetres per second in the cardiac patients (Table 17). These were not significantly different ($p > 0.80$).

During handgrip the DE slope increased to a mean value of 254 $\pm$ 12 millimetres per second in the normal subjects, but this was not significant ($p > 0.30$) (Table 16). In the cardiac patients the DE slope decreased minimally to 223 $\pm$ 20 millimetres per second during handgrip, which again was not significant ($p > 0.98$) (Table 17). The response in the cardiac patients did not differ significantly from that in the normal subjects ($p > 0.90$).

At rest, the absolute values for the DE slope in the individual cardiac patients did not correlate with left ventricular end-diastolic pressure, minimum diastolic pressure or peak negative dP/dt. Furthermore, during handgrip, the magnitude of the change in the DE slope did not correlate with

the magnitude of the changes in left ventricular end-diastolic pressure, minimum diastolic pressure or peak negative dP/dt.

D) The Initial Valve Closure Rate

At rest, the mean initial closure rate of the mitral valve was 116 $\pm$ 8 millimetres per second in the normal subjects (Table 16) and 77 $\pm$ 9 millimetres per second in the cardiac patients (Table 17). These were not significantly different ($p > 0.40$).

During handgrip, the initial valve closure rate decreased insignificantly to 112 $\pm$ 6 millimetres per second in the normal subjects ($p > 0.70$) (Table 16) while, in the cardiac patients, it increased insignificantly to 79 $\pm$ 8 millimetres per second ($p > 0.60$) (Table 17). The response in the cardiac patients did not differ significantly from that in the normal subjects ($p > 0.30$).

In the individual cardiac patients, the resting initial valve closure rate did not correlate with the resting values for left ventricular end-diastolic pressure, minimum diastolic pressure or peak negative dP/dt. Likewise, the change in the initial valve closure rate during handgrip did not correlate with the changes in left ventricular end-diastolic pressure, minimum diastolic pressure or peak negative left ventricular dP/dt.

E) The Duration of the Closing Movement

At rest, the average AC interval was 96 $\pm$ 4 milliseconds in the normal subjects (Table 16) and 108 $\pm$ 7 milliseconds in the cardiac patients (Table 17). These were not significantly different ($p > 0.70$).

During handgrip, the mean AC interval increased insignificantly in both groups, to 101 $\pm$ 2 milliseconds in the normal subjects ($p > 0.30$) (Table 16) and to 115 $\pm$ 6 milliseconds in the cardiac patients ($p > 0.50$) (Table 17). These responses were not significantly different ($p > 0.60$).

At rest, the duration of the AC interval did not correlate with resting left ventricular end-diastolic pressure or the amplitude of the left ventricular 'a' wave. There was also no correlation, in the cardiac patients, between the magnitude of the change in AC and the changes in either left ventricular end-diastolic pressure or the amplitude of the 'a' wave.

CHAPTER 7

Conclusions

Observations on the Normal Responses to Isometric and Dynamic Exercise

It has been established in the course of animal work that peak acceleration of aortic blood flow and the maximum amplitude of the praecordial accelerocardiogram (DE - figure 1) are highly sensitive tochanges in left ventricular contractility induced by such diverse mechanisms as coronary occlusion and the administration of calcium gluconate, catechol amines, beta adrenergic blocking drugs and general anaesthetics (Chung et al., 1974; Noble et al., 1966a, b, 1972; Reuben and Littler, 1973; Rosa and Kaplan, 1960a, b; Winter et al., 1967). Previous studies in man have, however, been confined to qualitative descriptions of the normal and abnormal patternsof the praecordial accelerocardiogram in healthy and disease (Mounsey, 1957, 1959; Rosa et al., 1961).

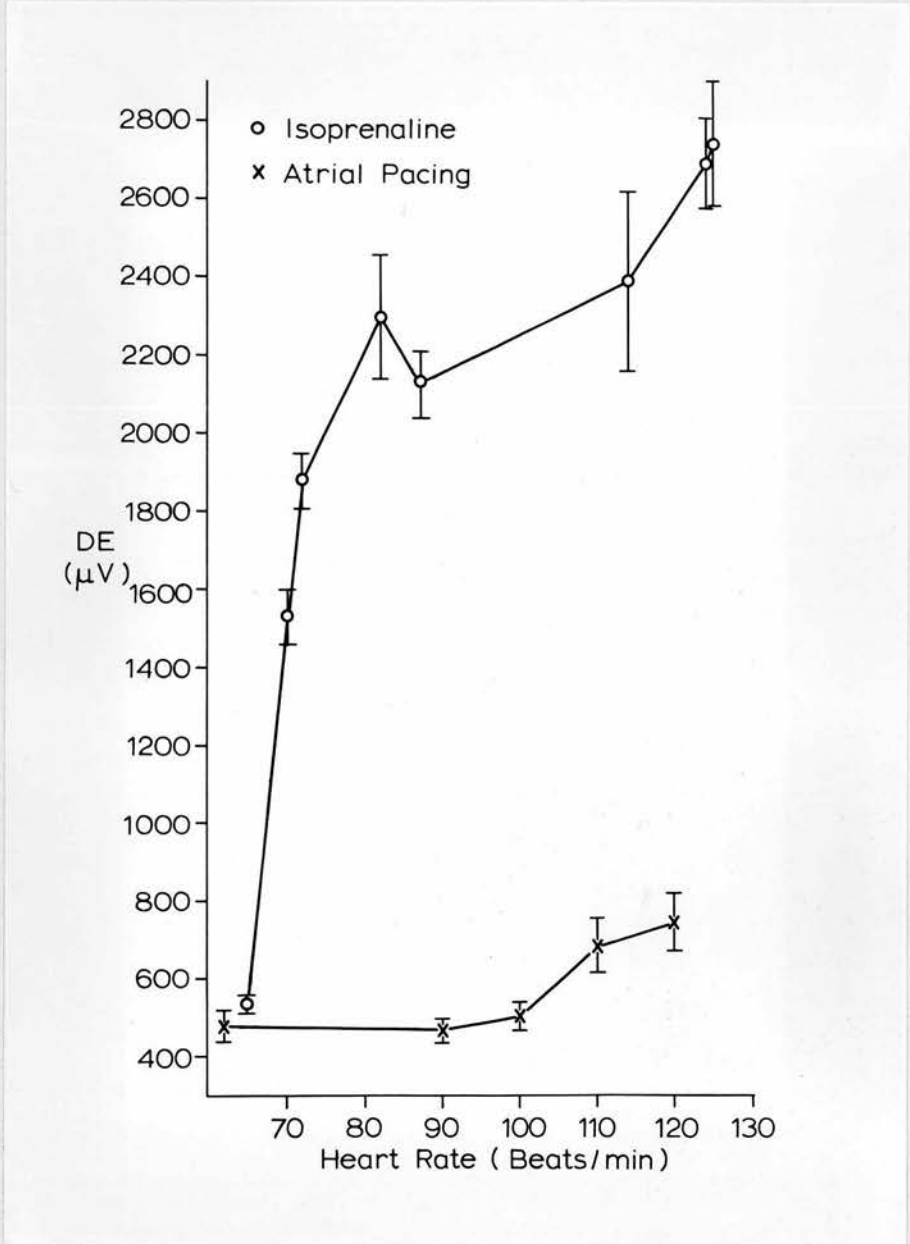
No attempt has been made in this study to systematically reassess the relationship between the maximum amplitude of the praecordial accelerocardiogram and central circulatory haemodynamics during controlled interventions in man, but figure 16 compares the effects on maximum praecordial acceleration of isoprenaline in one patient with hypertrophic obstructive cardiomyopathy and of rapid atrial pacing in one patient with suspected ischaemic heart disease. This figure illustrates the relative independence of maximum praecordial acceleration from changes in heart rate, in contrast to the pronounced effects of a positively inotrophic agent.

Previous workers have suggested that the normal left ventricular response to isometric exercise includes an increase in contractile state (Amende et al., 1972; Cohn et al., 1973; Grossman et al., 1973a; Helfant et al., 1971; Kivowitz et al., 1971; Krayenbuehl et al., 1972, 1973; Payne et al., 1973; Quinones et al., 1974b), but this was not reflected in an increase in the maximum amplitude of the praecordial accelero-cardiogram in the present study (Table 2; Figures 4, 7).

Much/...

Much of the evidence which favours an increase in contractility during handgrip is based on the study of ventricular function curves (Amende et al., 1972; Cohn et al., 1973a; Grossman et al., 1973a; Helfant et al., 1971; Kivowitz et al., 1971; Payne et al., 1973; Quinones et al., 1974b) but these have been shown to be unreliable in defining left ventricular contractile state in situations in which aortic pressure is changing (Sonnenblick et al., 1970) as it is during isometric handgrip. Otherwise, the only evidence in favour of an increase in left ventricular contractility during handgrip is the demonstration in four studies of increases in the derived isovolumetric indices of contractility, V_{max} (Grossman et al., 1973a; Krayenbuehl et al., 1973; Quinones et al., 1974b) and peak velocity of contractile element shortening (Krayenbuehl et al., 1972; Quinones et al., 1974b). However, in only one of these studies (Quinones et al., 1974b) was the level of isometric exercise comparable to that used in the present study and it seems possible that different autonomic and haemodynamic responses may operate at different levels of exercise. This has been shown to be true of dynamic exercise (Robinson, Epstein, Beiser and Braunwald, 1966). Comparison of the effects of atrial pacing and sustained handgrip at similar heart rate suggests that the increase in the isovolumetric indices of contractility during handgrip is partly due to the effects of the associated tachycardia (Krayenbuehl and Rutishauser, 1973; Quinones et al., 1974b). Unlike these indices, peak aortic and praecordial acceleration are relatively insensitive to changes in heart rate induced by atrial pacing (Noble et al., 1966c, 1972; Reuben and Littler, 1973) which may explain why the maximum amplitude of the accelerocardiogram did not increase during handgrip. Quinones and his colleagues suggested that left ventricular contractility was augmented, independent of the effects of heart rate, because they observed a greater increase in the derived isolumetric indices of contractility during handgrip than during atrial pacing in normal subjects (Quinones et al., 1974b). However, during atrial pacing left ventricular end-diastolic pressure and volume decrease (McCans and Parker, 1973; McLaurin, Rolett and Grossman, 1973b) whereas during sustained handgrip/...

Figure 16 Effects of Isoprenaline and Atrial Pacing on DE.



Each cross and circle represents the mean value of twenty consecutive cardiac cycles measured in one patient at various times after isoprenaline administration and at various paced heart rates.
Bars represent one standard deviation.
DE = maximum amplitude of the accelerocardiogram.

handgrip these remain constant (Amende et al., 1972; Krayenbuehl and Rutishauser, 1973; Stefadouros et al., 1974b). Since the isovolumetric indices have now been shown not to be independent of initial fibre length (Hamer, 1973) it would appear that the modestly lesser change in these indices during pacing as compared to handgrip can be attributed to the fact that pre-load declines during atrial pacing but not during handgrip.

The fact that maximum praecordial acceleration did not increase during handgrip in this study (Table 2; Figures 4, 7) confirms previous observations that ejection phase indices of left ventricular function, including mean velocity of circumferential fibre shortening and ejection fraction, do not increase during isometric exercise (Stefadouros et al., 1974a). Indeed Ludbrook and his associates, using the technique of wall motion video tracking, showed a pronounced decrease in the mean velocity of left ventricular wall movement during ejection in normal subjects performing sustained handgrip (Ludbrook et al., 1974b).

The rather equivocal results which have been produced by the studies of left ventricular function during handgrip, depending on which index of contractility is used, make it doubtful if any increase in contractility occurs, other than a small change secondary to the effect of increased heart rate. The results of the early investigations into the response to sustained handgrip in normal, healthy, young subjects indicate that there is no reason to suppose that left ventricular contractility increases in these subjects. The pressor response is entirely due to a rate-dependent increase in cardiac output, stroke volume remaining unchanged (Donald et al., 1967; Lind, 1970; Lind et al., 1964; Martin et al., 1974; Macdonald et al., 1966). Thus, left ventricular pump function is unchanged during handgrip. Furthermore, since the increase in blood pressure is entirely secondary to the increased cardiac output, peripher vascular resistance remaining unchanged, there is no increase in the resistance to left ventricular ejection, which has been invoked to explain the absence of any increase in the ejection phase indices of contractility during handgrip (Stefadouros et al, 1974a, b).

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In the present study there was no evidence to suggest that activation of the beta adrenergic nervous system occurs during handgrip, insofaras the changes in heart rate, blood pressure and the maximum amplitude of the accelerocardiogram were unchanged after the administration of propranolol to the normal subjects (Table 2; Figures 4 - 7). This confirms previous observations that beta blockade does not impair the chronotropic or pressor responses to handgrip but, under these circumstances, an increase in peripheral vascular resistance makes a greater contribution, and an increase in cardiac output a lesser one, to the rise in blood pressure (Martin et al., 1974; MacDonald et al., 1966). The lack of a demonstrable effect of propranolol on the accelerocardiographic response to handgrip is the first observation to suggest that the inotropic response to handgrip, like the chronotropic response, is independent of the beta adrenergic nervous system. It is thought that the tachycardia during handgrip is due to the withdrawal of vagal tone because the increase in heart rate is inhibited by atrophine (Freyschuss, 1970: Martin et al., 1974). However, a beta adrenergic contribution to the tachycardia has been demonstrated after atropinisation (Martin et al., 1974), indicating that alternative mechanisms do exist for increasing heart rate during handgrip. With this exception, activation of the beta adrenergic nervous system contributes little to the handgrip response in young, normal, healthy subjects.

In contrast, the predominant mechanism involved in the response to dynamic exercise in beta adrenergic activation (Epstein and Braunwald, 1966; Epstein et al., 1965; Sonnenblick et al., 1965) and the resultant increase in contractility was reflected in an increase in the maximum amplitude of the praecordial accelerocardiogram in this study (Table 7; Figures 4, 7). The large contribution which the beta adrenergic nervous system makes to the cardiovascular response to dynamic exercise is indicated by the degree of suppression of this response by propranolol (Table 7; Figures 4,5, 7). The incomplete suppression by propranolol of the chronotropic and accelerocardiographic responses to exercise is in agreement with the results of previous studies and suggests that other mechanisms may also contribute to the cardiovascular adjustments/...

adjustments of dynamic exercise (Epstein et al., 1965; Sonnenblick et al., 1965). Although, for the group as a whole, propranolol produced proportional reductions in the chronotropic and accelerocardiographic responses to exercise (Figure 10), in five of the six subjects the im pairment in terms of praecordial acceleration was greater. In the remaining subject undue sensitivity to propranolol was suggested by the irregular bradyarrhythmia observed after exercise. If this subject is excluded, propranolol caused significantly greater suppression of the accelerocardiographic response to exercise, as compared with the chronotropic response ($p < 0.01$). The results of previous haemodynamic studies also suggest that propranolol impairs the inotropic response to exercise more than the chronotropic response (Sonnenblick et al., 1965; Wiener et al., 1969). Whether this effect can be attributed to a depressant effect of the drug on the myocardium, independent of its beta adrenergic blocking properties, or whether it represents differences in the beta receptors which mediate the inotropic and chronotropic responses to exercise remains conjectural.

The results of this part of the study confirm and extend previous observations that the praecordial accelerocardiogram is responsive to increases in left ventricular inotropic state associated with activation of the beta adrenergic nervous system (Reuben and Littler, 1973; Rosa and Kaplan, 1960a), Since the sympathetic innervation of the heart is thought to play an important role in cardiac disease, this property of the accelerocardiogram is of potential practical significance.

Using the simple non-invasive technique of praecordial accelerocardiography it has also been possible to demonstrate a depressant effect of propranolol on the heart of normal, resting, supine subjects, in that the drug significantly reduced maximum praecordial acceleration (Table 8; Figure 7). This confirms previous observations, in dogs, that beta adrenergic blockade is associated with a reduction in peak aortic acceleration (Noble et al., 1966a; Reuben and Littler, 1973). There is also some evidence from previous work which suggests that propranolol depresses left ventricular function in normal resting human subjects. Various workers have observed that left

ventricular/...

ventricular maximum dP/dt and the mean rate of left ventricular ejection are reduced out of proportion to the magnitude of the associated bradycardia, when propranolol is administered to normal subjects (Dwyer et al., 1968; Robin et al., 1967; Wiener et al., 1969). Furthermore, ultrasound studies have shown a decrease in ejection fraction after the administration of propranolol to normal subjects (Frishman et al., 1974).

CHAPTER 8

Conclusions

Comparison of the Effects of Isometric Exercise on the Maximum Amplitude of the Praecordial Accelerocardiogram in Normal Subjects and Patients with Heart Disease.

The increases in heart rate, blood pressure, left ventricular end-diastolic pressure and maximum dP/dt which occurred during handgrip in the present study (Tables 2-4) are comparable to those described in previous studies at similar work loads (Amende et al., 1972; Donald et al., 1967; Fisher et al., 1973; Frank and Haberern, 1971; Kivowitz et al., 1971; Lind et al., 1964; Martin et a 1974; Matthews et al., 1974; McDonald et al., 1966; Payne et al., 1973; Quarry and Spodick, 1974; Quinones et al., 1974b). Furthermore, the stressful effects of handgrip in the normal subjects, the patients with aortic stenosis and the patients with myocardial disease, as judged from the magnitudes of the tachycardia and pressor response, were not significantly different. Therefore any difference observed in the response of the praecordial accelerocardiogram between the groups can not be attributed to differences in the level of isometric exercise even altho in the normal subjects handgrip was performed using a strain gauge dynanometer while the patients gripped a sphygmomanometer cuff. The normal subjects were significantly younger than the cardiac patients but, in the various groups, there was no relationship between the age of the subject and the change in maximum praecordial acceleration during handgrip. The normal subjects were not studied durin cardiac catheterisation but, in ten of the cardiac patients studied on the day before the procedure, the mean change in the maximum amplitude of the praecordial accelerocardiogram was not significantly different from that occurring during catheterisation. It seems unlikely, therefore, that differences in the experimen protocol or the stress of cardiac catheterisation can account for the differences observed in the accelerocardiographic response to handgrip.

The interesting and unexpected finding which emerges from this study is that taken as a whole, the patients with aortic stenosis and myocardial disease respond abnormally/

abnormally to the stress of isometric exercise with an increase in the maximum amplitude of the praecordial accelerocardiogram (Tables 3, 4). Individually, fifty percent of the patients in each of these groups responded in this way. The patients who showed this type of response could not be distinguished from the remainder in terms of the adequacy of the test (Tables 5, 6).

Although previous workers have suggested that an increase in contractility occurs in normal subjects during handgrip (Amende et al., 1972; Grossman et al., 1973a; Helfant et al., 1971; Kivowitz et al., 1971; Krayenbuehl et al., 1972; 1973; Payne et al., 1973; Quinones et al., 1974b; Stefadouros et al., 1974b), there is, as stated in chapter 7, some evidence to suggest that any improvement in left ventricular performance is largely due to the chronotropic effects of handgrip (Krayenbuehl and Rutishauser, 1973). Since the maximum amplitude of the accelerocardiogram is insensitive to changes in heart rate per se (Noble et al., 1966c, 197 Reuben and Littler, 1973) it does not increase during handgrip in normal subjects. The observation that a significant proportion of cardiac patients show an increase in maximum praecordial acceleration during handgrip suggests that these patients increase left ventricular contractile state during handgrip, independent of the effects of tachycardia per se. The only interventions which have been shown to cause increases in the maximum amplitude of the praecordial accelerocardiogram are dynamic exercise and increases in myocardial contractility induced by positively inotropic drugs (Reuben and Littler, 1973; Rosa and Kaplan, 1960a), in particular sympathomimetic amines. The most likely explanation of the increase in maximum praecordial acceleration observed in some of these cardiac patients during handgrip is that they activate the beta adrenergic nervous system in response to the stress of isometric exercise, unlike normal subjects in whom the response is relatively independent of this division of the autonomic nervous system (Martin etal., 1974; McDonald et al., 1966).

Plasma catecholamine levels have been shown to increase excessively during dynamic exercise in patients with cardiac failure (Braunwald, 1965; Braunwald and Chidsey, 1965; Chidsey...

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Chidsey, Harrison and Braunwald, 1962) and angina pectoris (Gazes, Richardson and Woods, 1959; Richardson, 1963). Furthermore, Pouget and his associates observed excessive shortening of the pre-ejection period during dynamic exercise in patients with angina pectoris as compared with normal subjects, and attributed this, in part, to excessive activation of the beta adrenergic nervous system (Pouget et al., 1971). The abnormally large increase in the amplitude of the ballistocardiogram which has been observed during dynamic exercise in patients with ischaemic heart disease (Starr, 1965) could be explained on a similar basis. It seems feasible, therefore, that certain patients with impaired myocardial reserve might also respond to the stress of isometric exercise with a compensatory increase in beta adrenergic drive.

There is also evidence of increased adrenergic tone at rest in patients with cardiac failure in that plasma and urinary levels of catecholamines are elevated (Braunwald and Chidsey, 1965; Chidsey, Braunwald and Morrow, 1965). Furthermore, sympathetic blocking drugs produce a marked clinical deterioration in patients with cardiac failure, in contrast to their relative lack of effect in normal subjects and patients without cardiac failure (Gaffney and Braunwald, 1963). Robinson and his colleagues have presented evidence that, in physiological situations in which sympathetic tone is increased at rest, the adrenergic nervous system plays a greater role in the mediation of certain circulatory reflexes, including the response to dynamic exercise (Robinson/

Robinson et al., 1966). This may be applicable to the circulatory response to handgrip in those patients in whom sympathetic tone is appreciable at rest. However, it should be pointed out that the evidence at present available suggests that the sympathetic nervous system is excessively active at rest only in patients with cardiac failure and not in patients with lesser degrees of functional impairment (Braunwald, 1965; Braunwald and Chidsey, 1965; Chidsey et al., 1965; Gaffney and Braunwald, 1963; Vogel and Chidsey, 1969). However, these previous studies have been based either on evidence of clinical deterioration induced by adrenergic blocking drugs (Braunwald, 1965; Gaffney and Braunwald, 1963) or on the evidence of increased plasma and urinary levels of catecholamines (Braunwald and Chidsey, 1965; Chidsey et al., 1965; Vogel and Chidsey, 1969) in patients with cardiac failure. Both of these end-points are probably rather insensitive, and it seems quite feasible to suggest that patients with less severe disease may also have increased sympathetic tone at rest. Indeed there is some evidence of this in acute, experimental pulmonary hypertension (Vogel and Chidsey, 1969) and in patients with aortic stenosis (Hamer and Fleming, 1969) and other forms of heart disease (Epstein and Braunwald, 1966).

The patients with aortic stenosis who failed to show an increase in maximum praecordial acceleration were those with a low cardiac index (Table 5; Figure 9). A reduction in cardiac index in aortic stenosis is a late event in the natural/

natural history of the disease (Dexter et al., 1958) and is said to signify the presence of left ventricular failure (Goldberg, Bakst and Bailey, 1954; Gorlin et al., 1955). It is possible that, in patients with a low cardiac index, myocardial impairment has reached a critical level, so that the compensatory increase in sympathetic stimulation during handgrip becomes insufficient to increase left ventricular contractility and the response, in terms of the praecordial accelerocardiogram, reverts to "normal". It is perhaps relevant that the heart is less responsive to electrical stimulation of the sympathetic nerves in advanced experimental cardiac failure (Covell, Chidsey and Braunwald, 1966). The pathological counterpart of this phenomenon might be the depletion of myocardial noradrenaline stores which has been described in severe cardiac failure (Braunwald, 1965; Braunwald and Chidsey, 1965; Chidsey et al., 1963, 1965; Vogel and Chidsey, 1969).

The patients with myocardial disease who failed to increase maximum praecordial acceleration during handgrip had a significantly higher resting left ventricular end-diastolic pressure than those who did (Table 6). While this is compatible with the suggestion that patients with poor myocardial function are unable to increase maximum praecordial acceleration during handgrip despite increased beta adrenergic activation, the mechanism underlying a raised left ventricular end-diastolic pressure in coronary artery disease is not absolutely established and may be an impairment of left/

left ventricular diastolic compliance rather than systolic, pump failure (Braunwald and Ross, 1963; Bristow, van Zee and Judkins, 1970). However, in the patients with aortic stenosis, in whom compliance problems are even more likely to be present, there was no difference in left ventricular end-diastolic pressure between the patients who increased maximum praecordial acceleration during handgrip and those who did not. Nevertheless it is probably not justifiable to conclude that patients with coronary heart disease and a raised left ventricular end-diastolic pressure necessarily have impaired systolic function of the left ventricle.

An association between an elevated left ventricular filling pressure and the presence of segmental abnormalities of contraction has been demonstrated in coronary artery disease (Cohn, Herman and Gorlin, 1974; Herman and Gorlin, 1969; Herman et al., 1967) and, more recently, handgrip has been shown to induce or accentuate localised wall motion abnormalities in some patients with this disease (Flessas et al., 1972; Ludbrook, Karliner and O'Rourke, 1974b). Interestingly, increases in beta adrenergic activation induced pharmacologically may also induce or accentuate left ventricular dyskinesis (Kerber et al., 1974). These observations could explain why patients with higher left ventricular end-diastolic pressures at rest failed to increase praecordial acceleration during handgrip (Table 6) despite a postulated increase in sympathetic activation.

Although the interpretation of the results of this

part/

part of the study is largely speculative, the hypotheses advanced in this chapter may readily be tested by comparing the effects of beta adrenergic blockade on the haemodynamic response to handgrip in normal subjects and cardiac patients, or by measuring catecholamine levels in plasma in normal subjects and cardiac patients during handgrip. If the suggestion is confirmed that cardiac patients with good left ventricular function, unlike strictly normal subjects, activate the adrenergic nervous system in response to handgrip, then one possible source of haemodynamic overlap between normal subjects and cardiac patients will be identified, leading, hopefully, to improvement in the detection of latent left ventricular dysfunction, using isometric handgrip as a stress test. The recognition of an adrenergic contribution in patients with heart disease but good left ventricular function at rest would also necessitate a more critical approach to the selection of control subjects in any future studies into the cardiovascular responses to handgrip.

The results of the present study also suggest that serial assessment of the accelerocardiographic response to handgrip might be of value in detecting the onset of cardiac decompensation in patients with aortic stenosis and myocardial disease and, therefore, in the optimum timing of surgical treatment.

There is one further clinical implication of a possible beta adrenergic contribution to the response to handgrip in cardiac patients. It will be recalled that isometric exercise/

exercise is a physiological stress encountered in everyday activities (Donald et al., 1967; Krayenbuehl and Rutishauser, 1973; Lind, 1970) and it has been repeatedly emphasised that the acute tachycardia and pressor effects of such a stress could be harmful in patients with cardiovascular disease (Ewing et al., 1973; Fisher et al., 1973; Grossman et al., 1973a; Kivowitz et al., 1971). Since the response to handgrip is independent of the beta adrenergic nervous system in normal subjects, it has been suggested that beta adrenergic blocking drugs might be inneffective in preventing these potentially dangerous effects in patients with heart disease (Martin et al., 1974). However, the results of this study would imply that this class of drugs might, in fact, be effective in suppressing the tachycardia and pressor response associated with isometric exercise and might therefore exert a protective therapeutic effect.

CHAPTER 9

Conclusions

The Time to Maximum Praecordial Acceleration

The E peak of the praecordial accelerocardiogram has previously been shown to occur around the time of onset of left ventricular ejection (Luisada, 1962; Rosa and Kaplan, 1960a). Although previous attempts have been made to measure the pre-ejection period from the apexcardiogram and its first time derivative (Gabor et al., 1972; Willems et al., 1971), no-one has investigated the relationship between pre-ejection period and the time to maximum praecordail acceleration, despite the fact that praecordial accelerocardiography is a much simpler technique to perform than apexcardiography. Even in the small group of normal subjects in the present study it has been possible to demonstrate a close correlation, at rest, between the time to peak acceleration and pre-ejection period, over a wide range of heart rates (Figure 11). The ability to measure pre-ejection period using this simple technique, and thus avoiding the cumbersome equipment required to measure systolic time intervals in the conventional way, would represent a potentially valuable addition to currently available non-invasive techniques.

In the normal subjects the time to maximum praecordial acceleration shortened significantly during handgrip (Table 9; Figure 12). In general, previous workers, using conventional techniques, have found no significant change in the duration of the pre-ejection period during handgrip, although in most/

most studies a tendency towards shortening of the pre-ejection period has been noted (Lindqvist et al., 1973; Ludbrook et al., 1974b; Martin et al., 1974; Quarry and Spodick, 1974; Siegel et al., 1972). This has not, however been the universal experience (Frank and Haberern, 1971). Interestingly, time to maximum left ventricular dP/dt, which is related to pre-ejection period, has been shown to shorten significantly in normal subjects during handgrip (Krayenbuehl et al., 1972).

Of the major determinants of the duration of the pre-ejection period, left ventricular end-diastolic pressure (Amende et al., 1972; Cohn et al., 1973b; Fisher et al., 1973; Grossman et al., 1973a; Helfant et al., 1971; Kivowitz et al., 1971; Krayenbuehl et al., 1972, 1973; Quinones et al., 1974b) and volume (Ludbrook et al., 1974b; Stefadouros et al., 1974a, b) do not change appreciably during handgrip in normal subjects. Aortic diastolic blood pressure increases markedly during handgrip (Amende et al., 1972; Donald et al., 1967; Ewing et al., 1973; Frank and Haberern, 1971; Freyschuss, 1970; Kivowitz et al., 1971; Krayenbuehl et al., 1972, 1973; Lind et al., 1964; Lindqvist et al., 1973; Martin et al., 1974; McDonald et al., 1966; Quarry and Spodick, 1974; Siegel et al., 1972; Stefadouros et al., 1974 a, b), which tends to prolong the pre-ejection period, while left ventricular dP/dt also increases (Grossman et al., 1973a; Kivowitz et al., 1971; Krayenbuehl et al., 1972, 1973; Quinones et al., 1974b), which tends to shorten it. The/

The net effect of handgrip, therefore, depends on the magnitude of these two antagonistic influences.

While the degree of shortening of the time to peak acceleration was slightly less in the cardiac patients as compared with the normal subjects, this was not statistically significant ($p > 0.20$) (Tables 9 - 11). This observation is in agreement with the results of a previous study in which pre-ejection period was measured in the conventional way (Siegel et al., 1972). The inability to distinguish between normal subjects and cardiac patients can not be attributed to differences in the magnitude of the pressor response to handgrip since this was not different in these two groups ($p > 0.80$).

The relationship between pre-ejection period, aortic diastolic pressure and maximum left ventricular dP/dt is complex and it did not prove possible, in the present study, to demonstrate any significant correlations between these variables at rest or during handgrip. Indeed, in the cardiac patients, no correlation could be shown between the change in time to maximum praecordial acceleration during handgrip and any of the clinical, haemodynamic or angiographic indices of left ventricular performance, at rest or during the stress. It appears, therefore, that changes in time to peak acceleration and, by inference, pre-ejection period during handgrip are of no value in the detection of left ventricular disease or in the assessment of the extent of the functional impairment associated with the disease.

Dynamic exercise caused a marked and significant ($p < 0.01$) shortening of the time to peak acceleration (Table 12; Figure 12). This conforms with previous observations that pre-ejection period and isovolumetric contraction time shorten during dynamic exercise (Ahmed et al., 1972; Aronow, 1970; Aronow et al., 1971a; Cardus, 1973; Frank and Haberern, 1971; Harris et al., 1973; Leon et al., 1972; Lindqvist et al., 1973; Maher et al., 1974; Miller et al., 1970; Pigott et al., 1971; Pouget et al., 1971; Whitsett and Naughton, 1971). Presumably this is due to the beta adrenergic stimulation which occurs during exercise (Epstein and Braunwald, 1966; Epstein et al., 1965; Sonnenblick et al., 1965) and which has been shown to shorten the pre-ejection period (Ahmed et al., 1972; Harris et al., 1966, 1967a; Hunt et al., 1970; Leon et al., 1972; Metzger et al., 1970; Talley et al., 1971). Confirmatory evidence comes from the effects of beta blockade in the present study, which completely abolished the shortening of the time to peak acceleration during dynamic exercise (Table 12; Figure 12).

In contrast, beta adrenergic blockade had no effect on the shortening of the time to maximum praecordial acceleration during handgrip (Table 9; Figure 12). This is compatible with present concepts regarding the autonomic mechanisms which mediate the response to handgrip, in particular their relative independence from beta adrenergic stimulation (Martin et al., 1974; McDonald et al., 1966). It will be recalled that the tachycardia of isometric handgrip is thought to be

due/

due to the withdrawal of vagal tone to the heart (Freyschuss, 1970; Martin et al., 1974) while the pressor response is largely attributable to an increase in cardiac output consequent upon the tachycardia (Amende et al., 1972; Donald et al., 1967; Lind, 1970; Lind et al., 1964; Martin et al., 1974; McDonald et al., 1966).

The pharmacological equivalent of this process would appear to be vagal blockade by means of the administration of atropine. However, this drug has been shown to cause no change in the pre-ejection period (Harris et al., 1967a,b; Martin et al., 1974; Talley et al., 1971), which is in contrast to the shortening of the time to peak acceleration observed during handgrip. A possible explanation for the failure of shortening of the pre-ejection period with increasing heart rate during atrial pacing or after the administration of atropine may be found in the work of Harley and his associates (Harley et al., 1969) who found evidence that pre-ejection period was inversely related to both heart rate and stroke volume. Both atropine and rapid atrial pacing are associated with a reduction in stroke volume, which tends to cancel out the effect of the tachycardia on the pre-ejection period. In contrast, stroke volume is maintained during handgrip and the pre-ejection period therefore shortens because of the tachycardia.

Furthermore, atropine inhibits the prolongation of the pre-ejection period which follows the administration of vasoconstrictor drugs (Harris et al., 1967b), which suggests that the prolongation of the pre-ejection period

which/

which occurs in this situation is the result of vagal baroreceptor reflexes, rather than a direct effect of increased aortic diastolic pressure per se. On the basis of this study it is possible to suggest an alternative reason for the shortening of pre-ejection period and time to peak acceleration which occurs during handgrip despite an increase in aortic diastolic pressure. When vagal outflow to the heart is suppressed, as it is said to be during handgrip (Donald et al., 1967; Ewing et al., 1973; Krayenbuehl and Rutishauser, 1973; Lind et al., 1964), an increase in aortic diastolic blood pressure will not tend to prolong the pre-ejection period. Consequently the increase in left ventricular dP/dt caused by the tachycardia, and which tends to shorten the pre-ejection period, is unopposed by any influence tending to prolong the pre-ejection period. The pre-ejection period therefore shortens.

Either hypothesis would explain the inverse correlation observed in the present study between the changes in time to peak acceleration and heart rate during handgrip (Figure 13).

At rest, propranolol caused no significant change in the time to peak acceleration (Figure 12), which conflicts with previous studies showing that propranolol prolongs the pre-ejection period (Harris et al., 1966, 1967a; Leon et al., 1972). However, other workers, using conventional techniques for measuring the pre-ejection period, have also failed to demonstrate any change following the administration of propranolol/

propranolol (Hunt et al., 1970; Martin et al., 1974). There are no obvious methodological differences, such as drug dosage or the posture of the subjects, which could account for these discrepancies.

It is clear, however, that further studies are required to clarify the relationship between pre-ejection period and events in the accelerocardiogram, at rest and during acute interventions.

CHAPTER 10

Conclusions.

Left Ventricular Diastolic Changes During Handgrip

The most consistent and pronounced abnormality in the left ventricular response to a variety of stresses is an excessive increase in filling pressure. This has been repeatedly demonstrated during isometric exercise (Amende et al., 1972; Cohn et al., 1973a, b; Fisher et al., 1973; Grossman et al., 1973a; Helfant et al., 1971; Kivowitz et al., 1971; Krayenbuehl et al., 1972, 1973; Quinones et al., 1974b), dynamic exercise (Dwyer et al., 1968; Khaja et al., 1970; Parker et al., 1966, 1967; Wiener et al., 1968, 1969), atrial pacing (Dwyer, 1970; Kasparian and Wiener, 1969; Khaja et al., 1970; Linnart, 1971; McLaurin, Rolett and Grossman, 1973b; Parker et al., 1969) and following the administration of vasoactive drugs (Brown et al., 1969; Cohn et al., 1973a; Robin et al., 1967). Since this phenomenon not infrequently occurs in patients who respond normally in terms of the systolic indices of left ventricular performance, it appears to be a most sensitive indicator of the presence of heart disease. There is also evidence that abnormal ventricular relaxation is a sensitive manifestation of impaired left ventricular function. In one study in patients with coronary heart disease, atrial pacing induced an abnormal reduction in peak negative dP/dt during isovolumetric relaxation, in contrast to the normal increase observed in maximum systolic dP/dt (McLaurin et al., 1973b). Ultrasound studies/

studies have shown that left ventricular failure (Carson and Kanter, 1971) and exercise-induced angina pectoris (Fogelman et al., 1972) are associated with reductions both in the rate of relaxation of the posterior left ventricular wall and in the velocity of systolic shortening. However, in both situations, the abnormal diastolic relaxation persisted after recovery, unlike the velocity of the systolic movement which returned to normal, suggesting that impaired ventricular relaxation is a more chronic abnormality in left ventricular disease.

It would be valuable if the pathological increase in left ventricular filling pressure during a stress test could be detected using non-invasive techniques, since this might be applied in screening for occult left ventricular dysfunction. Various workers have described the appearance or accentuation of a fourth heart sound on the phonocardiogram (Aronow et al., 1971b; Cohn et al., 1973b; Matthews et al., 1974; Siegel et al., 1972) and an increase in the amplitude of the 'a' wave of the apexcardiogram (Benchimol and Dimond, 1962; Dimond and Benchimol, 1963; Ginn et al., 1967; Rios and Massumi, 1965; Siegel et al., 1972) during isometric or dynamic exercise. However, technically satisfactory apexcardiograms may be difficult to record in a significant proportion of patients, while the value of conventional phonocardiography is somewhat limited by the fact that it is not a quantitative technique.

The praecordial accelerocardiogram bears a close similarity/

similarity in its configuration to a low-frequency phonocardiogram (Luisada, 1962) and has been used for this purpose in children (Bew et al., 1971). It differs from the phonocardiogram in that its response is linear from DC to 25 Hertz and it, therefore, records low-frequency praecordial vibrations quantitatively. As outlined in Chapter 1, the technique also possesses the important practical advantages of being relatively insensitive to respiratory movements (Luisada, 1962; Reuben and Littler, 1973; Rosa and Kaplan, 1960a), while positioning of the transducer is not as critical as it is with the apexcardiogram (Reuben and Littler, 1973).

The P wave of the praecordial accelerocardiogram has been shown to occur simultaneously with atrial systole (Luisada, 1962; Mounsey, 1959; Rosa and Kaplan, 1960a, Rosa et al., 1961) and its amplitude has been shown to be increased in patients with a fourth heart sound (Mounsey, 1957) and left ventricular hypertrophy (Mounsey, 1959). However, this previous work was subjectively based, while the results reported in the present study represent the first quantitative evaluation of the diastolic waves of the accelerocardiogram.

In the present study a linear correlation has been demonstrated between P/DE and left ventricular end-diastolic pressure, with a correlation co-efficient ($r = 0.60$) (Table 13; Figure 14) similar to that described in previous work with the apexcardiogram (Gibson et al., 1974; Voigt and Friesinger, 1970). In general, only a moderate correlation between the 'a' wave of the apexcardiogram and left ventricular/

ventricular end-diastolic pressure has been demonstrable and this has been attributed to a variety of factors. Firstly, the amplitude of the 'a' wave of the apexcardiogram depends upon the contribution which atrial systole makes to left ventricular end-diastolic pressure (Benchimol and Dimond, 1962; Dimond and Benchimol, 1963; Voigt and Friesinger, 1970). However, in the present study the correlation was not improved when the amplitude of the left ventricular 'a' wave was substituted for end-diastolic pressure. Secondly, the transmission of diastolic pressure waves through the chest wall depends on left ventricular wall stiffness and tension (Benchimol and Dimond, 1962; Cohn et al., 1973b; Gibson et al., 1974; Mounsey, 1959; Rios and Massumi, 1965; Siegel et al., 1972; Voigt and Friesinger, 1970) which influence the relationship between diastolic pressure and the praecordial pulsations, particularly in a heterogeneous group of patients some of whom have left ventricular hypertrophy or dyskinesis. Finally, in patients with left ventricular dilatation, changes in the mechanical coupling between heart and chest wall might modify the relationship between praecordial pulsations and end-diastolic pressure.

Although the average ratio P/DE in the patients with aortic stenosis and myocardial disease was greater than that in the normal subjects (Tables 14, 15), the variability within the groups was such that this was not significant ($p > 0.30$).

The increases in heart rate, blood pressure, left ventricular maximum dP/dt and end-diastolic pressure observed in/

in this study during handgrip (Tables 14, 15) are similar to those described in previous work (Amende et al., 1972; Donald et al., 1967; Fisher et al., 1973; Frank and Haberern, 1971; Grossman et al., 1973a; Kivowitz et al., 1971; Krayenbuehl et al., 1972, 1973; Lind et al., 1964; Martin et al., 1974; Matthews et al., 1974; McDonald et al., 1966; Payne et al., 1973; Quarry and Spodick, 1974; Quinones et al., 1974b). Furthermore, the increases in heart rate and blood pressure during handgrip were similar in the normal subjects and the cardiac patients, indicating that the intensity of the stress was comparable.

The amplitude of the P wave of the praecordial accelerocardiogram increased during handgrip in both the normal subjects and the patients with heart disease (Tables 14, 15). This was significant for the patients as a whole ($p < 0.02$) but not for the normal subjects ($p > 0.20$) (Tables 14, 15). However, there was no statistically significant difference between the two groups as regards the increase in the amplitude of the P wave during handgrip ($p > 0.30$). This might be due, in part, to the small number of subjects studied. A better separation might also have been achieved if a more intense level of isometric exercise had been employed. Perhaps the major factor which prevented clear discrimination between the groups was that it was necessary to express the changes in the amplitude of the P wave during handgrip in terms of a percentage, rather than in absolute units. The haemodynamic counterpart of this is obviously the/

the percentage change in end-diastolic pressure. However, the same percentage change in end-diastolic pressure may signify a normal response in subjects with a normal resting level and an abnormal response in subjects whose end-diastolic pressure is elevated at rest. The mean increase in the amplitude of the P wave of 9% during handgrip in the normal subjects is equivalent to a 21% increase in left ventricular end-diastolic pressure (from regression equation, Table 13) which, from a normal resting level, is compatible with the increases in end-diastolic pressure observed by other workers in normal subjects during handgrip (Helfant et al., 1971; Krayenbuehl et al., 1972; Quinones et al., 1974b).

Previous workers have attributed an increase in the amplitude of the 'a' wave of the apexcardiogram either to an increase in the force of atrial contraction in order to compensate for a reduction in left ventricular end-diastolic distensibility, or to an increase in left ventricular volume which improves the mechanical coupling between the ventricle and the transducer (Benchimol and Dimond, 1962; Gibson et al., 1974; Rios and Massumi, 1965; Siegel et al., 1972; Voigt and Friesinger, 1970). Whether the increase in left ventricular filling pressure which occurs during handgrip is the result of an acute change in compliance or of dilatation of the ventricle, due to acute left ventricular failure, is uncertain (Cohn et al., 1973a; Fisher et al., 1973; Grossman et al., 1973a; Siegel et al., 1972). An increase in left ventricular size during handgrip in patients with severe myocardial/

myocardial disease has recently been shown (Ludbrook et al, 1974), in contrast to the lack of change in normal subjects (Ludbrook et al., 1974b; Stefadouros et al., 1974b), which suggests that the increase in end-diastolic pressure in some patients may be due, at least in part, to acute left ventricular failure. However, Flessas and his colleagues, using a different technique, found a reduction in end-diastolic volume, despite increases in end-diastolic pressure, in a small group of cardiac patients, suggesting a decrease in left ventricular distensibility during handgrip (Flessas et al., 1972). The issue therefore remains in doubt.

Considerably more literature exists on the mechanisms which underlie the pathological increase in left ventricular filling pressure in cardiac patients during other stress tests, such as dynamic exercise and atrial pacing. However, even here agreement has not yet been reached, some workers favouring an acute decrease in compliance (Barry et al., 1974; Kasparian and Wiener, 1969; McLaurin et al., 1973b), while others favour acute left ventricular failure (McCans and Parker, 1973; Sharma et al., 1974), as the cause of the increase in left ventricular end-diastolic pressure during these stresses. To some extent these divergent conclusions can be explained by differences in methodology. One of the major problems in this type of study is that the pressure-volume relationship during diastole is not linear. Consequently, the magnitude of the increases in diastolic pressure and volume during a stress test must be interpreted in terms of the shape and slope of the pressure-volume curve at/

at the observed volume before an authoritative statement can be made about the cause of the increase in filling pressure (Bristow et al., 1970). The interpretation of pressure-volume relationships is further complicated in the presence of segmental abnormalities of contraction, which may be present at rest or induced de novo by the stress (Dwyer, 1970; Pasternac et al., 1972).

There is some evidence to suggest that impaired left ventricular compliance and left ventricular dilatation are associated with different patterns of left ventricular filling, as reflected in the echocardiogram of the anterior cusp of the mitral valve.

The slope of the opening movement of the mitral valve (DE - Figure 2) is reduced in patients with an elevated early diastolic pressure (Konecke et al., 1973). It is thought that these patients have left ventricular failure with a reducation in ejection fraction and an increase in end-systolic and early diastolic volume. Mitral valve opening therefore occurs against an increased left ventricular pressure and the DE slope of the echocardiogram is reduced.

On the other hand, impaired left ventricular compliance, whether due to hypertrophy or fibrosis, is not associated with changes in early diastolic pressure or DE slope (Konecke et al., 1973). However, the duration of the final closing movement after atrial systole is prolonged (Konecke et al., 1973). The mechanism behind this has already been described in Chapter 1.

Studies in patients with cardiomyopathy have also revealed/

revealed differences between patients with hypertrophied, as against those with dilated, left ventricles. In left ventricular dilatation left atrial pressure is high, with a steep 'y' descent in early diastole, while the initial closure rate of the mitral valve (EF - Figure 2) is normal (Quinones et al., 1974a; Shah et al., 1968a; Ziady et al., 1973). Since systolic failure of the ventricle is present, cardiac output is low. These patients characteristically have a third heart sound (Shah et al., 1968a). Impaired left ventricular compliance due to ventricular hypertrophy or fibrosis is associated with a more normal left atrial pressure, a slow 'y' descent and a much reduced initial valve closure rate (Quinones et al., 1974a; Shah et al, 1968a; Ziady et al., 1973). These patients tend to develop a fourth heart sound (Shah et al., 1968a).

However, the resting data in this study does not confirm the previously established correlations between ultrasound and haemodynamic measurements. No correlation could be demonstrated between the initial valve closure rate and left ventricular end-diastolic pressure, as described previously (Layton et al., 1973), although other workers have also been unable to confirm this correlation (Quinones et al., 1974a). It is interesting, however, that the mean initial valve closure rate in the cardiac patients was considerably lower than that in normal subjects although this did not achieve statistical significance (Tables 16, 17). This reduction in initial valve closure rate was largely due to extremely low values in the patients with aortic stenosis (Table 17) which may be related to previous observations that the initial valve closure rate is markedly dependent on left ventricular compliance (Duckak et al., 1972; Layton et al., 1973; Quinones et al., 1974a; Shah et al., 1968a; Ziady et al., 1973). It is not possible to comment further on this matter, since no attempt was made in this study to measure compliance. The results of the present study have not confirmed the previously described relationships between the velocity of mitral valve opening and minimum left ventricular diastolic pressure (Konecke et al., 1973) or between the duration of the final closing movement of the mitral valve and left ventricular end-diastolic pressure (Feigenbaum et al., 1970; Konecke et al., 1973).

al., 1973).

To some extent the differences between the present results and the results obtained by previous workers may be attributable to differences in methodology. In the present study the anterior mitral valve cusp echocardiogram was recorded using an analogue gate system (Chapter 2) in contrast to the more widely used strip-chart recorder which presents the movement patterns of many intra-cardiac structures simultaneously.

Echoes from the anterior cusp of the mitral valve can be recorded from a wide range of transducer positions and angles on the praecordium. Using a strip-chart recorder it is important to locate the posterior mitral valve cusp and to record the anterior cusp echo adjacent to this in order to ensure that the tracing is reproducible (Feigenbaum, 1972). If an analogue gate system is used, however, a suitable anterior cusp echo can only be obtained from a limited area on the praecordium because, in the majority of transducer positions the anterior cusp echo is not dominant throughout the cardiac cycle and the tracing consequently becomes unrecognisable because of the echo drop-out. This factor improves reporducibility when an analogue gate system is used, but the echo obtained is displaced towards the aortic root from the point of maximum excursion of the cusp and the tracing is not identical to that obtained with a strip-chart recorder. A further methodological difference concerns the measurement of the duration of the AC interval. The C point is defined as the point at which the mitral valve is completely closed and is reliably identified using a strip-chart recorder when simultaneous echoes of both mitral cusps are obtained. Using an analogue gate system, it is clearly not possible to do this and in the present study the C point was taken to be the most posterior position achieved by the anterior cusp during the cardiac cycle. Again, therefore, the measurements obtained using the two different techniques are not directly comparable.

Doubt has been expressed about the sensitivity of mitral valve echocardiography in the detection of impaired left ventricular function (Konecke et al., 1973) but, in the only acute study reported thus far, Feigenbaum and his colleagues observed the anticipated/...

anticipated changes in the mitral valve echocardiogram following the administration of glyceryl trinitrin (Feigenbaum et al., 1970). However, in the present study no consistent changes in any of the elements of the mitral valve echocardiogram could be detected in either the normal subjects or the cardiac patients during handgrip (Tables 16, 17) and no differences between these two groups could be shown.

The acute increases in left ventricular diastolic pressures in some of the patients in the present study during sustained handgrip are of the same order of magnitude as those differences in resting diastolic pressures in individual patients which were detectable using mitral valve echocardiography in previous studies (Konecke et al., 1973; Layton et al., 1973). Given the level of reproducibility of the ultrasound measurements outlined in Chapter 6, the larger changes in diastolic pressure should have been detectable in the present study. Indeed, in case 2 (Table 17) left ventricular end-diastolic pressure increased by 88% and the AC interval was correspondingly prolonged by 87%. However, the average changes in diastolic pressures for the groups as a whole were probably not sufficient to produce consistent changes in the mitral valve echocardiogram. Since the haemodynamic changes were fairly substantial this appears to be due largely to the lack of sensitivity of the technique to changes in diastolic pressure. Another explanation must also be consisted for the absence of any significiant changes in the echocardiogram with changes in diastolic pressure in the cardiac patients. This group was probably heterogeneous in that the increases in diastolic pressure in different patients might have been due to acute dilatation of the left ventricle or an acute decrease in compliance or to the acute development of dyskinesis, each of which might alter the pattern of ventricular filling, and thus the mitral valve echocardiogram, in different ways. Since it was not possible in this study, to define which of these mechanisms was operative in the individual patient this possibility can not be commented upon further. The situation is further complicated by any additional effects on the pattern of left ventricular filling of the increase in heart rate during handgrip.

However, it must be concluded that mitral valve echocardiography is unsuitable for detecting changes in left ventricular diastolic pressures during isometric handgrip, at least with the techniques employed in this study.

CHAPTER 11

General Conclusions

The value of non-invasive techniques in the indirect assessment of left ventricular function has been the subject of intensive study. It has frequently proved possible to demonstrate correlations between non-invasive indices of left ventricular performance and related haemodynamic indices measured at cardiac catheterisation. The correlation between the praecordial accelerocardiogram and circulatory dynamics has been as thoroughly validated in the experimental situation as has any other non-invasive technique (Reuben and Littler, 1973).

Although clinical physiologists have placed a lot of emphasis on finding an index of left ventricular contractility which is independent of the conditions of ventricular loading, no index has yet been discovered which conclusively satisfies these stringent criteria under all experimental conditions (van den Bos et al., 1973). It is partly because of this difficulty that non-invasive techniques have become rather disreputable as indices of left ventricular function.

However, as far as the clinician is concerned the ultimate test for a non-invasive technique is not whether it is independent of ventricular loading under highly artificial experimental circumstances, but whether it is useful clinically in the early detection of heart disease and whether the index of left ventricular performance which it provides is useful in predicting the natural history of the disease/

disease in the individual patient. Before these criteria can be considered it is necessary to show firstly that the technique is capable of discriminating between normal subjects and cardiac patients and secondly that it can be correlated in some way with independent estimates of left ventricular function. The results of the present study have shown that preaecordial accelerocardiography in conjunction with sustained isometric handgrip is capable of distinguishing between normal subjects and cardiac patients. Furthermore, differences were observed in the accelerocardiographic response to handgrip between patients with good left ventricular function and those with impaired left ventricular function. Long term follow-up studies will be necessary to ascertain whether praecordial accelerocardiography is of value in the clinical situation.

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