HEART RATE VARIABILITY IN MAN

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1988

"Declaration"

I declare that this thesis is my own composition and that the work described in it was carried out by myself.

"Acknowledgment"

I would like to express my sincere thanks to all the subjects who volunteered to do all those tedious and long experiments.
My special thanks go to my husband who had offered a lot of support, encouragement and assistance throughout the whole duration of this work.
The support and interest shown by Dr.Evelyn Telfer and Dr.R.Gosden are greatly appreciated.
Thanks go to Dr.J.Prescott for statistical advice and Ms.Lesley Crombie for her help in writing the programm for plotting the heart rate spectra. Later modifications and additions including the smoothing procedure were made by the author of the thesis. All other computations were also made by the author.
Special thanks go to : Dr.D.J.Ewing for providing medical cover for the autonomic blockade experiments ; Mr.W.Stephen, the departmental superintendent for his excellent cooperation ; Mr.T.Mackenzie, Mr.D.Thomson, Dr.R.Ribchester and Dr.M.Hunter for lending me computer software ; Dr.J.M.M.Neilson for help and advice ; Dr.W. Reid, Dr.J.Critchely and sister Mclay of Edinburgh Royal Infirmary for technical assistance ; Medical illustration department for typing the tables and drawing the histograms and Mrs. Sheila Arnott for typing the abstract.
The help with photocopying the figures provided by Dr.Damira Cirac is greatly appreciated.
Last, but not least, many thanks go to my supervisor Dr.Sheila Young for all the help and support. I also acknowledge thankfully her assistance in conducting most of the experiments, and volunteering to undergo all the tests often prior to the other subjects.

"Abbreviations"

ANS	autonomic nervous system.
a.u	arbitrary unit.
BP	blood pressure.
bpm	beats per minute.
CNS	central nervous system.
CV%	interval index.
ΔCV%	the difference between standing and supine CV%.
ECG	electrocardiogram.
EEG	electroencephalogram.
FHR	fetal heart rate.
FEV_1	forced expired volume in one second.
HR	heart rate.
ΔHR	the difference between standing and supine HR.
HRV	heart rate variability.
Hz.	Hertz.
LTV	long term variability.
MAD	mean absolute difference.
ΔMAD	the difference between standing and supine MAD.
MHR	mean heart rate.
MSA	muscle sympathetic activity.
ms	millisecond.
PNE	plasma norepinephrine.
RR interval	the duration in ms. between two R waves of the ECG.
RSA	respiratory sinus arrhythmia.
SEM	standard error of mean.
STV	short term variability.
W	Watts.

"Contents"

"ABSTRACT"

Changes in heart rate with respiration (i.e.respiratory sinus arrhythmia "RSA") have been known since the last century.More recently,it has been shown that there are other rhythms in heart rate not associated with respiration. Collectively, the "RSA" and the other rhythms are called heart rate variability "HRV". One of these slower rhythms occurs at the rate of around 6 cycles / min.("10 second"rhythm). The factors influencing this rhythm and its autonomic control were investigated in this thesis.

An initial survey of the effects of posture on "HRV" was carried out on 79 subjects. Maintained standing (chapter III) was found to be a strong stimulus to potentiate the "10 second" rhythm in about half the subjects who showed predominantly "RSA" when supine.

In chapter IV two different age groups were compared and the results showed that fewer older subjects exhibited a prominent "10 second" rhythm during maintained standing .

The mean heart rate (MHR) during maintained standing was significantly higher than supine MHR. So the difference in heart rate pattern between the two postures was possibly due to the difference in MHR. Therefore, in some oscillators (chapter V) the heart rate was increased to a level similar to that during maintained standing by exercising in the supine position. However, this increase in heart rate failed to induce the "10 second" rhythm.

The effect of tilting the subjects to 70° angle (chapter VI) caused a similar change in heart rate pattern to that of maintained standing .

Since both active and passive change of posture caused a potentiation of the "10 second" rhythm, investigations were made (chapter VII) to elucidate the contributing factors. The heart rate pattern changed from a predominantly "10 second" rhythm during standing in air to a predominantly "RSA" rhythm during standing immersed in water up to the level of the diaphragm. This change in heart rate pattern with the prevention of venous pooling suggests that the decrease in venous return during maintained standing and the subsequent change in the pattern of discharge from the receptors on the low pressure side of the circulation may be important for the increased prominence of the "10 second" rhythm.

The efferent pathways involved in controlling the "10 second" rhythm were investigated (chapter VIII) by using propranolol to block the sympathetic system and atropine to block the parasympathetic system. Propranolol caused a marked decrease in the amplitude of the "10 second" rhythm during maintained standing suggesting that the sympathetic system is important in its control. Atropine also decreased the "10 second" rhythm, however, the pathway mediating this effect is not clear.

In conclusion, the change in posture from supine to maintained standing caused a remarkable change in the heart rate pattern in about 50% of subjects. As the "RSA" is predominantly parasympathetic and in this study it was shown that the sympathetic

system was important in controlling the "10 second" rhythm, therefore the change in heart rate pattern with posture reflects the change in the balance between the sympathetic and parasympathetic supply to the heart. This effect of posture on heart rate pattern can be developed as a test for the autonomic nervous control of the heart.

Chapter I

GENERAL INTRODUCTION

For more than a century, the changes in heart rate with respiration i.e. Respiratory Sinus Arrhythmia "RSA" had been the only variation known in the heart rate of normal individuals. With the advent of cardiotachometers, the heart rate was measured on a beat-to-beat basis, and thus cyclical variation much slower than"RSA", and not related to respiration became known. These are mainly two rhythms: One occuring at the rate of about 6 cycles per minute ($\sim$ 0.1 Hz.), and the other is even slower, having a frequency of about 0.04 Hz.

The term Heart Rate Variability "HRV" was used previously to denote the variation in heart rate with respiration. Since the recognition of the other variabilities, it has been used in recent literature to describe both the "RSA" and the other rhythms. The latter definition is adopted in this thesis.

There has been an intensive research in to the phenomenon of "RSA" , its origin, mechanisms and factors affecting it. A review of the relevant literature will be given in section - 1.
In section - 2, the effects of two physiological conditions (i.e. sleep and mental activity) on "HRV" would be reviewed.
Heart rate variability was used in the clinical field to detect pathological conditions that might have an effect on the heart and/or its control. The reported effects of autonomic neuropathies, fetal hypoxia and central nervous system damage will be reviewed in section - 3.

In the last section , a review of the literature about the thermoregulatory ($\sim$ 0.04 Hz.) rhythm and the "10 second" ($\sim$ 0.1 Hz.) rhythm will be given.

1. RESPIRATORY SINUS ARRHYTHMIA

Changes in heart rate accompanying respiratory movements ("RSA") have been known to exist for a long time. The first description of this phenomenon is attributed to Ludwig in 1847 . It was defined earlier, as an increase in heart rate with inspiration and a decrease with expiration and it is still described as such in most text books of physiology and medicine (Ganong 1987, Davidson 1987). Manzotti in 1958, from breath holding experiments, concluded that deceleration occurred in response to inspiration but with a time delay of about 5 seconds. Ahmed et al (1982) also thought that inspiration was the stimulus and that the slowing coincided with expiration because of the time delay (2.5 sec) taken for the reflex.

Clynes in 1960 introduced a new concept in the relation between respiration and heart rate changes. He stated that there was a biphasic response of heart rate to both inspiration and expiration. Each response comprised a rise then a fall in heart rate. Both responses were in the same direction, but the expiratory one was usually of smaller amplitude and had longer acceleratory phase.

This concept was soon questioned by Davies and Neilson (1967) who agreed that inspiration gave biphasic response, but they thought that expiration had little or no effect on heart rate. Similar

observations were reported by Jennett & McKillop (1971) on 33 subjects.

Recently, Mehlsen et al (1987) supported the earlier findings reported by Clynes (1960) i. e. two biphasic responses and added that the observed pattern of "RSA" was the result of superposition of these two responses.

Clynes (1960) had also pointed out that the interaction between the two responses depended on the frequency of breathing. The fact that respiratory sinus arrhythmia is a frequency-dependent phenomenon was most impressively presented by the diagram of Angelone and Coulter (1964), which showed the peak of "RSA" occurring at a breathing rate of 5 - 6 / minutes. This dependency of the phasic relationship between lung volume and heart rate on the breathing frequency was later affirmed by Kelman & Wann (1971).

Another factor that influences the amplitude of the "RSA" is the tidal volume. Womack (1971) implemented a linear model to approximate the relationship between lung volume and heart rate, and managed to produce simulated heart rates similar to the actual experimental results. Furthermore, Hirsch & Bishop (1981) showed that this linear relationship between tidal volume and "RSA" amplitude held at each breathing frequency, thus "RSA" is tidal volume-dependent as well as frequency-dependent.

Selman et al (1982) performed the same type of experiments i.e. different tidal volumes at a given frequency of breathing, repeated with different frequencies. However, the increasing tidal volume led to a progressive reduction in the system gain.

Age also influences the amplitude of "RSA". Jennett & McKillop

(1971) reported a significant difference in the amplitude of "RSA" between those above 40 years and younger subjects at less than 25 years. Since then, several studies reported a progressive decrease in "RSA" with advancing age (Wheeler & Watkins 1973, Hellman & Stacy 1976, Waddington et al 1979, Cicmir et al 1980, Mackay et al 1980, Sato et al 1981, Smith & Smith 1981, Chipps et al 1981, Hirsch & Bishop 1981, Wieling et al 1982, Smith 1982, Persson & Solder 1983, Pfeifer et al 1983, Masaoka et al 1985, O'Brien et al 1986).

The exact mechanism causing "RSA" is unknown. To date, and in spite of the intensive research for the last 140 years, none of the theories put forward to explain the mechanism have been universally accepted. This reflects the complexity and diversity of the mechanism(s) involved. However, the possible mechanisms suggested are summarised below:

(i) A reflex of pulmonary origin:

Hering (1869) described an inhibitory respiratory reflex, then Adrian (1933) and later Paintal (1973) described the slowly adapting pulmonary stretch receptors with vagal afferents that mediate this reflex.

Clynes (1960), influenced by the results from his computer simulation, concluded that it was this reflex that initiated the changes in heart rate to the input stimulus (i.e. respiration). However, other investigators thought that this mechanism on its own could not explain the effect of either posture or exercise on the change in heart rate associated with respiration (Davies & Neilson 1967). Moreover, "RSA" was often detectable after bilateral

vagotomy, though of smaller amplitude (Levy et al 1966, Ramirez et al 1985), and lung inflation by positive pressure ventilation failed to produce "RSA" in conscious man (Freyschuss & Melcher 1975). Furthermore, changes in heart rate related to respiration had been documented in the human fetus (Timor-Tritsch et al 1977) in spite of absent stretching of the lungs.

(ii) Bainbridge reflex:

The increased venous return to the heart during inspiration leads to stimulation of atrial stretch receptors with vagal afferent fibres causing tachycardia. The efferent limb of this reflex was claimed to be solely in the sympathetic nerves to the heart (Ledsome & Linden 1964, Kappagoda et al 1974, Linden 1976), although there was a suggestion that vagal efferents were also involved (Burkhart & Ledsome 1974). Recent studies in man support this mechanism as an important factor in the genesis of "RSA" (Freyschuss & Melcher 1975, Melcher 1976).

(iii) Systemic arterial baroreflex:

Although the negative intrathoracic pressure during inspiration leads to increased venous return to the heart, the concommitant rapid expansion of the pulmonary vascular bed was thought to be more than adequate to accommodate the excess blood from the right ventricle. Therefore, the left ventricular output would drop leading to a fall in blood pressure and consequently the heart rate would increase through the baroreceptor reflex.
This mechanism was advanced by Manzotti in 1958 and later supported

by Davies & Neilson in 1967. However, Jennett & McKillop (1971) in seeking support for this theory, studied the relative time course of changes in heart rate and in arterial pressure, and found that the inspiratory increase in heart rate was associated with increasing arterial pressure rather than a fall. This positive correlation which negates the systemic arterial baroreceptors mechanism for the genesis of "RSA" was reconfirmed later by Melcher (1976). Also, the presence of "RSA" in the fetus(Timor-Tritsch et al 1977), where the continuous shunt of blood from the right to the left side of the heart maintains a constant flow to the left atrium with no consequent significant fall in blood pressure, is also against this theory.

(iv) The central theory:

This proposes that "RSA" is caused by irradiation of impulses from the respiratory to the vasomotor center. It has been based on several observations: (a) "RSA" persisted after stopping the respiratory movement by neuro-muscular blocking drugs such as curare (Heymans 1928) or Scoline (Joels & Samueloff 1956), or during periods of apnoea (Valentinuzzi & Geddes 1974), (b) it also persisted, though with much smaller amplitude, after cutting both vagi (Anrep et al 1936, Joels & Samueloff 1956, Levy et al 1966, McGrady et al 1966), (c) the disappearance of "RSA" during deep anaesthesia (Joels & Samueloff 1956, Levy et al 1966).

After reviewing the different theories that have been advanced to explain the mechanism for the genesis of the "RSA" it becomes

evident that no single theory can adequately account for all the observations on "RSA". Anrep et al (1936), McGrady et al (1966) and Valentinuzzi & Geddes (1974) concluded that both the central irradiation from the respiratory centre and the pulmonary stretch reflex are important in controlling "RSA". Hirsch & Bishop (1981) could not exclude the central theory from the observations made by others, although their own results favoured a peripheral mechanism. Selman et al (1982) thought that it was possible that both the central respiratory drive and atrial stretch reflex contributed to the phenomenon of "RSA". They excluded the pulmonary stretch reflex as a possible cause of "RSA" as Freschyuss & Melcher (1975) had found that positive pressure ventilation failed to elicit a response, whereas negative inspiratory pressure increased the amplitude of both "RSA" and the net filling pressures of the ventricles.

2. PHYSIOLOGICAL CONDITIONS AFFECTING "HRV"

2.1 Sleep

It has been known for a long time that the heart rate decreases progessively over the night, and that there are periodic changes that coincide with the regular recurrence of stage I - rapid eye movement (REM) (Snyder et al 1964). However, the mean heart rate during the various stages of sleep was not significantly different, but the standard deviation was found to be more helpful in differentiating stage I - REM from deep sleep (stage III & IV) (Snisarenko 1978). Generally, the variability during a cycle of sleep decreased with the depth of sleep (Aldredge & Welch 1973).

In full term newborn infants, Miyazaki et al (1979) showed that the MHR and SD were significantly higher during active sleep (AS) than quiet sleep (QS). They defined (AS) as the stage of sleep when there was body movement, eye movement and irregular respiration, whereas quiet sleep (QS) when there was regular respiration with no body or eye movement . They also studied the sequential curves of RR intervals and found that slow oscillations were prevalent in (AS) and fast oscillations in (QS), but they added that it was not always possible to identify (QS) and (AS) by sequential curves alone.

In spite of the apparent failure of using the heart rate to develop a sleep pattern detection process, the idea persisted. The newly applied technique of spectral analysis, using Fourier transform which can show variabilities at different frequencies, seems to help in achieving this goal. Lisenby et al (1976) were the first to apply the Fourier analysis on heart rate data during sleep and they succeeded with an average accuracy of 80%, in distinguishing between REM (awake, stage I and REM) and non-REM (stages II,III & IV). During REM the power spectra were characterised by a maximum amplitude peak in the low frequency range (0 - 0.05) while during non-REM, the maximum amplitude peak was at 0.25 - 0.35 cycles/beat. DeBoer (1985) using the same technique, compared the variability during day time rest with periods of quiet sleep, and he also found a maximum amplitude peak at the respiratory frequency during non-REM stages. However, this peak was also present during the awake stage and it did not seem to increase in amplitude during non-REM stage (from his published figures B3 & B4), but the peak at

the low frequency ($\sim$ 0.1 Hz.) was almost completely absent.

Earlier study by DeHaan et al (1977) on healthy term infants at one to three days of age showed a highly significant difference in spectral densities of HRV between active sleep and quiet sleep at frequencies less than 10 cycles per minute.They also commented that it was always possible to identify QS and AS by just looking at the spectral densities plots of the variations in heart rate.

During sleep, the overall variability seems to decrease in man (Mancia et al 1983) and neonatal lambs (Siimes et al 1984), but increases in adult dogs (Haddad et al 1984). However, the spectral peak at the respiratory frequency ("RSA") increased in all species (Lisenby et al 1976, Pagani et al 1985, Siimes et al 1984 & Haddad et al 1984).

2.2 Mental Load

Earlier, investigators used the mean heart rate as an index to measure the strain imposed on the subjects during mental loading. Usually, the MHR increases during mental loading by about 15% (Hyndman 1978, Hitchen et al, 1980, Camman et al 1983).
This response was not universal, and a biphasic response has been reported (Kozlove and Stryukov 1979) showing firstly a significant increase in MHR with increasing intensity of the work load and secondly a gradual relative decrease.
Furthermore, it has been found that the MHR stayed approximately the same, but the "RSA" decreased markedly during a simple binary choice - reaction task (Kalsbeek and Ettema 1963) .

The inconsistent changes in MHR, in spite of marked changes in work load in aircraft pilots during test flights, prompted Sayers (1971) to pursue analysis of heart rate variability during mental work rather than MHR alone, as this sometimes failed to reflect the increasing task load. He and other investigators, using the spectral analysis technique, found that the effect of mental work is usually a reduction in the total heart rate variability (Sayers 1971 & 1973, Mulder & Meulen 1973, Luczak & Laurig 1973, Hyndman 1978, Hitchen et al 1980 and Heselgrave et al 1979). However, an increase in "HRV" has been reported in several cases when the mean successive difference was used as a measure of "HRV" in 142 men (Camman et al 1983) . Contradictory conclusions, regarding changes in "HRV", can occur depending on the type of "HRV" analysis used , as was shown by Heselgrave et al (1979).

Most authors agree that the amplitude of the 0.1 Hz. peak in "HRV" decreases during mental load (Sayers 1971 & 1973, Mulder & Meulen 1973, Hyndman 1978) but the effect on the respiratory peak is not consistent. A shift of the signal power in the 0.25-0.4 Hz. towards the lower frequency region has been reported by Sayers (1973), while others have reported a shift to higher frequencies (Hyndman 1978 and Hitchen et al 1980).

Whether "HRV" can be used as an indicator of mental stress is uncertain. Hyndman and Gregory (1975) found no significant change in average total power (a.t.p) of the low pass filtered cardiac event series with increasing task intensity, but there was an intensity related rebound, which, as they suggested, can be used as

a measure of the degree of mental loading. However, Hitchen et al (1980) found an intensity related increase in the degree of shift of the respiratory component towards higher frequencies and they proposed that this can be used as a measure for the level of stress induced by certain tasks, and also as an indication of how much stress is imposed on different individuals doing the same task.

Other indices of "HRV" are thought to be more sensitive measures of the load of the task e.g. number of reversal points in the ECG (Mulder & Meulen 1973) or successive difference mean square (Heselgrave et al 1979). The validity of the latter have been challenged by Wastell (1981).

The type of task performed seems to affect the result . It has been found that mental arithmetic of various types and degrees of difficulty did not evoke significant changes in a.t.p, but a.t.p decreased substantially during the performance of a decision making task although physical activity per se did not evoke these changes (Hyndman & Gregory 1975).

To clarify the discrepancies between different studies on the effect of mental load on "HRV", Bronis (1983) hypothesized that as "HRV" is a reflection of the autonomic nervous system (ANS) activity in the investigated subjects at the given time and situation, the different results are due to the different states and reactivity of the ANS .These results highlighted the importance of obtaining a reference (resting) "HRV" spectra from the subjects on each day. A relationship between physiological factors underlying "HRV" spectra and psychological state of the

subject has been found (Rompelman et al 1980) , which supported the above hypothesis and led to the suggestion that psychiatric patients are probably subjected to a permanently high mental load.

3. PATHOLOGICAL CONDITIONS AFFECTING "HRV"

3.1 Autonomic neuropathies

(a) Diabetes mellitus

The resting mean heart rate is usually higher in diabetics than in control subjects (Wheeler & Watkins 1973, Ewing et al 1974, Murray et al 1975, Page & Watkins 1977, Bennett et al 1978, Dyrberg et al 1981 Wieling et al 1983), and it is considered to be a sign of cardiac autonomic dysfunction.

Although there is a tendency of MHR to be faster, the difference between diabetic patients and control subjects was found to be statistically insignificant (Chipps et al 1981, Ewing et al 1981, Persson & Solders 1983, and Lishner et al 1987). These findings contrasted with those of Sundkvist et al (1979), Pfeifer et al (1982) and Bernardi et al (1986), where significant differences were found. Moreover, Bellavere et al (1987) found that a significantly higher MHR in diabetics depended upon whether the patients had autonomic neuropathy ($P<0.05$) or not ($P>0.05$).

The finding of a decreased respiratory related heart rate variability in diabetic patients with autonomic neuropathy (Wheeler & Watkins 1973), has initiated a chain of research aiming at developing a simple, reproducible and non-invasive tests, to

detect autonomic neuropathy and to follow the natural history of the disease.

This link between heart rate variability and autonomic neuropathy in diabetic patients was reconfirmed by several studies (Page & Watkins 1977, Cicmir et al 1980, Chipps et al 1981, Pfeifer et al 1982, MacKay 1983, Perrson & Solders 1983, Wieling et al 1983). More recently McEwen & Sima (1987) have reported similar finding in spontaneously diabetic BB rats.

Using a more sensitive method of analysis, Murray et al (1975) were able to detect autonomic neuropathy in diabetic patients without any clinical features suggestive of autonomic lesions. The damage to the autonomic nerves, by the time symptoms have developed was thought to be irreversible(Ewing et al 1980) and carry a poor prognosis (Ewing 1978), while a very good metabolic control in the early stages might achieve some reversal of autonomic abnormalities (Ewing & Clark 1982). Thus, a pre-symptomatic diagnosis seems to be helpful in preventing irreversible late stages. In addition, the reported cardiorespiratory arrest in 8 young diabetics, which was thought to be due to impaired autonomic responses to hypoxia (Page & Watkins 1978) has highlighted the importance of diagnosing asymptomatic cases of autonomic neuropathy.

Several methods for the early detection of autonomic neuropathy were developed. The "HRV" during deep breathing at low frequencies (augmented HRV) was shown to be a better discriminator between patients with or without autonomic neuropathy (Bennett et al 1977 & 1978, Dyrberg et al 1981) than "HRV" during quiet breathing.

Furthermore, augmented HRV was thought to be more sensitive than heart rate variability (SD) during standing (Bennett et al 1977, Dyrberg et al 1981).

The initial response to standing or tilting was definitely decreased in patients with autonomic neuropathy (AN) (Page & Watkins 1977, Ewing et al 1978, MacKay et al 1980, Sundkvist et al 1980, Van Brederode at al 1980, Wieling et al 1983, Persson & Solders 1983), however, those without (AN) showed similar responses to controls (Bennett et al 1975, MacKay et al 1980, Dyrberg et al 1981).

In the search for a simpler test that can be carried out in a busy outpatient clinic, Smith and Smith (1981) described a single breath test in which the longest RR interval during expiration (E) and the shortest during inspiration (I) are measured to calculate the E/I ratio. It has been suggested (Smith & Smith 1983) that the E/I ratio was better than the E-I difference which was described by Wieling & Borst (1983), as it was independent of differences in resting mean heart rate. However, reproducibility was better if the average E/I ratios for 6 breaths were taken, a test described earlier by Sundkvist et al (1979).

Almost all the above mentioned tests need the subject's co-operation. To obviate this, a new method of measuring cardiac parasympathetic activity was developed (Ewing et al 1984).This was based on analysing a 24 hour ECG record and measuring the mean number of times per hour that successive RR intervals varied by more than 50 ms. This method seemed to be more sensitive than the

other tests for cardiovascular reflexes in use at the time , as it was clearly abnormal in half, and at the lower end of the normal range in the other half of a group of diabetics who gave normal responses to a battery of cardiovascular tests. There are certain limitations to this method, most obviously is its inappropriate use in patients with arrhythmia or large number of extrasystoles and this was acknowledged by the authors themselves (Ewing et al 1984).

Another method, proposed by Weinberg & Pfeifer in (1984), and used by McEwen & Sima (1987) to assess autonomic neuropathy in spontaneously diabetic BB rats, was thought to be more sensitive in measuring "HRV". The measurement was given the designation $\overline{R}$ and it represents the length of the vector mean for points (cardiac events) wrapped mathematically around a unit circle, the length of which is equal to the length of the respiration. Significant differences in $\overline{R}$ values between diabetic and non-diabetic rats were obtained 16 weeks earlier than those obtained using standard deviations. However, the complex mathematics involved, probably would not make it a very popular method to be used routinely.

A less complicated, but interestingly new observation was reported by two groups of researchers at the same time (Kronert et al 1986 & Comi et al 1986). Both groups carried out tests of cardiovascular reflexes described by Ewing & Clarke (1982) which included: 1) Heart rate response to Valsalva manouvre. 2) "HRV" during deep breathing. 3) Immediate heart rate response to standing. 4) Blood pressure response to standing and 5) Blood pressure response to sustained handgrip. Kronert et al (1986) repeated these tests 6

times in the same day, while Comi et al (1986) repeated the tests on 5 consecutive days. They both used the standard deviation of the different results obtained, on repetition of the tests, as a measure of the individual variability. Both groups reported reduced intra-individual variability in diabetic patients with parasympathetic failure. Moreover, Kronert et al (1986) reported a significant reductions in the intra-individual variability of the Valsalva manoeuvre in patients without autonomic neuropathy when the Valsalva ratios were still normal, and this makes the test a sensitive detector of autonomic neuropathy in asymptomatic patients. However, repeating five cumbersome tests, six times a day or five times a week, is not a very practical and easy way of detecting possible autonomic dysfunctions in patients suffering from diabetes mellitus. Also,each of the tests on all the occasions have to be carried out by the same investigator to avoid intra-investigator variability.

The spectral analysis of "HRV" was used to study diabetic patients with autonomic neuropathy by Kitney et al (1982). It was found that patients with autonomic neuropathy showed a marked reduction in "HRV" amplitude, and in addition, a shift in the peak of the "HRV" - frequency response to the left (towards low frequencies).

MacKay (1983), without using spectral analysis, reached the same conclusions. He measured "HRV" at different rates of deep breathing, and found that patients with autonomic neuropathy had significantly smaller "HRV", and the maximum variation occurred at slower breathing rates. Moreover, he found that patients without autonomic neuropathy, also had maximum responses at significantly

slower rates ,but "HRV" amplitues were normal . In contrast, a study of 26 asymptomatic patients during normal breathing (Brodie et al 1983)showed a marked reduction in the size of all the spectral peaks (down to 5% of comparable controls).

A similar reduction in all peaks was reported in diabetic patients compared with controls (Lishner et al 1987),but when diabetics were subdivided according to the presence or absence of autonomic neuropathy, there was no significant difference between the two groups, although those patients with peripheral neuropathy had smaller peaks.

In contrast to the previously cited studies, a study of 12 children with diabetes mellitus found that both the quantity and the frequency distribution of the "HRV" were normal during either regular or deep breathing (Lindqvist et al 1986) .

Bernardi et al (1986) investigated specifically the relationship between heart rate variation and breathing and compared it to the other measures of "HRV" (i.e. MHR, SD and RR intervals range). They first computed the cross spectrum of respiration and the RR intervals tachogram, and then transformed it back as a tachogram, to obtain what they called the cross correlation function (CC). Their results showed that both the SD and the CC were good separators between the groups of normals and diabetics with or without autonomic neuropathy, but the CC method had a higher degree of statistical significance.

The general impression on cardiac autonomic dysfunction in diabetes

mellitus is that vagal denervation is the most important lesion while sympathetic defects are less frequent and less severe (Page & Watkins 1977). This conclusion, stems from the fact that most methods used to detect autonomic neuropathy, test the parasympathetic branch of the autonomic nervous system to the heart. Most sympathetic tests are not well developed and depend on blood pressure responses which are subject to several variables. Moreover, they detect abnormalities only when there is severe extensive, peripheral sympathetic damage (Ewing & Clarke 1982).

The finding by Fagius (1982) that micro-neurographic recording of sympathetic nerve activity was impaired in 64% of diabetic patients with polyneuropathy, drew the attention to the fact that sympathetic involvement in diabetic polyneuropathy occurs more frequently than it was thought to be. However, the intraneural insertion of microelectrodes in conscious patients is clearly too invasive, and it is difficult to perform routinely.

Bellavere et al (1987) studied the immediate response to lying down, and calculated the ratio between, the maximum RR interval at 20 to 25th beat after lying down, and the minimum RR interval at the first 5 beats (SL2). They considered SL2 a mixed, but predominantly sympathetic test, depending on the finding by Bellavere & Ewing (1982) that the later part of the cardiac response to lying down (after the first 10 beats) depended predominantly on sympathetic withdrawal. However, the calculation of this ratio (i.e. SL2) involves more parasympathetic elements than sympathetic because the minimum RR interval at the first 5 beats is completely under parasympathetic control (Bellavere &

Ewing 1982). Furthermore, the SL2 value was not significantly different in diabetic patients without autonomic neuropathy from control group. Therefore, there is an obvious need to develop a more sensitive, simple, reliable and non-invasive tests for cardiac sympathetic activity.

The evidences for the effect of the duration of the disease on "HRV" are inconclusive. Some showed that the decrease in "HRV" measures became more marked with increasing duration of diabetes (Gundersen & Neubauer 1977, Dyrberg et al 1981, Wieling 1983 and McEwen & Sima 1987), while others found no significant independent effect of the duration of the disease on "HRV" indices (Sundkvist et al 1979, Cicmir et al 1980 and Chipps et al 1981).

The presence of other complications of diabetes like retinopathy might also correlate with a decrease in "HRV" (Sundkvist et al 1979, Cicmir et al 1980, Dyrberg et al 1981, Morguet & Springer 1981 and Wieling 1983), but a significant relationship was not always found (Chipps et al 1981).

(b) **Other conditions with autonomic neuropathies**

In the last decade, autonomic neuropathy in patients with **chronic renal failure** on hemodialysis, has become increasingly recognised. The use of "HRV" as a screening test for the presence of any dysfunction in the autonomic nervous control of the heart was suggested by Ewing & Winney (1975). They showed that "HRV" at rest was decreased in uraemic patients in the absence of symptoms suggestive of autonomic neuropathy.

Heart rate variability during deep breathing was also found to be significantly decreased in dialysis patients (Zoccali et al 1982). However, it seems to be reversible, as coefficient of variation of RR intervals improved following successful renal transplantation (Endre et al 1982). Furthermore, the significant increase in "HRV" indices, especially for the long term variability, after a single hemodialysis session, raised the suggestion that autonomic neuropathy in patients with chronic renal failure might be functional to some extent (Forsstrom et al 1986).

Although autonomic dysfunction is a well known complication of **chronic alcoholism** , only recently "HRV" being used to assess autonomic functions in alcoholics.

Weise et al (1985) showed that "HRV" measured as mean difference between successive RR intervals was reduced in alcoholics with symptomatic autonomic neuropathy. A follow up study showed that improvement in "HRV" occurred in those patients with short to moderately-long duration of drinking history and they suggested that those alcoholics must have had functional rather than organic damage (Weise et al 1986). Thus, a more sensitive method for the early detection of autonomic neuropathy in alcoholics would be beneficial as long as the damage was still functional and reversible with abstinence from alcohol. The cross-correlation method adopted by Bernardi et al (1986), was thought to be the best, as it managed to detect 11 patients with abnormal heart rate respiration relationship, out of a total of 16 alcoholics with no symptoms of autonomic or peripheral neuropathies.

The study of the intrinsic cardiac function in man was made possible by pharmacological denervation using combined sympathetic and parasympathetic blockers (Jose 1966, Jose & Taylor 1969). The intrinsic heart rate was found to be depressed in patients with **cardiac diseases** and the decrease was related to the severity of the disease (Jose 1966). Whether this depression in diseased heart was due to a defect in the function of the sino-atrial node as Jose (1966) suggested, or due to impairment in parasympathetic control of the heart (Eckberg et al 1971) was not clear. However, the response of the heart with chronic Chagas' disease to atropine, supported the contention that it is the derangement in the autonomic control of the heart rather than a local effect (Amorim et al 1982). Moreover, in patients with congestive heart failure, the restoration of normal reflex responses to orthostatic stress during treatment with the vasodilator drug Felodipine added more support to the suggestion made by Eckberg et al (1971) (Timmis et al 1984). The nature of the autonomic neuropathy in heart diseases is still unclear but evidence exists for dysfunction at multiple sites in the baroreceptor reflex arc (Timmis et al 1984).

The role of the autonomic nervous system in **sudden cardiac death** has initiated a new area in the study of the risk factors for sudden death. Based on the postulated relationship between autonomic activity and vulnerability of the heart to ventricular arrhythmia, "HRV" analysis has been used as an indirect estimate of the level of the autonomic activity.

Heart rate variability was found to be reduced in patients known to be at high risk of sudden cardiac death (Myers et al 1986), and also in patients who died suddenly (Martin et al 1987). It was

also found to be a significant predictor of mortality after acute myocardial infarction (Kleiger et al 1987).

In both, babies with **idiopathic respiratory distress syndrome** (IRDS) and victims of sudden infant death syndrome (SIDS) or **"cot death"** , disturbances in the cardiorespiratory control system are thought to be involved. A lower "HRV" (both short term and overall) in patients with IRDS, which decreased further as the condition deteriorated was shown by Kero (1974).
To assess the degree of severity of IRDS and to predict the outcome for individual infants, different combinations of parameters were necessary (Jenkins et al 1983).
So far, heart rate monitoring and characterisation of "HRV", has failed to predict which infant will die of SIDS from a normal population (Wilson et al 1985, Stevens et al 1985), however, research in this mysterious codition is still in its infancy, and results are very conflicting.

In addition to the above, heart rate variability had been used to detect involvement of the autonomic nervous system in a wide variety of systemic diseases, such as, **multiple sclerosis** (Neubauer & Gundersen 1978), **rheumatoid arthritis** (Lindqvist et al 1986), **hypertension** (Pagani et al 1984) and **allergic asthma** (Tokuyama et al 1985).

3.2 Fetal hypoxia

Prior to the era of the cardiotachometers, the periodic auscultation of the fetal heart was used to detect clinical signs

of fetal distress during labour. With the advance in electronic technology it became possible to monitor the fetal heart rate (FHR) continuously and soon it was realised that a certain degree of irregularity was a normal feature of the fetal heart rate .

Swartwout et al (1961) were the first to report periodic oscillations (3-5 cycles / min.) in FHR in the absence of detectable uterine contractions. Mendez-Bauer et al (1963) independently reported the presence of oscillations in FHR with a frequency ranging from 2 to 10 cycles/min.
Simultaneously Hon & Lee (1963) showed that FHR became smoother and smoother as death was approached in 5 cases with unfortunate outcomes. Thus, the link between the irregularity normally seen in FHR records and fetal well-being started to grow.

The vast amount of data and the difficulty in making direct comparsion between results from different studies prompted Yeh et al (1973) to implement automatic processing methods to quantify the beat-to-beat variation in FHR. Several classifications and different indices emerged, which when reviewed by DeHaan (1973), did not offer a consistent result in assessing the fetal condition. A similar result was found by Laros et al (1977). DeHaan (1973) acknowledged that the "HRV" phenomenon in the FHR was not sufficiently defined, and suggested animal experiments and mathematical modelling to get more insight of the physiological mechanisms involved in the generation of FHR variability.

The finding of Beard et al (1971) that baseline bradycardia without decelerations and with good beat-to-beat variation was not due to

fetal asphyxia, was important. Equally so, was the finding of Paul et al (1975) that baseline FHR variability, on its own, immediately prior to birth, correlated with Apgar score at 1 and 5 minutes. Furthermore, they pointed out that smoothness of FHR records could be due to factors, other than asphyxia, such as immaturity, fetal inactivity or sleep and maternal drug administration e.g. Diazepam.

Most of the studies were carried out on FHR during labour. Rochard et al (1976) monitored the FHR in the antepartum period and demonstrated that there was also a close correlation between non-stressed (antenatal) patterns and neonatal outcome. They reported a progressive diminution in beat-to-beat variation of baseline heart rate as death approached in 12 cases. However, due account of gestational age was essential in interpreting antenatal FHR records (Visser et al 1981). Moreover, Kariniemi et al(1982) found also a negative correlation between non-stressed fetal "HRV" indices and maternal hypertension and tachycardia triggered by smoking.

Results from clinical studies had shown repeatedly that fetal "HRV" indices correlated with fetal scalp pH and neonatal outcome determined by Apgar score (Beard et al 1971, Paul et al 1975, Curzen et al 1984). However, results from laboratory experiments on the effect of acute hypoxia on animals fetal "HRV" seems at variance with the clinical experience. Dalton et al (1977) reported an increase in fetal "HRV" in sheep during hypoxia. Other investigators soon confirmed this finding (Stange et al 1977 and Parer et al 1980). Furthermore, Zugaib et al (1980) found that

in the neonatal lamb, the reaction to acute hypoxia depended upon the age of the animal, in the younger ones (2 - 3 weeks old), both long term and short term variabilities decreased during hypoxia while the 4 - 8 weeks old lambs showed increased variability in the early period of hypoxia.

A recent report (Thaler et al 1985) seems to show that human fetus reacts in a very similar way to experimental animals, when exposed to acute hypoxia. FHR variability increased markedly when the oxygen concentration inspired by the mother was dropped (accidently) to 10% only. However, this initial increase in FHR variability lasted for about 3 minutes followed by a complete loss. During recovery, there was a resurgence in FHR variability again, which was very similar to the findings in anaesthetised adult dogs (unpublished observations).

A problem specific to the fetal heart rate monitoring is the technical acquisition of the signal. Paul et al (1975) recommended the use of direct fetal ECG rather than the ultrasonogram or phonocardiogram because the latter two generate false FHR variability due to "jitter". Visser et al (1981) found that beat-to-beat variation was twice as great when ultrasound was used. Statistical modelling of FHR variability by Jarish and Detwiler (1980) showed that doppler ultrasound recordings has ten fold increase in random error due to jitter and this supported the clinicians impression that FHR variability derived from ultrasound was often fallacious.

3.3 Central nervous system damage

Vallbona et al (1965) were the first to find a correlation between absent "HRV" and central nervous system (CNS) dysfunction. They showed that patients with deep coma had fixed heart rates, similar to the heart rate pattern during deep anaesthesia or out of a heart-lung preparation.

Progress in utilising "HRV" in monitoring fetal conditions and the assumption that FHR variability reflects the condition of the central nervous system, regenerates the interest in studying "HRV" in patients with CNS lesions. Lowensohn et al (1977) reported a decreased "HRV" in patients with increased intracranial pressure (ICP) which returned to normal when the ICP decreased. However, a study on a larger number of patients (Leipzig & Lowensohn 1986) showed that the correlation between "HRV" & ICP was not as strong as was previously postulated.

Kero et al (1978) studied 12 childern (1 month - 15 years) with brain death for various causes (trauma, poisoning, infection etc.). In all patients, the beat-to-beat variability was slightly lower and the overall variability was much lower than normal ranges for age - matched controls. In addition, all patients showed a periodic oscillation of 6 second duration (10/min) in their heart rate , while "RSA" component persisted in only 5 patients.

Periodicity in the heart rate pattern was also noted in 34 patients with marked degree of neurological impairment, out of 102 patients admitted to an intensive care unit with acute neurological disorders (Leipzig & Lowensohn 1986).

The correlation between the degree of heart rate abnormality and the EEG background was established by Miyazaki et al (1979). They showed that "HRV" reflected very well the abnormality of the CNS and suggested to use "HRV" as a parameter in evaluating patients with neurological disorders. The repeated finding of flat heart rate records in patients with: cerebral death (Evans 1976), flat EEG (Miyazaki et al 1979) or with complete cerebral infarction (Persson & Solders 1983), all confirm the earlier finding of Vallbona et al (1965) that patients with severe CNS damage lose their "HRV" almost completely.

Clinically, it was also important to see if "HRV" can be of any help in broadcasting the outcome of the patients. In 15 newborn babies with severe asphyxial damage, those who showed a marked loss of "HRV", 11 died and the two survived had severe neurological sequale. Moreover, in the 4 who survived, the onset of clinical improvement was concomitant with the reappearance of "HRV" (Nishida et al 1981).

In serial evaluation of patients with acute neurological disorders, "HRV" was found to be a simple parameter to monitor, and when compared with multimodality evoked potential testing, it took shorter time to perform and required less technical skill. However, it was somewhat less prognostic for outcome than clinical examination using Glasgow Coma Scale, though it was good, and moreover there was no inter-observers variatiion (Leipzig & Lowensohn 1986).

4. THE SLOW RHYTHMS IN HEART RATE

As early as 1956, cycles of 6-12 second duration were described in the heart rate of normal individuals (Lacey and Lacey). However, the presence of these slower rhythms became better known after the symposium on "HRV" was published in Ergonomics in 1973. There are possibly two reasons for this delay: (a) those earlier publications were not easily accessible. (b) the new analytical method used (i.e spectral analysis) made the existence of such rhythms more convincing.

The heart rate spectrum (Sayers 1973) showed three prominent peaks at different frequencies. The peak at high frequency is the "RSA" and its position in the spectrum varies with the breathing frequency. The low frequency peak is at about 0.04 Hz. and was thought to be due to a spontaneous activity in the thermoregulatory mechanism (Thrmoregulatory rhythm). The peak at mid-frequency ($\sim$ 0.1 Hz.) was thought to arise from the blood pressure control mechanism ("10 second" rhythm).

4.1 Thermoregulatory rhythm

The presence of slow oscillations in the blood flow has been known for a long time. Burton (1939) reported the presence of these slow oscillations in the blood flow of the fingers. The duration of these oscillations varied greatly from 15 to 120 seconds but, on average, they were about 40 seconds. The amplitude of the oscillations varied also in different subjects, but there was less intra-individual variation. Burton (1939) showed as well, that the

occurrence of these normal fluctuations in the blood flow depended upon an intact peripheral sympathetic system. However, the simultaneous occurrence of these oscillations in the digits of all extremities, and the concurrent increase in heart rate and blood pressure, led him to conclude that these all were driven by a physiological centre. He also speculated that these rhythms might be caused, or at least modified by, a temperature regulating system.

Hyndman et al (1971) restudied the finger blood flow signal and found similar slow fluctuations. They showed that these oscillations were due to adjustments in the cutaneous circulation by the thermoregulatory system, as they managed to entrain them by applying thermal stimuli with different frequencies [Entrainment is the effect that, under certain circumstances, the oscillation frequency changes to the frequency of an applied stimulus (Kitney 1977)].

The effect of these slow oscillations in the blood flow on the heart rate has been thoroughly studied by Kitney (1974,1977) who managed to incorporate this thermal effect in a computer simulation of the human cardiovascular system. The power spectrum of the heart rate showed a peak at $\sim$ 0.04 Hz. (Kitney 1977), which reflected the slow oscillations of thermoregulatory origin as these and the finger blood flow oscillations were selectively entrained by applied thermal stimuli (Kitney 1974).

The entrainment phenomenon (in both finger blood flow and heart rate signals) was explained by the presence of a non-linear system which is spontaneously oscillating as a result of an inherent time delay (Hyndman et al 1971, Kitney 1977). The duration of these

slow oscillations varied greatly as mentioned before (15 - 120 sec.). This variation in the frequency was thought to arise from variation in the time delay associated with the response of the peripheral smooth muscle (Kitney 1977).

Another possibility is that this rhythm originates from a thermoregulatory centre which oscillates spontaneously. Such a centre is thought to be functional in small preterm infants, and its control power to increase with increasing maturity (Lindqvist et al 1983).

4.2 "10 second" rhythm

The presence of waves in the BP related to respiration, was known as early as 1847 when Ludwig introduced the recording manometer to physiology (Penaz 1978). Later Traube in 1865 and Hering in 1869 described slow waves in the blood pressure of curarized animals. However these were also related to respiration, and thought to be due to irradiation of impulses from the respiratory to the vasomotor center (Schweitzer 1945). In 1876, Mayer described a different phenomenon. He showed that towards the end of experiments on animals, the failing cardio-circulatory system begins to show regular slow oscillations in BP with a frequency of 1 - 5 cycles/min. These slow oscillations were independent of respiration.

Terminological confusion about all these types of oscillations in BP prompted Schweitzer in 1945 to suggest classification according to the mechanism underlying them.

In addition to the problem of nomenclature, controversy over the

origin of these waves exists. Guyton & Harris (1951) suggested that Mayer waves were oscillations of the pressoreceptor negative feed back mechanism controlling the blood pressure, as they were abolished by deep anaesthesia, total spinal anaesthesia or complete denervation of the pressoreceptors. They added that the duration of the oscillations (average 25.2 sec.) is governed by the time delay of the carotid sinus reflex which is 13 sec.

This concept, of the oscillations being due to waxing and waning in the activity level of the autonomic system, seems to be holding even in recent literature (Koizumi et al 1985),although this has been disputed by Taylor & Gebber (1975) who thought that the oscillations were centrally originated but entrained to the cardiac cycle by the baroreceptor reflexes.

Anderson et al (1950) supported the peripheral origin of these waves, however, they thought that the chemoreceptors played the important part in the genesis, rather than the baroreceptors. Later Ferreti et al (1965) succeeded in inducing Mayer waves by metabolic acidosis in dogs with normal blood pressure and without the need for bleeding. Contrary to their expectation, the waves persisted after denervation of both carotid and aortic chemoreceptors and baroreceptors.

The latter finding was taken by Preiss and Polosa (1974) in favour of their central oscillator theory for the genesis of Mayer waves, and they called it "Mayer waves oscillator", but they did not exclude a modulating effect from the peripheral input. They suggested that the oscillator is probably located in the spinal cord, a suggestion which was made earlier by Kaminski et al (1970).

In man, the presence of slow oscillations in the blood pressure was reported by Dornhorst et al (1952). These were not related to respiration in 1 : 1 ratio and they even persisted during apnoea. They had a duration, much faster than the typical Mayer waves of the order of 10 seconds.

Whether these "10 second" oscillations in normal humans under stable conditions are the same as the slower Mayer waves that occur in animals under deteriorating conditions is unclear. There has been a trend by some investigators to call these "10 second" oscillations in humans as the Traube-Hering-Mayer waves (Penaz 1978, Ahmed et al 1983). However, grouping all these different oscillations under one name is rather confusing.

Recently, the presence of the "10 second" rhythm in human's BP was reconfirmed and in addition, a similar rhythm was shown to occur in the heart rate (Hyndman et al 1971, Sayers 1971 & 1973, Coenen et al 1977).

A few studies on "HRV" have described the effects of sleep and mental load on the "10 second" rhythm (reviewed in section - 2 of this chapter). However, little is known about the incidence, origin and control of these oscillations or the other physiological factors that affect them.

There has been a suggestion that these "10 second" oscillations in the heart rate were possibly an intrinsic feature of the BP regulatory system due to the time-delay in the sino-aortic reflex (Sayers 1973). However, this suggestion was made from results of cardiovascular models. These models, to say the least, did not

incorporate all the different factors involved in cardiovascular system regulation.

Therefore, this study was conducted to elucidate the factors influencing the genesis of this rhythm in humans and the control mechanisms involved.

Chapter II

MATERIALS & METHODS

1. SUBJECTS

For the initial survey, the total number of volunteers was 79 (45 male, 34 female). Each subject was asked to fill in a data sheet giving details of his/her date of birth, sex, height, weight, profession, current health status, medical and family history, smoking habits and his/her routine physical activity . A thorough physical examination, including BP measurement, was given for all the subjects. ECG and FEV_1 were done for some subjects prior to certain experiments, the details of which are given in chapter VII and VIII.

Ethical permission had been obtained from the University Ethical Committee for all the experiments. The subjects were mainly medical or postgraduate students and departmental technicians. Seventy one of them were young (18 - 30 yr) (43 male, 28 female) and eight were older (40 - 65 yr) (2 male, 6 female). All were normotensive and in good health on the day of the experiment. None was receiving medication that affected the autonomic nervous system and only 7 (8.6%) were cigarette smokers (mild). The experiments were carried out at least one hour after the last meal. For further experiments, subjects were chosen from among the original population and some of them participated in nearly all the experiments. Details of the number of subjects for each experiment will be given in the relevant sections.

2. RECORDINGS

ECG was recorded with a bipolar precordial lead. The upper electrode was at the manubrium sterni and the lower one was in the vicinity of the apical region. These positions were chosen to provide a good ECG signal and to minimize EMG artefacts. The amplified signal was used to trigger a Devices cardiotachometer. Respiration was recorded via a mouthpiece, using a pneumotachograph and Mercury CS5 electrospirometer. ECG, beat by beat heart rate, inspiratory flow and volume were all recorded on a Mingograph 803 (Siemens-Elema ,Sweden) .The ECG was also monitored continuously on an oscilloscope. Simultaneously, ECG and inspiratory volume were recorded on a 4 channel tape recorder(Tandberg series 100) for further analysis (Fig.2 - 1). Magnetometer coils (Cambridge Respiratory Monitor) were used sometimes to record respiration in addition to the pneumotachograh. Room temperature was kept between (20 to 22°C.). Calibration of the heart rate by Wavetek frequency generator and inspiratory volume by a spirometer were made prior to and at the end of each experiment.

3. EXPERIMENTAL PROTOCOLS

These will be discussed separately for the different experiments in chapters III to VIII.

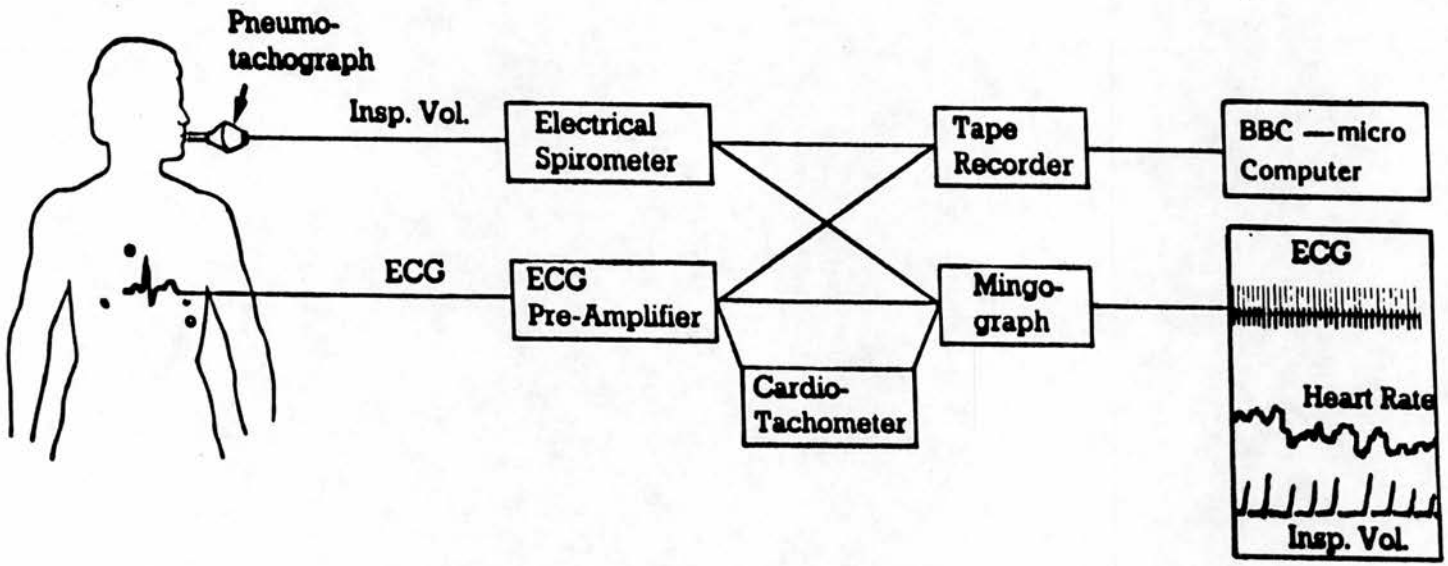


Fig.(2-1). Schematic diagram of the recording system.

4. ANALYSIS

4.1 *Measurement of RR intervals*

The ECG, taken from a precordial lead that gave maximum QRS deflection, was amplified and stored on FM tapes. Then, off line, the tapes were replayed in real time, through a Unilab computer interface. In conjunction with a BBC microcomputer's software, the RR intervals were digitized and stored on disks.

Samples of 300 intervals were digitized from the tapes, then outliers and mistriggers were excluded and samples of 256 intervals were stored in each file for further processing. It has been shown that the fall off in spectral definition was only slight when 256 intervals were used instead of 512 or 1024 intervals (Selman et al 1982), and even segments with 128 or 64 intervals would give essentially the same power spectra (Haddad et al 1984). In addition, the time needed to collect a large sample, especially when the heart rate is slow, would be considerably longer. Therefore, usually samples of 256 intervals were used because it was felt that the improvement gained did not warrant the longer experimental time.

Data from each file was displayed and visually examined following the analogue-to-digital conversion and prior to application of other programmes. A print out of the RR intervals before and after exclusion of mistriggers could be obtained, if needed. A print out of RR intervals tachograms were plotted for all the files ($\sim$ 300 in total) for rechecking.

The problem of mistriggers is inherent in the heart rate data, regardless of good recording instruments and data acquisition technique. This is due to the fact that heart rate is subjected to missed intervals or false triggering consequent to baseline shift due to movement, coughing, or even swallowing , etc. Difficulties in obtaining artefact-free ECG has prevented certain studies from being undertaken. One notable example was the failure of Haddad et al (1984) to compare heart rate variability between puppies and adult dogs during wakefulness because of the considerable movement the puppies made while awake. Therefore, vigorous checking and rechecking procedures were necessary to be confident about the quality of the data before submitting it for further analysis.

Whenever possible, longer records of ECG than actually needed for the analysis were taken so the part with the least mistriggers could be chosen. But, in a few circumstances, when the records were not long enough and especially when the heart rate was slow, the total number of RR intervals, after exclusion of mistriggers, did not add up to 256 (2^8) intervals, so arrays of 128 (2^7) were used instead. The same arrays were used to compute statistical indices as well as Fourier Transforms which needed this specific number of intervals.

4.2 *Measurement of Mean Heart Rate*

The mean heart rate (MHR) was chosen instead of mean RR interval because clinically MHR is more meaningful. For the initial survey

of the effect of posture on heart rate pattern (chapter III), the MHR was calculated manually for at least 2 minutes. For the other chapters (IV to VIII), MHR was computed from the RR intervals measured as explained above. The total time varied from file to file, and it depended on the rate, but in general, it was between 2 and 5 minutes.

To see how valid the two minutes calculation was, compared with longer periods, comparison was made in 22 subjects between the supine MHR measured over 2 minutes in two consecutive periods with the average for the whole 4 minutes (Table 2 - 1). The mean for all the subjects was not significantly different between each of the 2 minutes period and the average, or between the first and the second 2 minutes period (Fig. 2 - 2). Also, in 20 subjects, the standing MHR measured over 2 minutes in 5 consecutive periods was compared with the average for the whole 10 minutes (Table 2-2). The means for all the subjects in the 5 periods and the average were not significantly different (Fig 2 - 3).

4.3 *Measurement of Heart Rate Variability*

4.3.1 Introduction:

Heart rate variability has been generally defined as "the variation in heart rate". This is such a loose definition that has been applied on different types of variations in heart rate due to different mechanisms and pathways.

Heart rate variability has been used widely to imply the variation in heart rate with respiration, either normal quiet respiration or

	1st	2nd	Average
	MHR/2 min	MHR/2 min	MHR/4 min
1	60.0	59.0	59.5
2	74.5	70.5	72.5
3	65.0	63.5	64.0
4	57.5	60.0	59.0
5	59.0	62.5	61.0
6	60.0	61.0	60.5
7	76.5	77.5	77.0
8	81.0	80.0	80.5
9	58.5	59.5	59.0
10	76.0	78.0	77.0
11	66.0	66.0	66.0
12	63.0	60.5	62.0
13	75.0	74.5	75.0
14	69.5	73.0	71.0
15	65.5	66.0	66.0
16	70.0	79.0	74.5
17	77.5	74.5	76.0
18	70.0	69.5	70.0
19	70.5	70.0	70.0
20	94.5	91.0	93.0
21	84.0	88.0	86.0
22	82.0	80.0	81.0
Mean	70.7	71.1	70.9
± SEM	2.0	2.0	2.0

Table (2-1). The supine heart rate measured over 2 minutes in the 1st. and 2nd periods compared with the average MHR over the whole 4 minutes.

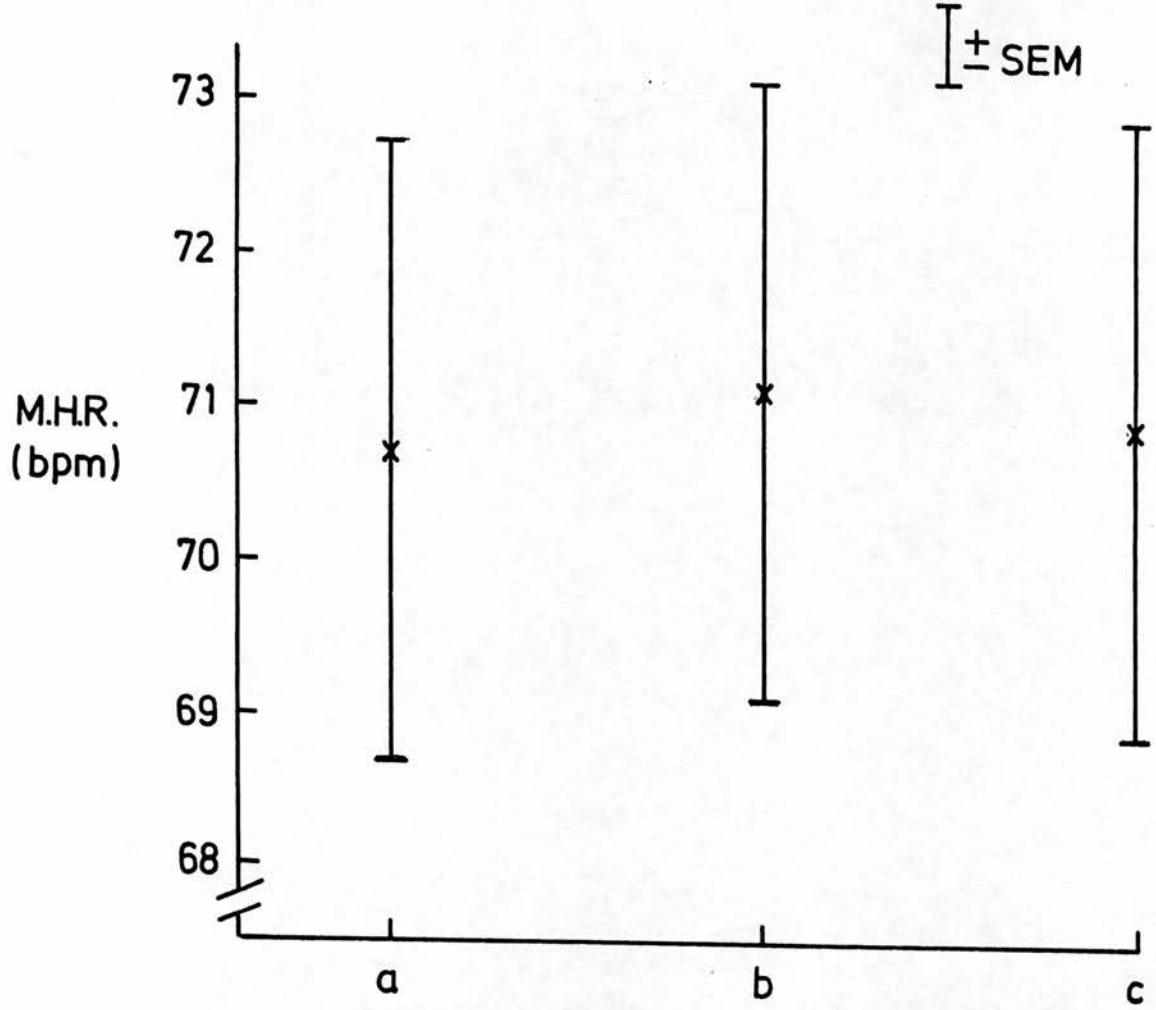


Fig.(2-2). The mean supine heart rate for 22 subjects measured over 2 minutes in (a) and (b), compared with the mean average for the whole 4 minutes in (c).

	1st	2nd	3rd	4th	5th	Average
	MHR/2 min	MHR/2min	MHR/2 min	MHR/2 min	MHR/2 min	MHR/10 min
1	114.5	111.5	107.5	110.0	108.0	110.0
2	90.0	90.0	89.5	92.0	88.5	90.0
3	119.5	115.5	115.0	112.0	107.5	114.0
4	88.0	93.5	92.5	88.0	89.5	90.0
5	88.5	95.0	95.0	93.5	98.5	94.0
6	104.0	100.5	98.5	97.5	102.0	100.5
7	99.0	98.5	103.0	101.0	102.0	101.0
8	115.0	108.5	113.0	107.5	112.5	111.0
9	68.5	68.0	69.0	72.5	74.5	70.5
10	98.0	102.0	106.0	103.0	106.5	103.0
11	101.5	105.5	103.5	105.0	103.5	104.0
12	84.0	84.5	84.0	84.5	83.5	84.0
13	135.5	138.0	134.0	130.0	132.0	134.0
14	114.5	118.5	108.5	118.5	125.0	117.0
15	116.5	102.5	111.5	109.5	103.5	109.0
16	110.0	113.0	118.0	116.0	107.5	113.0
17	96.5	93.5	104.5	106.0	106.5	101.0
18	98.0	100.5	98.0	101.5	97.5	99.0
19	71.0	73.5	78.0	79.0	80.0	76.0
20	99.0	101.5	101.0	101.5	99.5	100.5
Mean	100.6	100.7	101.5	101.4	101.4	101.1
±SEM	3.7	3.5	3.2	3.1	3.1	3.2

Table (2-2). The standing heart rate measured over 2 minutes in the 1st., 2nd., 3rd., 4th. and 5th. periods compared with the average MHR over the whole 10 minutes.

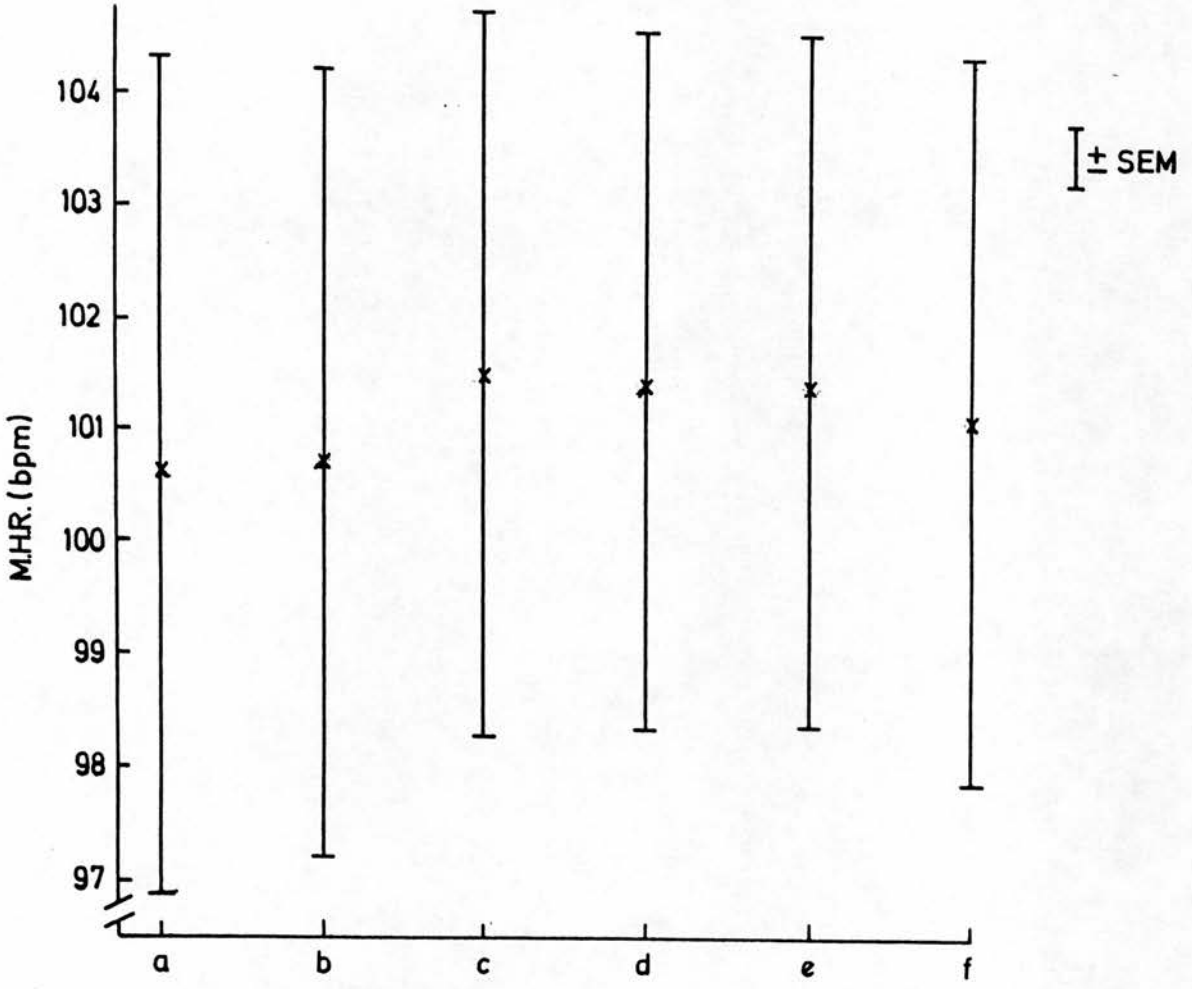


Fig.(2-3). The mean standing heart rate for 20 subjects measured over 2 minutes in (a), (b), (c), (d) and (e), compared with the mean average for the whole 10 minutes in (f).

forced respiration. Several indices have been used to measure this "HRV" such as the E/I ratio for a single breath (Smith 1982, Smith & Smith 1983), the avarage E/I ratio for 6 breaths (SundKvist et al 1979), the avarage E/I ratio for the whole sample (Ewing et al 1981 a , Zoccali et al 1982 , O'Brien et al 1986), the E - I difference for 6 breaths (Wieling et al 1982), the maximum - minimum difference (Wheeler & Watkins 1973, Ewing & Winney 1975, Page & Watkins 1977, Bennett et al 1978, MacKay et al 1980, Dyrberg et al 1981, Ewing et al 1981 a , Fouad et al 1984, Forsstrom et al 1986, O'Brien et al 1986), the peak to trough difference (MacKay 1983), the amplitude of change from baseline heart rate (Masaoka et al 1985), and others. All had been used as measures of "HRV" to distinguish those patients with abnormal "HRV" due to diseases such as diabetes mellitus from normal subjects, and there were claims and counterclaims as to which one of these was the best to use. But the fact is, all of the above mentioned indices describe only one type of variability in heart rate i.e. the respiratory linked changes "RSA" which is mediated mainly by one branch of the autonomic nervous system namely the parasympathetic pathway (Wheeler & Watkins 1973).

Other changes do occur in heart rate. The beat-to-beat variation is well known and specific indices have been used to measure it. The mean square successive difference (MSSD) has been found, on one hand, to be the best measure for the early detection of autonomic nervous system abnormalities (Gundersen & Neubaur 1977), but Ewing et al (1981) found it not very helpful in separating diabetic patients with abnormal autonomic function tests from those with normal tests.

Other indices such as Mean Absolute Difference (MAD) (Dalton et al 1977,Dalton et al 1983, Van Dellen et al 1985), Root Mean Square Successive Difference (RMSSD) (Kero 1974, Antila 1979, Siimes et al 1984, Van Dellen et al 1985, Forsstrom et al 1986 Lindqvist et al 1986), Successive Difference Mean Square (SDMS) (Heslegrave et al 1979), Mean Successive Difference (MSD) (Ewing et al 1981 a , Weise et al 1985 & 1986, Bernardi et al 1986), and others, have all been used to measure beat-to-beat variability.

To describe the overall variation in heart rate, the standard deviation (SD), or its variant, the root mean square of differences from the mean (RMSM) have been the most widely used indices (Kero 1974, Murray et al 1975, Cashman 1977, Ewing 1978, Waddington et al 1979, Antila 1979, Smith & Smith 1981, Pfeifer et al 1982, Siimes et al 1984, Van Dellen et al 1985, O'Brien et al 1986, Mancia et al 1986, Lindqvist et al 1986, Forsstrom et al 1986,McEwen & Sima 1987, Kleiger et al 1987) and others. But, reproducibility of SD in normal subjects has been shown to be poor (Ewing 1978), and its use alone to assess cardiac autonomic function was thought to be unreliable (McEwen & Sima 1987) and may even be misleading (Bennett et al 1977). In addition, as the SD correlates with the mean heart rate, it can only be applied when the mean heart rate is relatively constant (Ewing et al 1981 a). Also different sets of data with different mean absolute differences (MAD) can have identical standard deviations (SD) and vice versa (DeBoer 1985), which shows clearly that a single measure is not sufficient to fully describe the variability in the data. Jenkins et al (1983) reached the same conclusion when they tried

to predict the course of babies with the respiratory distress syndrome. They showed that it was necessary to compute a total of 13 parameters of "HRV" and to use different combinations (ranged between 2 and 5) to describe various clinical conditions and to gain different clinical information . Thus, no single parameter taken alone had proved to be as valuable as a combination of parameters. Jarish and Detwiler (1980) also found that using SD and variance had failed to help them predict the fetal pH or Apgar scores.

The other major drawback to the use of these indices is that the individual contribution of the different frequencies to the overall variability remains unknown, and if sources of "HRV" are differentially affected, with the total variability remaining the same, the score for total "HRV" would not show the effect, and consequently wrong conclusions might be drawn.

Spectral analysis of cardiac frequency allows a decomposition of the data into the amount of the variability contributed by different frequencies, thus it can show differential changes in addition to the change in total variation.

In 1968 Penaz published the first "HRV" spectra (Penaz 1978), but application of Fast Fourier Transform (FFT) for the analysis of "HRV" became well known after the publication of the symposium on "HRV" in Ergonomics (1973). When the spectral analysis technique was utilised to measure "HRV" (Sayers 1973 , Mulder & Meullen 1973 , Luczak and Laurig 1973),it became clear that two other variabilities in heart rate other than the respiratory sinus

arrhythmia could be detected: One at $\sim$ 0.1 Hz. and the other one even slower at $\sim$ 0.04 Hz. The slow frequency of the other rhythms contributed to the difficulty in recognizing them by direct examination of heart rate records.

The changes in "HRV" are of a very complex nature, sometimes involving the re-organization of its spectral profile with a shift of the spectrum to a lower or higher frequency (Sayers 1973, Hyndman 1978, Van Den Akker et al 1983), or a change in the phase spectrum only without a significant change in the amplitude spectrum (Sayers 1973). Therefore, spectral analysis is a more appropriate method for analysing "HRV", especially when the slower rhythms are being investigated.

There are two phases in the spectral analysis technique:

Phase I: Signal acquisition

The variability signal can be derived from the ECG in different ways. The simplest one was described by Sayers (1973). In this method, the signal is the RR intervals plotted as a function of the interval number (interval tachogram). The plot can be considered as a regularly sampled waveform, and Fourier analysis can then be applied to derive the heart rate spectrum. Because the original signal, the interval tachogram, was a function of the interval number and not time, the abscissa will be expressed in "cycles/beat", however, this frequency is easily converted to "Hz." equivalent by dividing it by the mean RR intervals in seconds. This method has been used by Sayers (1973 & 1980), Chess et al

(1975), Lisenby et al (1976), Charnock & Manenica (1978), Musha et al (1983), Jennings & Mack (1984), Pagani et al (1984), DeBoer (1985), and Pagani et al (1986).

Another way of deriving the variability signal is by low-pass filtered event series (LPFES) described by Hyndman & Gregory (1975). This can be done in two ways, analogue and digital. The digital convolution is preferable, where interval tachogram is passed through sinx/x. Then the centre of the filter is incremented in steps of the sampling interval; T = 1/fc where fc is the cut off frequency of the filter. This regularly sampled filtered signal is then Fourier analysed.

Although the LPFES may be a better way of deriving the signal, it has several important drawbacks. It is not easily computed from the event-series signal, and the shape of the resulting spectra depends on the filter used for creation of the signal (Rompelman 1985). This will lead to problems when results, like the ratio between the different peaks in the spectrum, are compared from different studies when different filters were used. Another disadvantage was pointed out by Kitney et al (1982) as they found that it has generated a large amount of noise at the cut off frequency, especially at higher frequencies.

The resulting spectra from both methods mentioned above i.e. the interval tachogram and the LPFES, are similar if the variation of the intervals is small compared with the mean interval length (Rompelman et al 1977, Luczak & Laurig 1973,Kitney et al 1982, Van Dellen et al 1985, Baselli et al 1986).

Also both are equally useful when one is interested only in the presence and relative amplitude of periodicities in the event series (DeBoer 1985). The use of interval tachograms has the advantage of a shorter computation time .

Phase II: Fourier analysis

This can be done either by Fast Fourier Transform (FFT) or Autoregressive spectral analysis (AR). The latter gives high resolution spectral estimation from short time series (Kitney et al 1984), but the results of spectral estimates by the two methods have been found to be in good agreement with each other (Van Den Akker et al 1983). In addition, Van Dellen et al (1985) considered (AR) spectra less appropriate for "HRV" analysis because it needed at least 10 parameters to get an adequate description of a cardiac interval signal with only two or three spectral peaks.

4.3.2 Analysis of HRV:

In this thesis, two statistical indices supplemented by the results of spectral analysis were used to describe heart rate variability.

(A) Statistical indices:

In the search to find an appropriate index that can describe the changes in "HRV" , initially 18 different statistics were calculated for all the files. Table (2 - 3) lists these indices and shows the computational equations used to derive them.

1. Mean RR intervals ($\overline{RR}$) $= \dfrac{\sum_{i=1}^{n} RR_i}{n}$

2. SD of RR intervals (SDRR) $= \sqrt{\dfrac{\sum_{i=1}^{n} (RR_i - \overline{RR})^2}{n-1}}$

3. Variance of RR intervals $= \dfrac{\sum_{i=1}^{n} (RR_i - \overline{RR})^2}{n-1}$

4. Coefficient of variation of RR intervals (CV) $= \dfrac{SDRR}{\overline{RR}}$

5. SEM of RR intervals $= \dfrac{SDRR}{\sqrt{n}}$

6. Interval Index (CV%) $= \dfrac{SDRR}{\overline{RR}} \times 100$

7. Mean Heart Rate (MHR) $= \dfrac{60 \times 1000}{\overline{RR}}$

8. SD of heart rate (SDHR) as in (2) above but (60 X 1000 / RR_i) instead of (RR_i) and MHR instead of $\overline{RR}$.

9. CV of heart rate $= \dfrac{SDHR}{MHR}$

10. SEM of heart rate $= \dfrac{SDHR}{\sqrt{n}}$

11. Mean Absolute Differences (MAD) $= \dfrac{\sum_{i=1}^{n-1} \left| RR_{(i+1)} - RR_i \right|}{n-1}$

To be continued.....

12. SD of Absolute Differences (SDAD) = as in (2) above but $|RR_{(i+1)} - RR_i|$ instead of (RR_i) and MAD instead of $\overline{RR}$.

13. CV of absolute differences = $\frac{SDAD}{MAD}$

14. SEM of absolute differences = $\frac{SDAD}{\sqrt{n-1}}$

15. Root Mean Square Successive Differences (RMSSD) = $\sqrt{\frac{\sum_{i=1}^{n-1} (RR_{(i+1)} - RR_i)^2}{n-1}}$

16. Total Difference (TD) = $\sum_{i=1}^{n-1} RR_{(i+1)} - RR_i$

17. Mean Successive Differences (MSD) = $\frac{TD}{n-1}$

18. Root Mean Square of differences from the Mean (RMSM) = $\sqrt{\frac{\sum_{i=1}^{n} (RR_i - \overline{RR})^2}{n}}$

Table (2 - 3). A list of all the statistical indices with the mathematical formulae used for computation.

$RR(_i)$ is the i^{th} RR interval in the array and (n) is the number of RR intervals in that array.

It is important to emphasise that in calculating these 18 different indices, it was not intended to evaluate each one, or to make comparison between them. The main purpose was to see if it was possible to describe the "HRV" results by using one of these indices.

As it is clear from the table, most of these indices are derivation of some basic statistics, therefore, a selection of two indices only was made.

(i) Mean Absolute Difference (MAD)

This describes the beat-to-beat variation, sometimes called short term variability (STV). It is derived from the following equation:

$$MAD = \frac{\sum_{i=1}^{n-1} \left| RR_{(i+1)} - RR_{(i)} \right|}{n-1}$$

Where $RR_{(i)}$ is the i^{th} RR interval in the array and (n) is the number of RR intervals in that array.

The Root Mean Square Successive Difference (RMSSD) also gives the same measure, but since the correlation between the two was high (r=0.999), only MAD results will be compared.

Others, such as the Total Difference (TD) and the Mean Successive Difference (MSD) are not very good indices to use. Suppose a file has an equal total positive and total negative beat-to-beat variation, then they will cancel each other and give a "NIL" result for the total difference (TD) and for the mean successive difference (MSD). This result would give no indication whatsoever, as to how much the real variation was in that file. In addition, TD and MSD would give no more information than what the MAD does.

(ii) Interval Index (CV%)

This has been used as an index of long term variability (LTV) by several workers (Yeh et al 1973, Kariniemi & Hukkinen 1977, Laros et al 1977, Stallworth et al 1981, Kariniemi & Ammala 1981 & Kariniemi et al 1982). It is calculated as the percentage of the coefficient of variation of RR intervals or :

CV% = (SD of RR intervals / Mean RR intervals) X 100.

From this equation it is clear that, as the numerator (the SD) measures the overall variation in the RR interval array, so the CV% includes the beat-to-beat variability (STV) as well as the LTV.

A criticism of the use of CV% alone as a valid index to describe LTV will be given in a later chapter.

(B) Spectral analysis :

Since the above mentioned indices, namely MAD and CV% could not describe fully all the changes in "HRV", the spectral estimates of heart rates were calculated also.

The interval tachogram was used as the signal, and Fast Fourier Transform (FFT) subroutine from EMAS (Edinburgh MultiAccess System) was then applied. The resulting "raw" spectrum was submitted to sequential spectral smoothing windows (Penaz 1978) and the smoothed amplitude spectrum was then plotted (Fig.2 - 4).

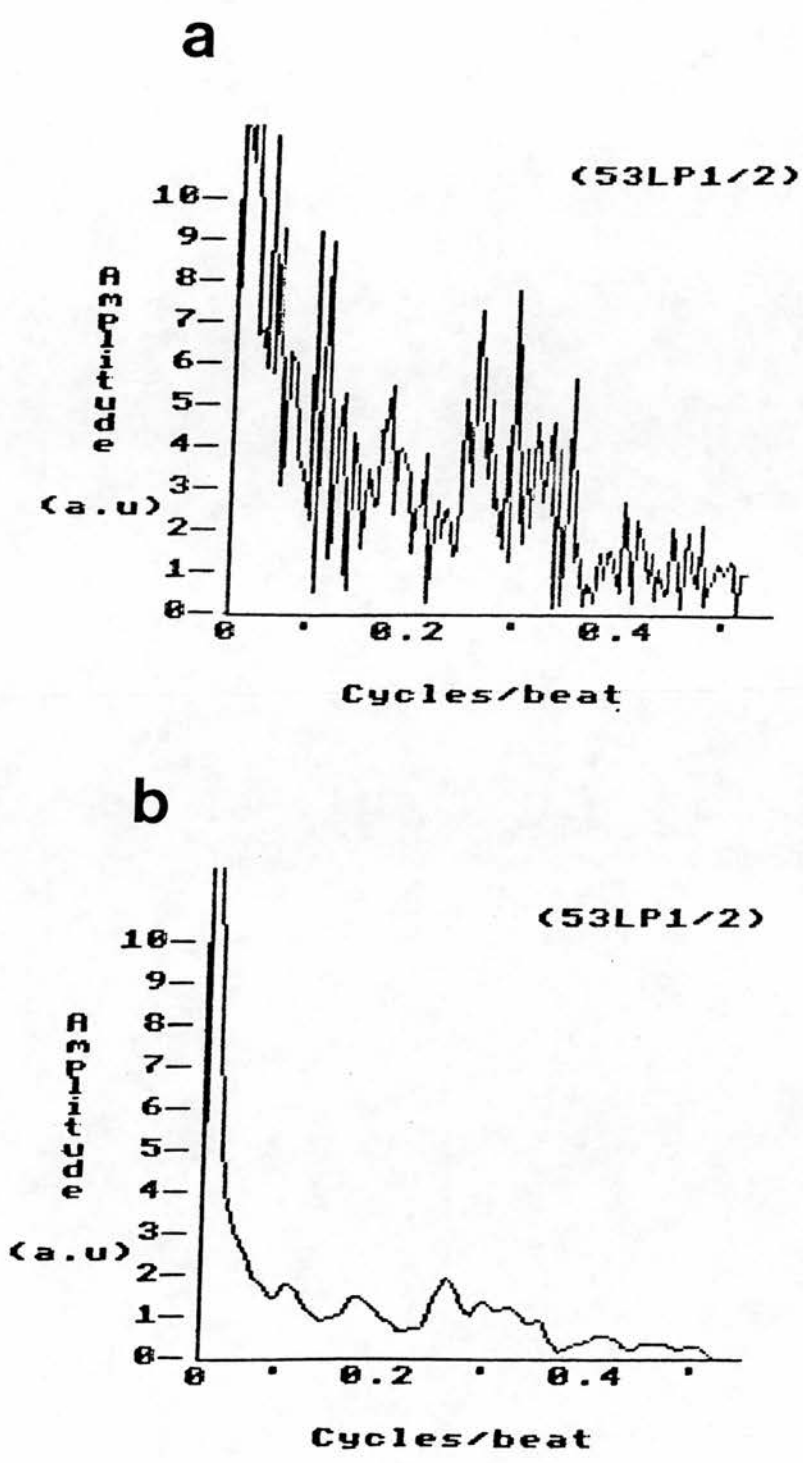


Fig.(2-4). The heart rate spectrum before (a) and after (b) smoothing.

(a.u.= arbitrary unit)

4.4 Measurement of Respiratory Rate

For the correct interpretation of the results from the spectral analysis of heart rate, it was necessary to note the respiratory frequency.

The importance of knowing the respiratory frequency, before deriving any conclusion from the heart rate spectra, is demonstrated in Fig (2 -5).
The heart rate spectrum of this subject shows a single large peak at $\sim$ 0.1 cycles/beat, and the conclusion would be that this subject has no considerable "RSA" because of the absence of any peak at the higher frequencies, the usual respiration frequencies. But this conclusion is wrong, when we know that the subject was breathing at the rate of 8/min, and it is most likely that the large peak in her heart rate spectrum was probably a combination of "RSA" and the "10 second" rhythm. The "RSA" was at the slow frequency range because of the slow breathing rate of the subject.

Therefore, the respiratory rate was calculated manually for all the files. Comparison was made in 12 subjects between the respiratory rate measured over one minute in 5 consecutive periods and the average respiratory rate for the whole 5 minutes Table (2 - 4). The results showed that the mean respiratory rate for all the subjects in the 5 periods and the average were not statistically significant (Fig.2 - 6).

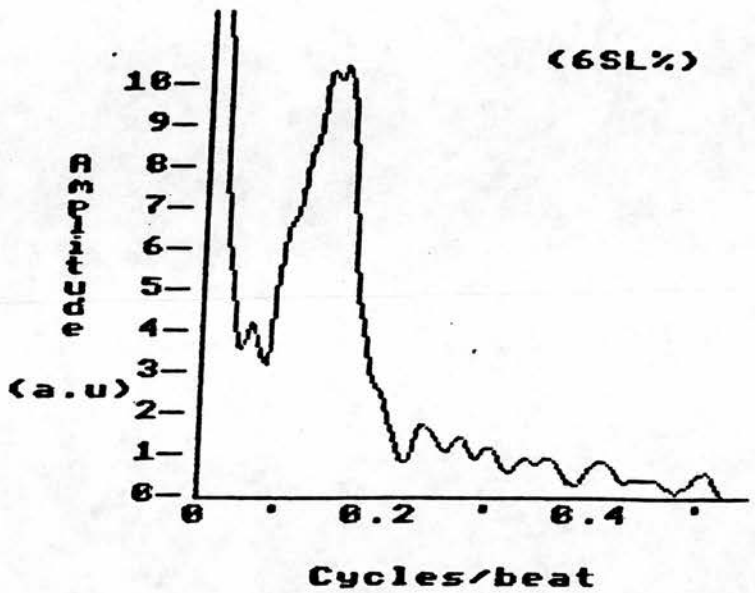


Fig.(2-5). The heart rate spectra of one subject breathing slowly and showing a single large peak at the low frequency.

	1st	2nd	3rd	4th	5th	Average
	RR/1 min	RR/1 min	RR/1 min	RR/1 min	RR/1 min	RR/5 min
1	22	22	22	20	18	21
2	16	16	15	14	17	16
3	19	18	18	16	20	18
4	19	16	18	16	18	17
5	24	23	22	23	20	22
6	19	17	18	21	21	19
7	14	10	10	13	14	12
8	14	15	14	16	15	15
9	13	18	17	14	15	15
10	19	19	19	18	20	19
11	25	24	27	25	21	24
12	17	17	17	18	17	17
Mean	18.4	17.9	18.1	17.8	18.0	17.9
±SEM	1.1	1.1	1.2	1.1	0.7	0.9

Table(2-4). The respiratory rate (RR) measured in the 1st., 2nd., 3rd., 4th. and 5th. minute compared with the average for the whole 5 minutes.

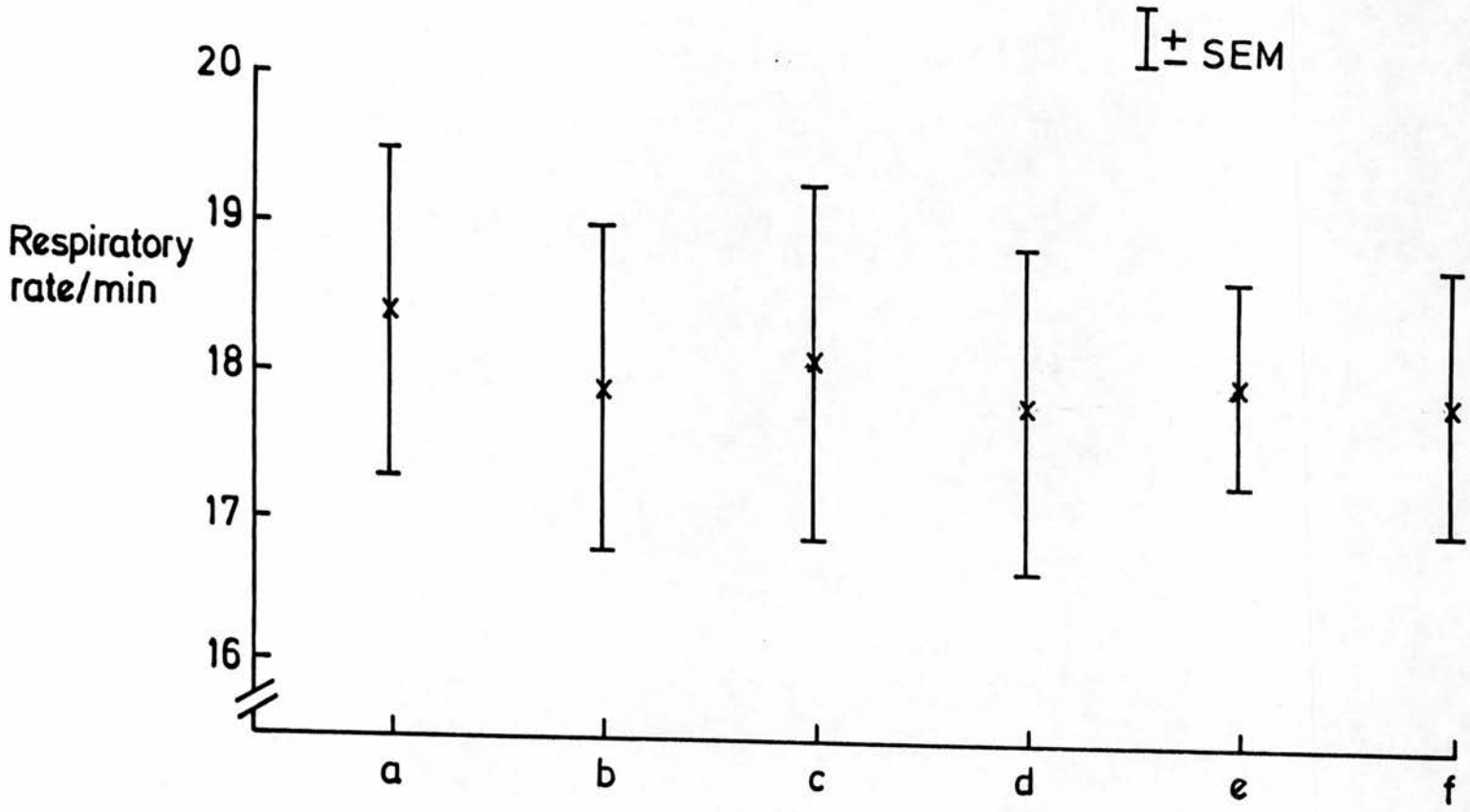


Fig.(2-6). The mean respiratory rate for 12 subjects measured over one minute in (a), (b), (c), (d) and (e) compared with the mean average for the whole 5 minutes in (f).

5. STATISTICAL ANALYSIS

To test the significance of difference in MHR, the paired and unpaired-t-test were used. For the MAD and CV%, the non-parametric Wilcoxon signed rank test for the paired and Mann-Whitney U test for the unpaired data were used. Because of the low power of sensitivity of these two tests compared with the Student- t-test, a p value of < 0.1 was considered significant.

For the results of MHR, MAD and CV% from the immersion experiments (chapter VII), two-way analysis of variance followed by Newman-Keuls test was used.

The "UNISTAT" statistical package for the BBC was used for all the above tests.

Chapter III

EFFECTS OF POSTURE ON "HRV"

INTRODUCTION

The erect posture of man is one of his most conspicuous characters. The evolution of this orthograde posture entailed a structural revolution in many parts and systems of the body and necessitated the development of certain compensatory mechanisms, this is particularly true in the cardiovascular system.

The effects of different postures on cardiovascular dynamics have been investigated since the early days of physiology and this is illustrated in the following review:

Effect of posture on mean heart rate

It is generally thought that the MHR during maintained standing is always higher than supine MHR (Gauer & Thron 1965, Debru et al 1979).However, results from studies on large number of subjects showed that in the majority of people(95-97%), the MHR during maintained standing was higher, but in 2 - 3 % of subjects there was no change in MHR, and in 1-2% there was even a slight decrease [Schneider & Truesdell 1922(2000 cases), Currens 1948 (1000 cases)].

It has been suggested that the standing-lying difference is equal to the sum of the standing-sitting difference and the sitting-lying difference (McWilliam 1933). This was confirmed when the increase in MHR on changing posture from supine to sitting(18%)

was found to be only half the increase in MHR on changing to the standing posture (35%) (Ward et al 1966).

Effect of posture on blood pressure

During maintained standing the diastolic blood pressure is higher than the supine value while the systolic blood pressure is either the same or slightly increased; consequently the pulse pressure in the majority of cases is lower, and the mean arterial BP is either the same or slightly increased. This was true both in adults (Schneider & Truesdell 1922, Hellebrandt & Franseen 1943, Currens 1948, Debru et al 1979, Gauer & Thron 1965) and children (McCrory et al 1982) .

Effect of posture on cardiac output & stroke volume

The advent of cardiac catheterization by Forsmann in 1929 and the later development of the technique by Cournand and Ranges in 1941 had enabled McMichael & Sharpey-Schaefer (1944) to use direct Fick method to estimate cardiac output (CO). In healthy volunteers, the CO was found to decrease in the standing position by about 25%. Similar results were reported by Wang et al 1960 (-21%) and Ward et al 1966 (-27%) .

This decrease in CO during maintained standing was due to the larger decrease in stroke volume (SV) (-41% , -45%)(Wang et al 1960, Ward et al 1966 respectively) and this was partially compensated by the increase in MHR (+35%)(Ward et al 1966).

Effect of posture on total peripheral resistance

Standing causes a marked decrease in stroke volume which leads to a decrease in cardiac output. This decrease in cardiac output is smaller than expected due to compensation by an increase in heart rate and a reflex vasoconstriction.The latter leads to an increase in total peripheral resistance (TPR), which was reported to be in the range of 30 to 40% (Gauer & Thron 1965), and even up to 65% during standing (Ward et al 1966).

The increased TPR during standing is thought to be due to increased outflow of sympathetic vasoconstriction impulses to the vascular bed of skeletal muscles in the upright posture (Gauer & Thron 1965). This was later confirmed by direct recording of sympathetic activity from muscle nerves in man (Burke et al 1977).

Effect of posture on baroreflex activity

This has been a subject of debate. Pickering et al (1971) found that the erect posture caused a decrease in the reflex bradycardia induced by the injection of the pressor drug phenylphrine. In contrast, Eckberg et al (1976) reported that the upright posture augmented the reflex bradycardia when the BP was manipulated by application of positive and negative pressure to the neck.
The discrepancy in the results could be due to the different methods used to test the baroreflex sensitivity. However,two further studies (Tyden 1977, Harrison et al 1986) used the neck collar method and found a decrease in baroreflex gain with standing, similar to the results obtained using the phenylphrine

injection (Pickering et al 1971).

Alternatively,the discrepancy could be due to a timing difference as to when the measurement of baroreflex activity was made after the change in posture .The alteration in the cardiac component of the baroreflex was found to be apparent only minutes following the change in posture (Harrison et al 1986), so measurements made earlier might not reflect the true changes in baroreflex gain.

Hormonal changes during change of posture

In addition to the neurogenic reflexes, standing activates hormonal responses that help to preserve cardiac output in the face of decreasing venous return. The main hormones involved are vasopressin and renin-angiotensin-aldosterone system.

Segar and Moore 1968 were the first to notice that blood **vasopressin** level increased significantly when subjects change posture from supine to standing.

Elevation of plasma vasopressin level was found in other conditions that lead to a shift of blood out of the thorax, e.g. centrifugation using positive G, lower body negative pressure (-30mmHg) or exposure to hot environment (50°C) for two hours (Moore 1971). The vasopressin response to postural change was confirmed by Davies et al 1976 (tilt to 85°) and more recently by Simpson et al 1986 (tilt to 50°), but tilting to 40° did not elicit a measurable increase (Bie et al 1986).

Recently, the increased vasopressin level in the erect posture has been used as a clinical test to investigate diabetic autonomic

neuropathy.An unsuspected proportion of patients were found unable to increase their vasopressin levels appropriately on standing (Cignarelli et al 1986) and therefore the authors suggested the use of this test to assess the integrity of the afferent component of the autonomic nervous system.They pointed out ,however,that this test on its own can not indicate the site of the lesion unless combined with another test such as the norepinephrine response to standing .

A central nervous system role for vasopressin in cardiovascular regulation was suggested when the response, in vasoconstriction - deficient rats with diabetes insipidus, was improved after treatment with vasopressin peripherally and/or centrally (Berecek et al 1983). Recent research suggested area postrema as the site of action of vasopressin (Applegate et al 1987).

An increased level of plasma **renin** activity and **aldosterone** concentration has been consistently found during standing (Gauer & Thron 1965, Sassard et al 1976, Bakris et al 1986) and tilting (Davies et al 1976, Sancho et al 1976). But, administration of converting enzyme inhibitor (CEI) caused a fall in aldosterone level during tilting (Sancho et al 1976 , Dusing et al 1987) .Thus, it seems that **angiotensin II** is required for the hemodynamic adjustment to upright tilt .

A central mechanism for angiotensin II action in short term cardiovascular regulation was suggested by Lumbers et al (1979) and Tonnaer et al (1982). However, the frequency-selective effect of CEI on HRV spectra of conscious dogs, was thought to be in favour of a peripheral action of angiotensin II (Akselrod et al 1981).

The initial response to standing

On standing, there is a shift of blood volume from the thorax to the lower limbs. The blood tends to pool in the legs with a consequent fall in blood pressure.The baroreflexes are quick to respond by peripheral vasoconstriction and tachycardia (Gauer & Thron 1965).

Recently, **the initial response of the heart rate** during the act of standing up, have been described in detail (Ewing et al 1978, Borst et al 1982). The heart rate increases initially, then there is a relative decrease followed by a gradual increase until it reaches a stable level.

The initial increase in heart rate usually has two peaks unless the subject arises slowly (Borst et al 1982). The immediate primary peak is associated with contraction of skeletal muscles and it is absent on passive change of posture (i.e. Tilting up) (Borst et al 1982). This initial increase was also evident on changing posture from standing to supine but not on passive tilting down (Bellavere and Ewing 1982).

The secondary more gradual heart rate increase after 5 seconds of standing and the subsequent rapid decrease between about 12 and 20 seconds, corresponds through the baroreceptor reflex with a striking fall, recovery and sometimes overshoot of arterial pressure (Borst et al 1982). The rebound bradycardia following the initial rise in heart rate is thought to be determined by the

muscular activity involved rather than by the speed of the manoeuvre, as it was absent during tilting whether fast or slow, in contrast to its presence in both fast and slow standing (Ewing et al 1980).

The initial heart rate response to standing was shown to be predominantly under parasympathetic control (Ewing et al 1980). There is vagal withdrawal initially, causing tachycardia, followed by vagal reactivation. Patients with autonomic parasympathetic neuropathy showed patterns of responses similar to the patterns in normal subjects under the effect of Atropine (Ewing et al 1980). Therefore, the immediate response to standing can give an indication about the state of the parasympathetic control of the heart, and thus has been used as a simple, non-invasive test.

Abnormal responses were found in patients with autonomic neuropathy due to: diabetes mellitus (Page & Watkins 1977, Ewing et al 1978, MacKay et al 1980, Wieling et al 1983), chronic renal failure (Zoccali et al 1982), chronic Chagas' cardiac disease (Marin- Neto et al 1980, Amorim et al 1982) and congestive heart failure (Timmis et al 1984).

<u>The changes in blood pressure in response to standing up</u> are in the opposite direction to the changes in heart rate.

The availability of self-recording sphygmomanometer that could measure blood pressure rapidly (3 - 4 times a minute), made it possible to record the changes in BP that takes place immediately after standing up (Wald et al 1937). The systolic BP decreased

markedly at about 10 seconds after standing, then at about 30 seconds, it either recovered to the recumbent level or even sometimes passed that level (overshoot).

More than 45 years later, Borst et al (1982 & 1984) using continuous intra-arterial pressure measurement, gave a remarkably similar description of the changes and the time course of the initial BP response to standing. The only difference was that they reported an immediate jump in systolic BP which was thought to result from compression of the arteries by the contracting postural muscles. This was very brief, and it could not have been detected without the continuous intra-arterial measurement. Moreover, there is the possibility that it was due to a movement artefact, which the sensitive transducer has picked it up.

The initial changes in heart rate and blood pressure during tilting were different from those during active standing , but contraction of abdominal muscles during tilt cancelled those differences (Borst et al 1982). The larger decrease in venous return due to the absence of contraction of abdominal muscles during tilt, was thought to be the cause for the greater drop in systolic BP on tilting compared with standing (Wald et al 1937).

However,it has been suggested (Rossberg and Martinez 1983) that the initial response of heart rate and blood pressure to tilt, depended upon the respiratory cycle. When tilt was performed during expiration, there was significantly higher values of heart rate increase and longer duration of the initial complex, and this

was attributed to the different sensitivity of the arterial baroreflex during the respiratory cycle (Eckberg 1980).

Physical training was found to have no effect on the time course of the initial heart rate response (Borst et al 1982) or the initial BP response to standing (Wald et al 1937).

It is clear from the preceeding review that changes in mean heart rate during change of posture and the initial response of the heart rate to standing have been thoroughly investigated. However, very little attention has been paid to the change in heart rate pattern with the change in posture from supine to maintained standing. Therefore, this was studied in the present investigation.

METHODS

Subjects

The effect of change of posture from supine to maintained standing was studied in 79 subjects. After preliminary visual inspection of the records , four subjects with frequent ectopics were excluded , and the results from 75 subjects (42 male, 33 female) were analysed. Sixty seven of them were young (18 - 30 yr.) with a mean age of 20.7±0.3 (SEM) (40 male, 27 female). The remaining 8 were older (40 - 65 yr.) with a mean age of 47.9 ± 2.9 (2 male, 6 female).

Experimental protocol

Recordings of ECG and respiration were carried out as described in chapter II in the supine and standing postures for at least 5 minutes. In 33 subjects the supine - standing manoeuvre was repeated for a second time in the same session, and in 24 subjects the manoeuvre was also repeated on a different day. The subjects were instructed to keep unnecessary movements to a minimum. The actual recordings were started only when the subjects were well settled.

Analysis

The MHR was calculated manually for at least 2 minutes (chapter II). The first minute of standing and thus the initial response was excluded and only MHR during maintained standing was studied.

The MHR during the first act of supine - standing manoeuvre was compared with the MHR during the second act of supine - standing in 33 subjects in whom the manoeuvre was repeated twice in the same session (Table 3 - 1). The first supine MHR (68.4 $\pm$ 1.7) was significantly ($p<0.001$) higher than the second supine MHR (64.4 $\pm$ 1.6) (Fig. 3 - 1) while the standing MHR was not significantly different in both acts (85.7 $\pm$ 2.2, 84.7 $\pm$ 1.8).Therefore, the difference between the MHR during maintained standing and supine MHR (Δ HR) in the second act (20.2 $\pm$ 1.7) was higher ($p<0.01$) than the first (17.3 $\pm$ 1.9).

The first supine MHR (68.4 $\pm$ 1.7) was also, significantly ($P<0.001$) higher than the average for both acts (66.4 $\pm$ 1.6).

	Supine		Standing		△H.R.	
	I	II	I	II	I	II
1.	65	57	88	85	23	28
2.	75	70	86	83	11	13
3.	65	63.5	64	76	−1	12.5
4.	66	60	71	72	5	12
5.	69	63	84	83	15	20
6.	52	60	63	69	11	9
7.	88	76	120	116	32	40
8.	67	64	83	84	16	20
9.	74	74	83	83.5	9	9.5
10.	68	61	97	90	29	29
11.	68	59	91	85	23	26
12.	78	69	85	86	7	17
13.	54	54	67	69	13	15
14.	65	57.5	96.5	94.5	31.5	37
15.	75	77	81	82	6	5
16.	67	79	79	92	12	13
17.	67	53	113	97	46	44
18.	54	56	94	86	40	30
19.	72	65	84	80	12	15
20.	78	71	88	91.5	10	20.5
21.	78	78	83	85	5	7
22.	59.5	59	76.5	75	17	16
23.	73	73	105.5	94	32.5	21
24.	62	50.5	78	76	16	25.5
25.	52.5	48	74	74	21.5	26
26.	76	77	82	88	6	11
27.	71	68	79	74	8	6
28.	50	48	73	70	23	22
29.	81	71	102	102	21	31
30.	75	61	84	78	9	17
31.	57	56	85	88	28	32
32.	85	79	100	100	15	21
33.	71	68	89	85	18	17
Mean	68.4	64.4	85.7	84.7	17.3	20.2
± SEM	1.7	1.6	2.2	1.8	1.9	1.7

Table(3-1). The MHR during the first (I) and second (II) acts of supine-standing manoeuvre and the difference between standing and supine MHR (△HR) in the two acts.

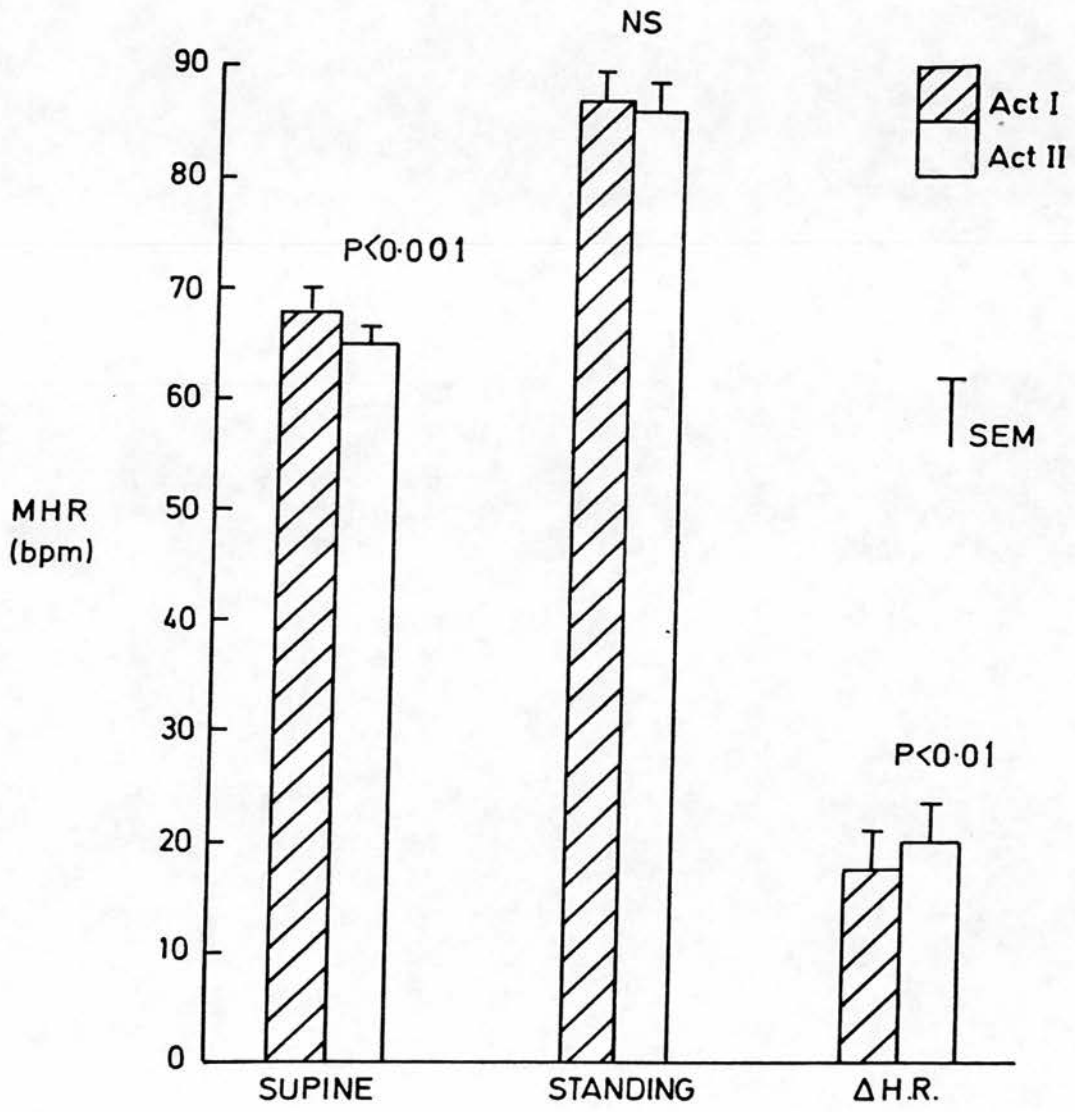


Fig.(3-1). The mean of MHR and Δ HR for 33 subjects during the first (I) and second (II) acts of supine-standing manoeuvre.

Since the findings about the significant difference in MHR with the repetition of the act became apparent only after the analysis, and since not all the subjects had performed the manoeuvre twice, subsequent comparison of MHR was done on the MHR during the first act only for all the subjects.

It is important to point out that although there was a significant difference between the two supine MHR, it was very small (5.9%) compared with the difference between supine and standing MHR (25.3%), which was significant ($p<0.001$) in both acts (Fig. 3-2).

Statistical analysis

For the comparison of MHR results, the Student-t-test was used, while the Wilcoxon's signed rank test was used for the MAD and CV% results.

RESULTS

MHR

The mean heart rate (Mean $\pm$ SEM) during supine and standing postures, and the difference between the two (Δ HR) for all the 75 subjects are shown in (Table 3-2). The MHR during maintained standing (83.5 $\pm$ 1.4) was significantly ($p<0.001$) higher than supine MHR (66.9 $\pm$ 1.2). The Δ HR was weakly ($r = -0.22$) but significantly ($P<0.05$) related to the supine MHR (Fig. 3-3). The regression equation was: Δ HR = 30.66 - (0.21 X supine MHR).

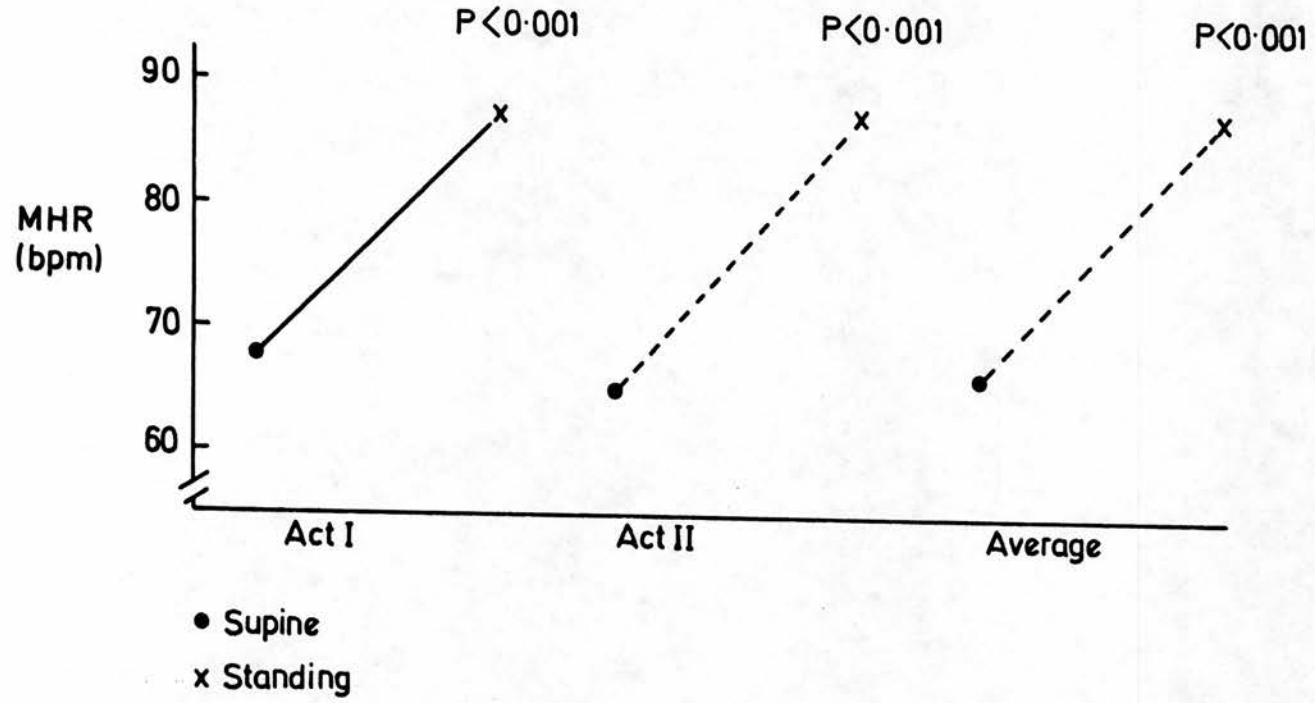


Fig.(3-2) shows that in both acts (I and II) as well as in the average for both acts, the MHR during standing was significantly higher than supine MHR.

	Age (yr.)	Supine	Standing	Δ HR
Range	18 – 65	50 – 91	59 – 120	(– 1) – 46
Mean	23.6	66.9	83.5	16.5
± SEM	1.1	1.2	1.4	1.1
SD	9.2	10.1	12.2	9.5

Table(3-2). The MHR during supine and standing postures and the difference between the two (ΔHR) for all the 75 subjects.

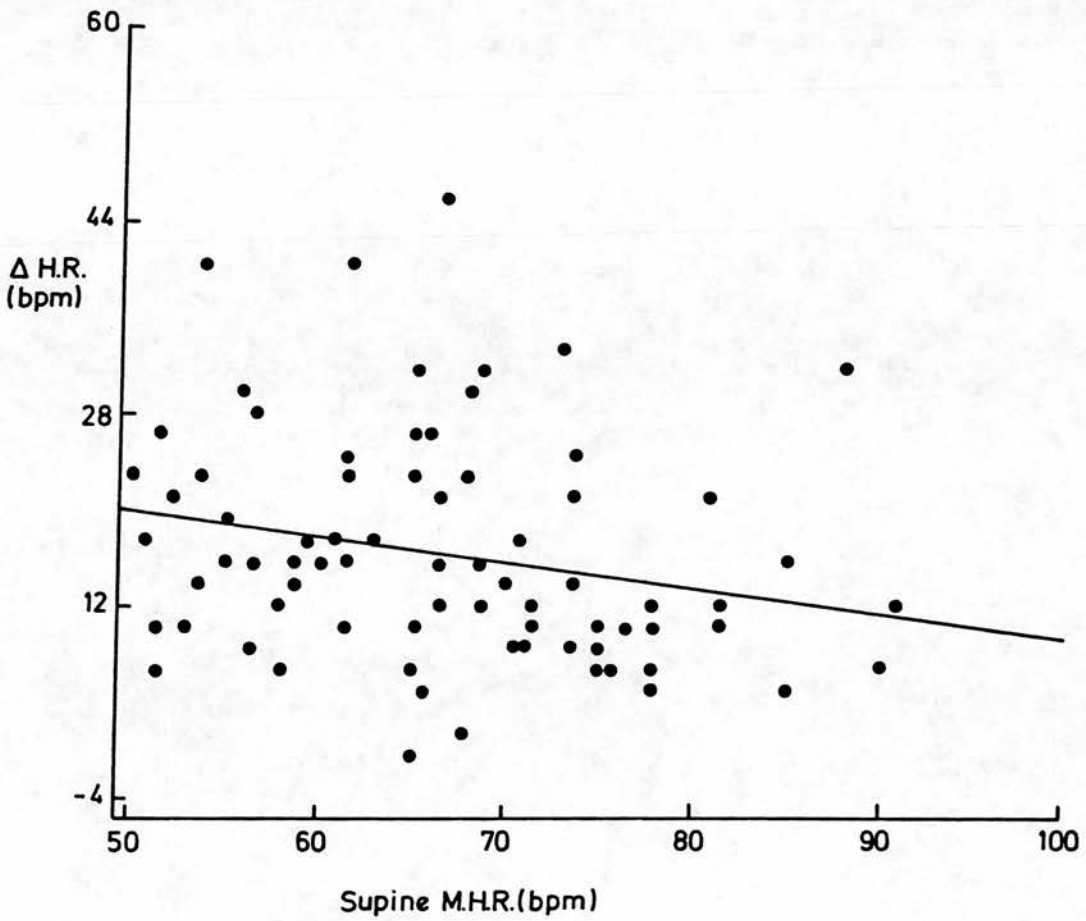


Fig.(3-3) shows the weak correlation (r= -0.22) between ΔHR and supine MHR but it was significant at the 5% level.

In 24 subjects, the MHR during supine and standing postures on two different days were compared (Table 3 - 3). There was no significant difference in MHR during supine or standing postures, nor there was any significant difference in △ HR on the two days (Fig. 3 - 4). The standing MHR was significantly ($P<0.001$) higher than supine MHR on the two occasions (Fig. 3 - 5).

MAD

Table (3 - 4) shows the MHR, MAD and CV% for 31 subjects during both supine and standing postures. The correlation between these three indices is shown in Table (3 - 5). As can be seen from this table, there was a significant ($P<0.001$) negative correlation between MHR and MAD during both supine ($r = - 0.56$) and standing ($r = - 0.57$) postures. The MAD during standing (16.5 ± 1.7) was significantly ($P<0.01$) lower than the supine MAD (44.3 ± 5.7). This was possibly due to the strong negative correlation with the MHR. However, normalized MAD [MAD% = (MAD / mean RR intervals) X 100] during standing (2.4%) was still lower than supine MAD% (5.1%).

CV%

In contrast to the strong negative relation between MHR and MAD, the correlation between MHR and CV% was very poor (NS) in both supine and standing postures ($r = - 0.24, - 0.08$ respectively) (Table 3 - 5).

	Supine		Standing		△H.R.	
	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2
1.	88.0	81.0	120.0	95.0	32.0	14.0
2.	67.0	66.0	82.0	71.0	15.0	5.0
3.	54.0	61.0	94.0	91.0	40.0	30.0
4.	78.0	89.0	85.0	101.0	7.0	12.0
5.	67.0	66.0	113.0	101.5	46.0	35.5
6.	68.0	74.0	97.0	91.0	29.0	17.0
7.	73.0	70.0	105.5	89.0	32.5	19.0
8.	56.0	50.0	83.0	73.0	27.0	23.0
9.	65.0	68.0	88.0	99.0	23.0	31.0
10.	65.0	59.0	96.5	99.0	31.5	40.0
11.	57.0	56.0	85.0	81.0	28.0	25.0
12.	68.0	66.0	91.0	88.0	23.0	22.0
13.	71.0	70.0	79.0	90.5	8.0	20.5
14.	71.0	71.5	89.0	86.5	18.0	15.0
15.	81.0	76.0	91.0	82.0	10.0	6.0
16.	75.0	72.5	86.0	84.5	11.0	12.0
17.	71.0	66.0	80.0	79.0	9.0	13.0
18.	68.0	69.0	69.0	77.0	1.0	8.0
19.	75.0	81.0	81.0	83.0	6.0	2.0
20.	78.0	74.5	88.0	90.0	10.0	15.5
21.	52.5	50.0	74.0	74.0	21.5	24.0
22.	67.0	73.5	79.0	85.5	12.0	12.0
23.	63.0	54.0	82.0	67.0	19.0	13.0
24.	58.5	52.0	74.0	63.0	15.5	11.0
Mean	68.2	67.3	88.0	85.1	19.8	17.7
± SEM	1.8	2.1	2.5	2.2	2.4	2.0

Table(3-3). The MHR during supine and standing postures and △HR on two different days.

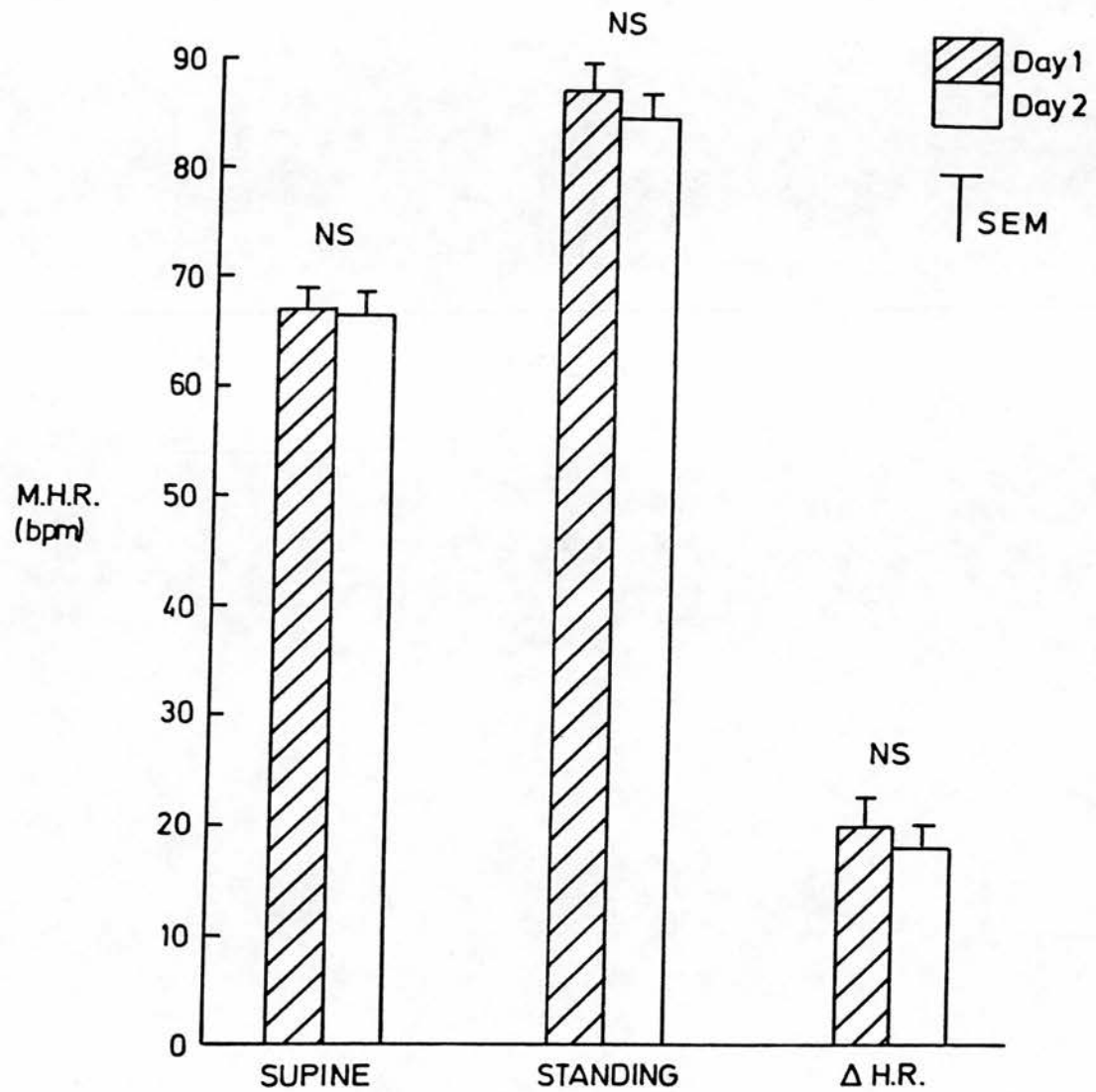


Fig.(3-4). The mean of MHR and Δ HR for 24 subjects on two different days.

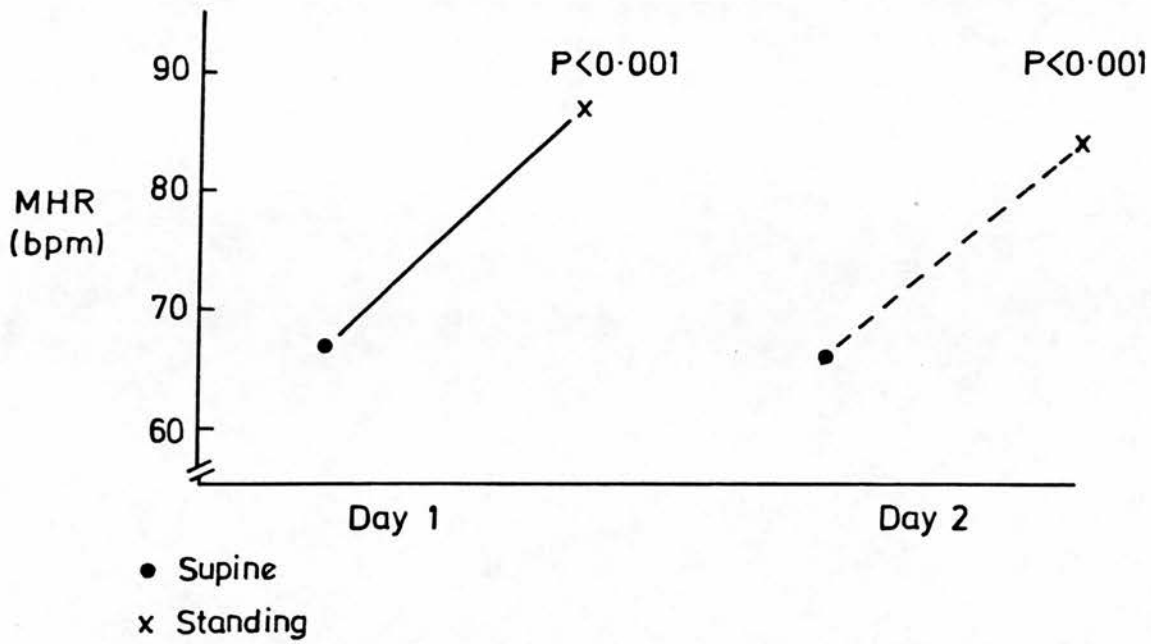


Fig.(3-5) shows that on both day 1 and day 2, the MHR during standing was significantly higher than supine MHR.

	Supine			Standing		
	MHR	MAD	CV%	MHR	MAD	CV%
1	79.0	11.1	3.0	108.0	5.2	4.8
2	93.0	11.2	3.8	100.0	10.1	4.8
3	81.0	21.7	5.3	91.0	13.6	3.3
4	67.0	43.1	5.2	82.0	21.3	9.9
5	69.0	56.8	8.8	87.0	21.2	7.0
6	59.0	48.7	5.5	69.0	35.1	7.6
7	68.0	43.6	5.5	76.0	39.0	8.0
8	62.0	29.4	3.3	73.0	24.3	7.1
9	69.0	14.7	2.9	84.0	9.3	3.6
10	88.5	25.7	5.9	93.0	8.3	2.8
11	59.0	69.0	6.5	73.0	9.2	3.7
12	72.0	13.8	3.5	83.0	12.8	4.4
13	58.0	29.2	4.6	70.0	11.2	3.2
14	80.0	28.6	3.8	85.0	17.9	4.3
15	74.0	20.9	3.5	82.0	10.0	3.3
16	68.0	54.6	11.7	88.0	22.6	7.7
17	51.0	112.7	8.6	74.0	39.1	11.5
18	52.0	15.9	2.8	61.0	17.9	6.0
19	68.0	27.1	4.8	99.0	6.0	4.1
20	66.5	106.1	18.7	86.0	28.3	11.5
21	81.0	18.6	5.4	95.0	7.8	4.4
22	74.0	34.0	7.9	91.0	17.4	9.6
23	79.0	17.2	2.9	93.0	7.7	4.4
24	69.0	41.5	6.7	86.0	12.3	5.3
25	57.5	79.4	8.9	94.5	15.1	9.8
26	62.5	46.3	6.9	84.0	11.3	4.3
27	61.0	38.6	9.5	91.0	13.3	7.2
28	73.0	27.4	4.1	105.5	8.2	7.6
29	70.0	52.5	9.7	90.5	13.5	5.0
30	70.0	122.0	16.1	85.0	27.2	8.8
31	54.0	111.4	7.7	81.0	16.0	4.3
Mean	68.9	44.3	6.6	85.8	16.5	6.1
±SEM	1.8	5.7	0.7	1.9	1.7	0.5

Table(3-4) shows the effect of posture on the mean heart rate (MHR), the mean absolute difference (MAD) and the interval index (CV%).

	MAD		CV%	
	Supine	Standing	Supine	Standing
MHR	r = −0.56 (***)	r = −0.57 (***)	r = −0.24 (NS)	r = −0.08 (NS)
MAD			r = 0.84 (***)	r = 0.70 (***)

Table(3-5) shows the correlation and its significance between MHR, MAD and CV% during both supine and standing postures.
Pearson's correlation was applied on the Log transformed data from 31 subjects. *** = $p<0.001$, NS = not significant.

The CV% during standing (6.1 ± 0.5) was not significantly different from the supine CV% (6.6 ± 0.7) but it was slightly lower. This slight insignificant decrease in CV% during standing was very small when we consider the strong ($P<0.001$) positive correlation between MAD and CV% ($r=0.70$) (Table 3 - 5) and the significant ($P<0.01$) decrease in MAD during standing (Table 3 - 4).

HRV

In the supine posture, the predominant rhythm in heart rate was the respiratory sinus arrhythmia ("RSA"). On changing to the standing posture, an initial complex response took place (Fig. 3 - 6). Later, the heart rate recovered again, within a minute, to a more stable condition, but the pattern then varied in different subjects.

In about half the subjects studied, the heart rate pattern during maintained standing was very different from the predominantly "RSA" rhythm during supine posture.

Fig. (3 - 7) illustrates the effect of changing posture from supine to maintained standing in one subject. When the subject was lying down (a), the rhythm was clearly linked to respiration i.e."RSA", and the heart rate spectrum (b) showed a large peak at the respiratory frequency ($\sim$ 0.27 cycles/beat) . However , during maintained standing (c), the heart rate pattern was completely different. Slow "10 second" oscillations, not related to respiration replaced the "RSA" and became the predominant rhythm and this is reflected on the heart rate spectrum in (d) which shows a very large peak at $\sim$ 0.1 cycles/beat. In addition, the

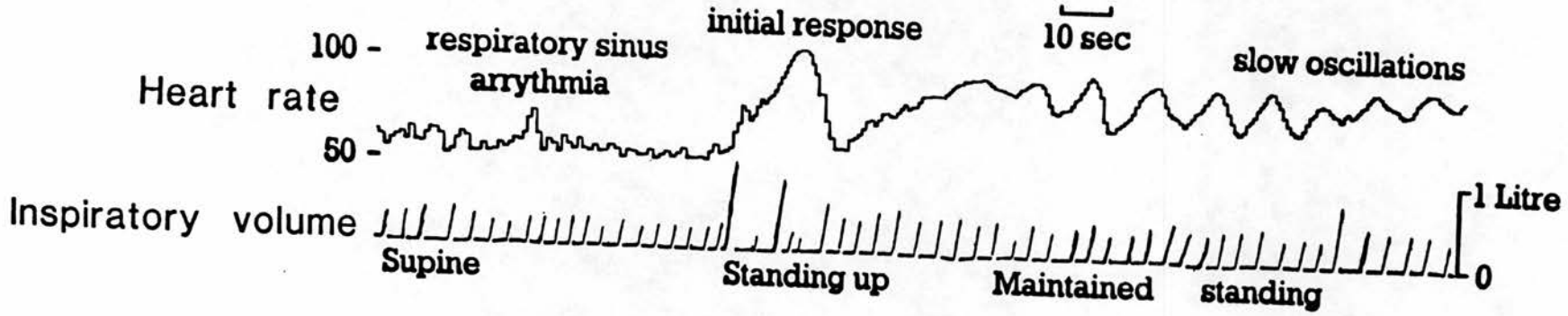


Fig.(3-6) shows the initial heart rate response to standing. It also shows that during supine posture the respiratory sinus arrhythmia was the predominant rhythm while during maintained standing, the slow "10 second" oscillations were predominant.

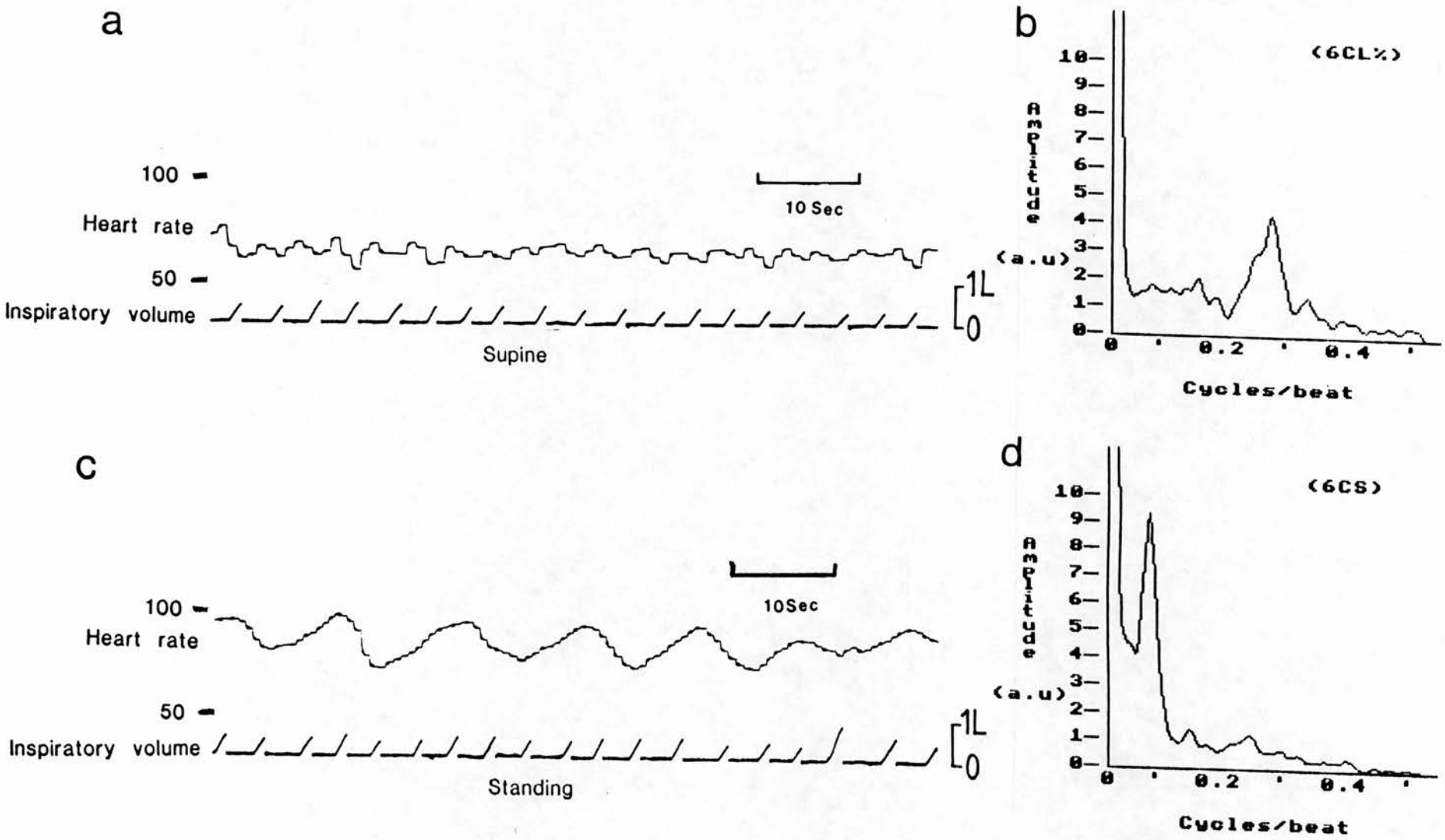


Fig.(3-7) shows the effect of posture on heart rate pattern in one of the "oscillators". See text for details.

respiratory peak at $\sim$ 0.24 cycles/beat has been markedly reduced in size.

In other subjects , the change of posture did not cause such a remarkable change in heart rate pattern . Fig. (3 - 8) shows that, during both supine (a) and maintained standing (c), the predominant rhythm was the respiratory sinus arrhythmia, and there were no clear slow oscillations. The heart rate spectra (b) and (d) were also very similar.

Subjects who showed the "10 second" oscillations during maintained standing were called "oscillators", and those who did not were called "non-oscillators". Accordingly 36 subjects (48%) were "oscillators" and the remaining 39 subjects (52%) were "non-oscillators".
The sex, age, mean heart rate in the supine and standing postures, and also Δ HR for the individual "oscillators" and the "non-oscillators" are shown in Tables (3 - 6) and (3 - 7) respectively.

It is important to point out , that this subjective classification of the subjects on the basis of visual inspection of heart rate records (Sattar & Young 1983) yielded a good correspondence with the results obtained later by spectral analysis.

Table (3 - 8) compares the MHR in the supine and maintained standing postures, and also Δ HR in the two groups i.e. "oscillators" and "non-oscillators". As can be seen from the table there was a great overlap between the two groups, but the MHR for all the "oscillators" during maintained standing (89.5 $\pm$ 1.9) was

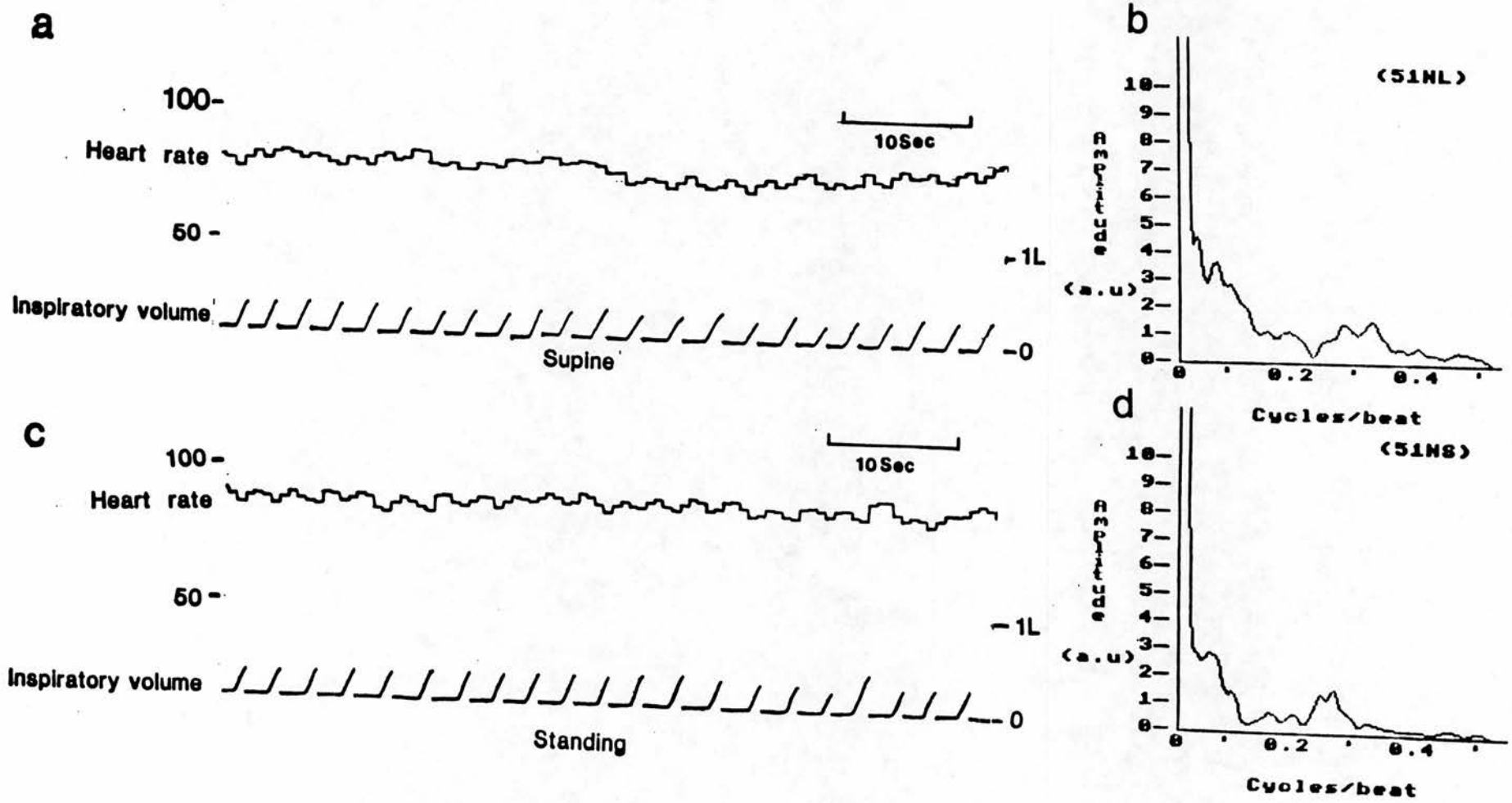


Fig.(3-8) shows the effect of posture on heart rate pattern in one of the "non-oscilltors". See text for details.

	Sex	Age	Supine	Standing	△H.R.
1.	M	29	65	88	23
2.	M	19	75	86	11
3.	M	19	71	80	9
4.	F	19	66	71	5
5.	M	19	82	93	11
6.	M	19	72	83	11
7.	F	18	88	120	32
8.	F	23	74	83	9
9.	F	20	68	97	29
10.	M	19	62	85	23
11.	M	19	77	88	11
12.	M	21	68	91	23
13.	M	20	78	85	7
14.	M	21	61	78	17
15.	F	19	74	95	21
16.	M	21	62	103	41
17.	M	21	65	96.5	31.5
18.	M	18	67	113	46
19.	M	19	54	94	40
20.	M	24	72	84	12
21.	M	20	78	88	10
22.	M	19	69	100	21
23.	F	20	67	88	21
24.	M	19	58	86	30
25.	M	30	59.5	76.5	17
26.	M	23	73	105.5	32.5
27.	F	20	74	88	14
28.	M	21	52.5	74	21.5
29.	F	22	71	79	8
30.	M	19	54	77	23
31.	F	24	50	73	23
32.	M	28	81	102	21
33.	M	20	62	87	25
34.	F	21	57	85	28
35.	M	19	74	99	25
36.	M	25	85	100	15
	Range	18 – 30	50 – 88	71 – 120	5 – 46
	Mean	21.0	68.4	89.5	20.8
	± SEM	0.5	1.6	1.9	1.7

Table(3-6). THe sex, age, MHR during supine and standing postures and Δ HR in the "oscillators".

	Sex	Age	Supine	Standing	△H.R.
1.	M	19	66	93	27
2.	M	19	57	72	15
3.	M	23	65	64	–1
4.	F	19	85	90	5
5.	M	52	69	84	15
6.	F	21	52	63	11
7.	F	43	90	96	6
8.	M	51	59	73	14
9.	F	18	67	83	16
10.	F	19	68	69	1
11.	F	20	51	68	17
12.	M	19	82	94	12
13.	F	19	52	79	27
14.	F	47	69	81	12
15.	M	19	91	103	12
16.	M	19	52	59	7
17.	F	22	54	67	13
18.	F	19	65	71	6
19.	F	19	75	81	6
20.	F	40	58	70	12
21.	M	25	55	74	19
22.	M	19	60	76	16
23.	F	21	59	75	16
24.	F	22	67	79	12
25.	F	19	53	63	10
26.	F	42	78	83	5
27.	F	18	78	90	12
28.	M	19	57	66	9
29.	F	19	63	80	17
30.	F	21	58	64	6
31.	M	23	55	70	15
32.	M	26	62	78	16
33.	M	21	62	73	11
34.	F	28	76	82	6
35.	F	65	75	84	9
36.	F	18	70	84	14
37.	M	20	65	75	10
38.	M	19	65	92	27
39.	F	43	71	89	18
	Range	18 – 65	51 – 91	59 – 103	(– 1) – 27
	Mean	26.0	65.5	77.9	12.3
	± SEM	1.9	1.7	1.7	1.0

Table(3-7). The sex, age, MHR during supine and standing postures and Δ HR in the "non-oscillators".

	GROUP	MEAN ± SEM	P	RANGE
SUPINE	"Oscillators"	68.4 ± 1.6	NS	50 – 88
	"Non – oscillators"	65.5 ± 1.7		51 – 91
STANDING	"Oscillators"	89.5 ± 1.9	<0.001	71 – 120
	"Non – oscillators"	77.9 ± 1.7		59 – 103
△ H.R. (The difference between standing and supine MHR)	"Oscillators"	20.8 ± 1.7	<0.001	5 – 46
	"Non – oscillators"	12.3 ± 1.0		(– 1) – 27

Table(3-8) compares the ranges and means of MHR during supine and standing postures and also △HR of all the "oscillators" with the "non-oscillators".

significantly (P<0.001) higher than the MHR for the "non-oscillators" (77.9 ± 1.7) (Fig. 3 - 9).

The MHR in the supine posture was not significantly different in the two groups (68.4 ± 1.6) (65.5 ± 1.7) (Fig.3-9), consequently Δ HR was significantly (P<0.001) bigger in the "oscillators" (20.8 ± 1.7) than the "non-oscillators" (12.3 ± 1.0) (Fig. 3 - 10).

Both the "oscillators" as well as the "non-oscillators" had a MHR during maintained standing which was significantly (P<0.001) higher than supine MHR (Fig. 3-11).

Twenty six out of 42 males (62%) were oscillators, while the female oscillators were only 10 out of total of 33 (30%).

<u>More about the effect of posture in the "oscillators"</u>

Although the "10 second" rhythm was more prominent during standing, a few subjects showed this rhythm even when supine . Fig. (3 - 12) shows that when the subject was supine in (a), the "10 second" rhythm was there, but of small amplitude. During maintained standing in (c) the "10 second" rhythm became clearer and smoother. From the heart rate spectra, it can be seen that in the supine posture (b), there was a relatively large peak at ∼ 0.1 cycles/beat, which corresponds to the "10 second" rhythm, and the peak at the respiratory frequency (∼ 0.2 cycles/beat) was very small. Then, when the subject was standing (d), the peak at ∼ 0.1 cycles / beat has increased in size , while the respiratory peak at ∼ 0.18 cycles/beat has almost disappeared. So, the presence of the peak at ∼ 0.1 cycles/beat during supine posture, reflects the prominent appearance of the "10 second" rhythm, and the increase in the size of this peak during standing reflects the increased

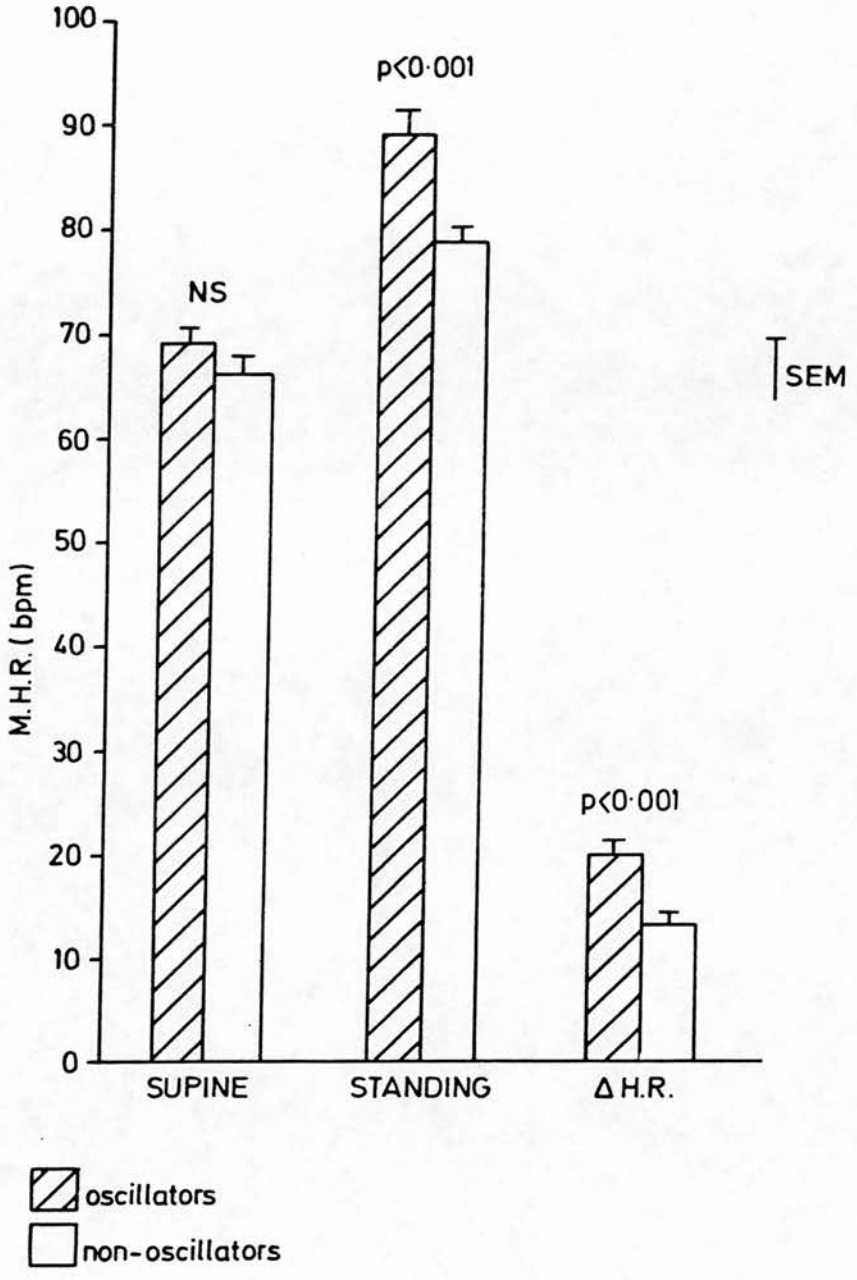


Fig.(3-9) compares the mean of MHR during supine and standing postures and ΔHR between the "oscillators" and the "non-oscillators".

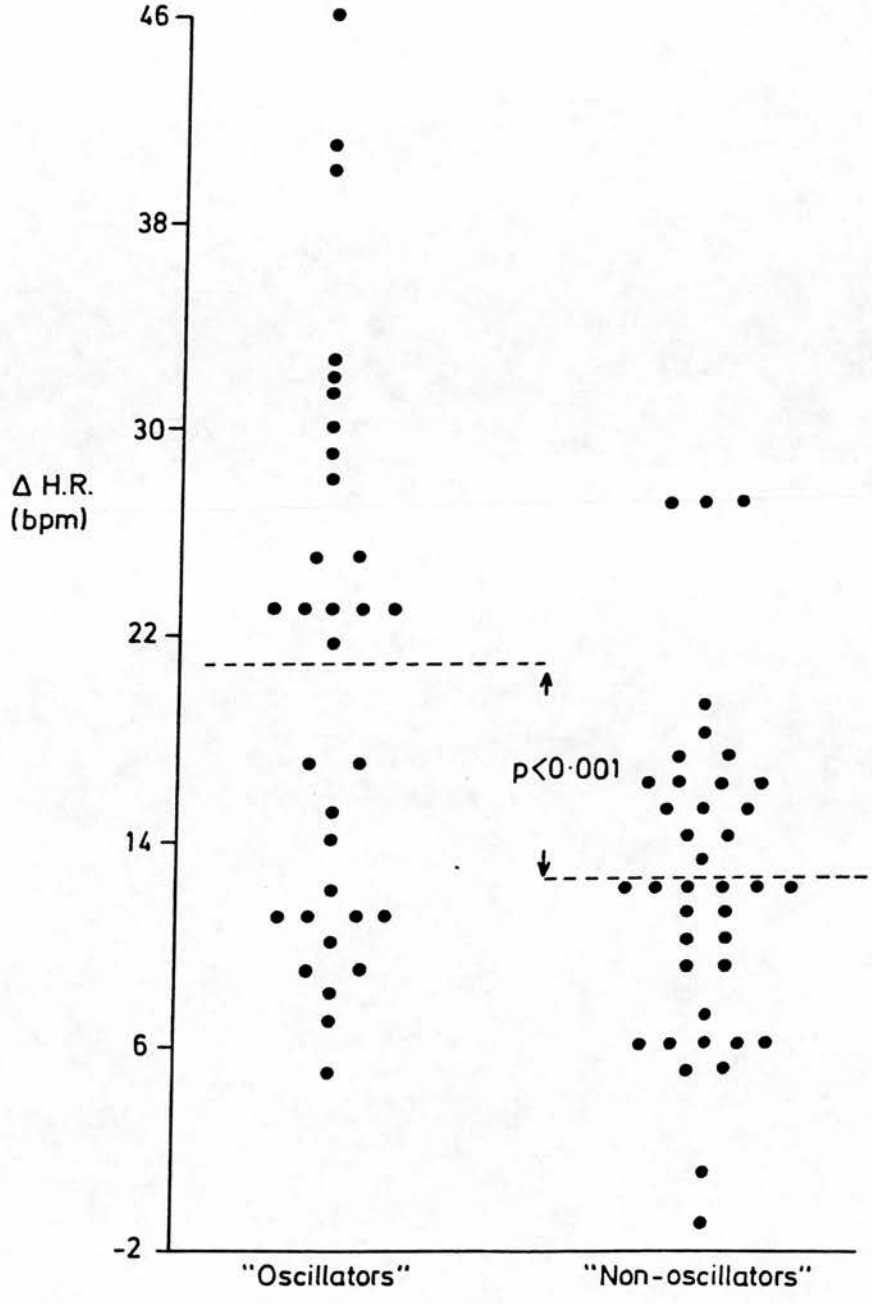


Fig.(3-10) shows the wide overlap in △HR (the difference between standing and supine MHR) among the "oscillators" and the "non-oscillators" but on the whole, the mean △HR for the "oscillators" was significantly higher than the mean △HR for the "non-oscillators".(The dotted lines are the means)

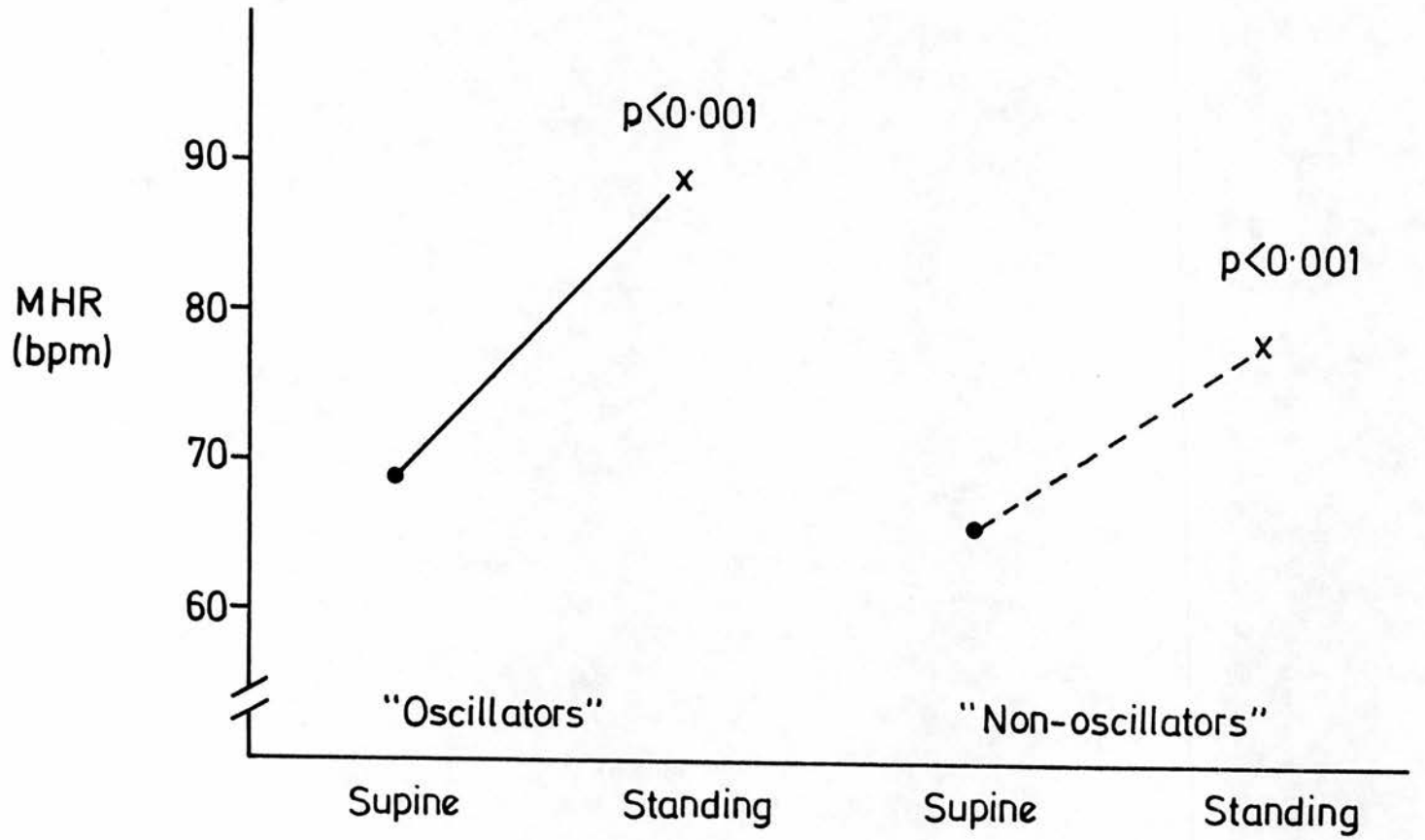


Fig.(3-11) shows that in both the "oscillators" and the "non-oscillators", the MHR during standing was significantly higher than supine MHR.

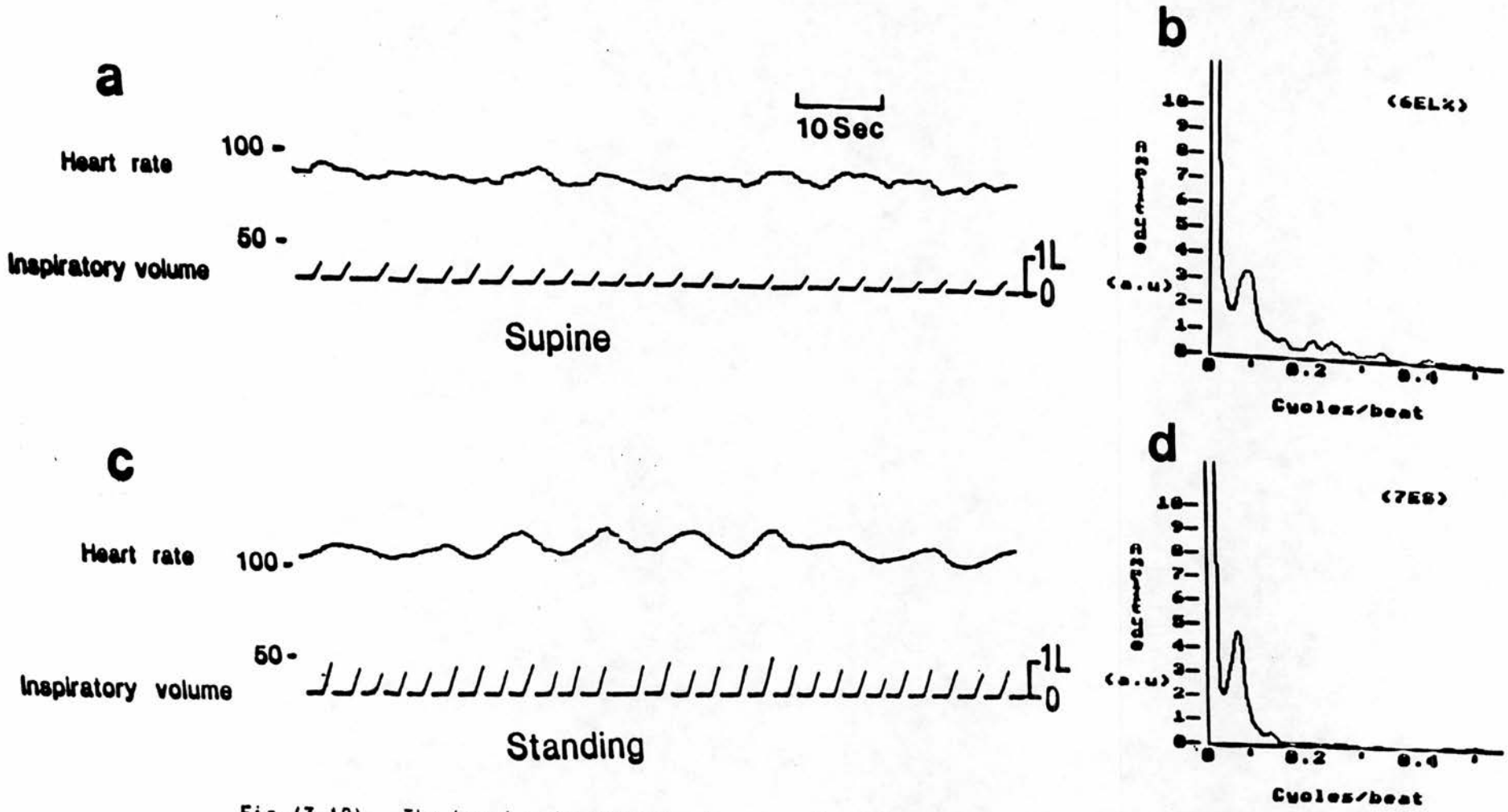


Fig.(3-12). The heart rate pattern in one "oscillator" showing the slow "10 second" oscilations in the supine posture.During standing, these oscillations became even bigger in amplitude and more regular.

amplitude of this rhythm. The smoothness of the "10 second" oscillations during standing is most probably due to the decrease in the amplitude of the "RSA".

Later analysis by spectral technique showed that during supine posture, more subjects exhibited a peak of moderate size at $\sim$ 0.1 cycles/beat,but the "10 second"rhythm was not clearly identifiable by visual inspection of heart rate records . This is illustrated in Fig. (3 - 13) which shows that although the heart rate spectrum during supine posture (b) did show a peak of moderate size at $\sim$ 0.1 cycles/beat, the predominant rhythm in the heart rate (a) was the "RSA". Re-examining the heart rate spectrum (b) again, it becomes clear that, in addition to the peak at $\sim$ 0.1 cycles / beat , there is another, even bigger peak at $\sim$ 0.3 cycles/beat, which is at the respiratory frequency, and this is why the "RSA" rhythm was more prominent than the "10 second" rhythm in this subject.

During maintained standing, the oscillators (by definition) showed the slow "10 second" oscillations in their heart rate record, however the pattern was not the same for all the subjects. Some had a very prominent "10 second" rhythm with very little "RSA", and the heart rate spectrum showed a very large peak at $\sim$ 0.1 cycles/beat as in (a) of (Fig. 3 - 14). In others, both "RSA" as well as the "10 second" rhythm were present during standing, and the heart rate spectrum showed two peaks, a large one at $\sim$ 0.1 cycles/beat, and a relatively smaller peak at the respiratory frequency as in (b) of Fig.(3 - 14).

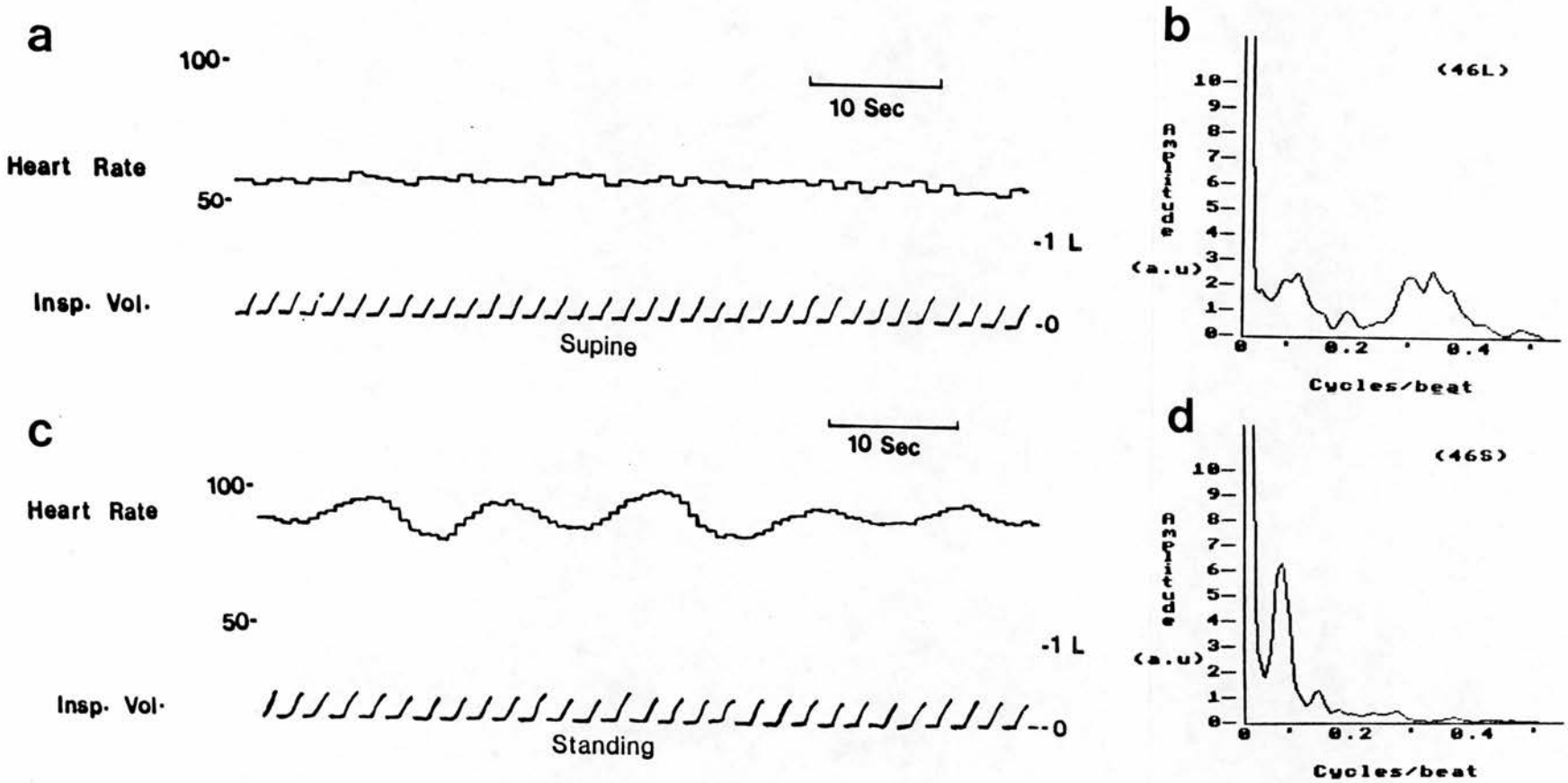


Fig.(3-13) explains why the respiratory sinus arrhythmia was the predominant rhythm during the supine posture despite the presence of a peak at a low frequency. See text for details.

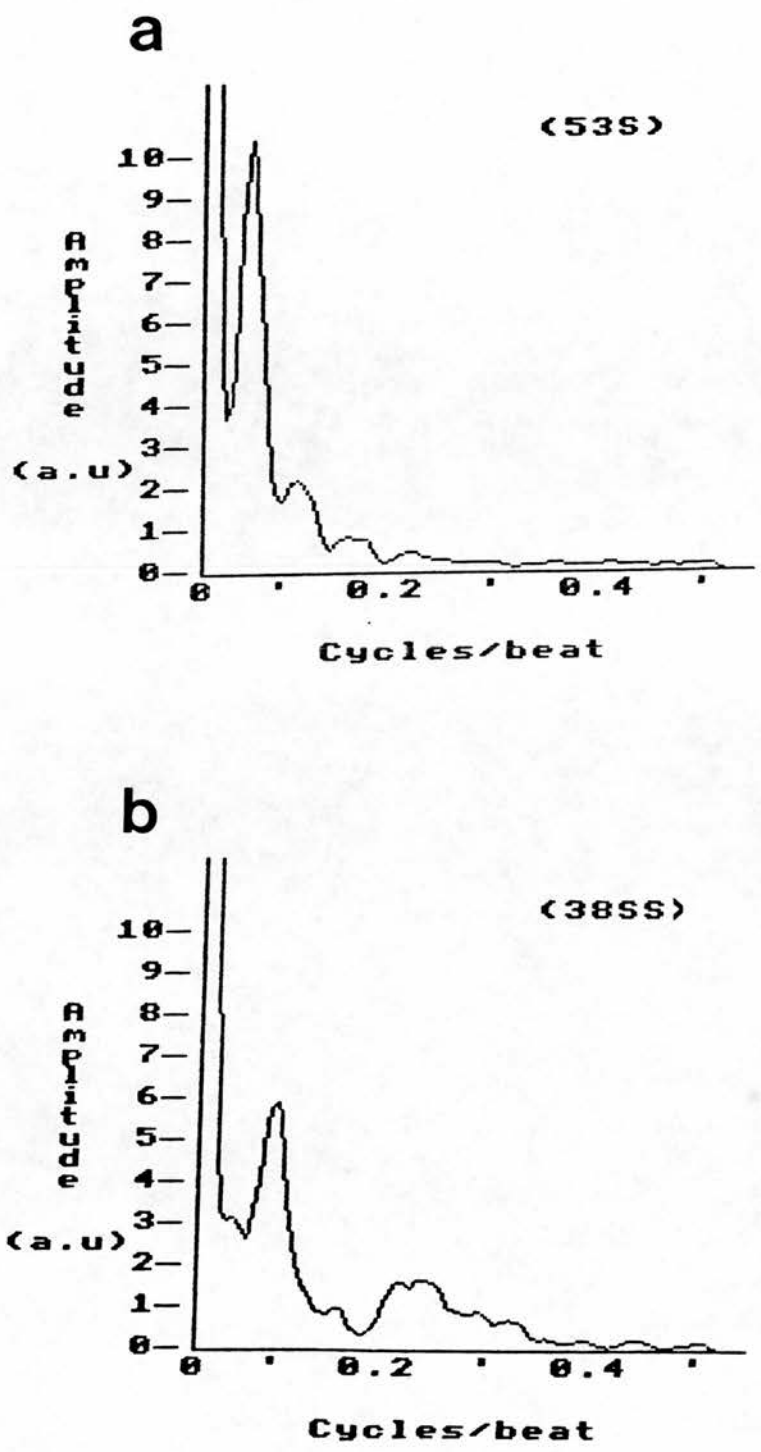


Fig.(3-14). The heart rate spectra during standing in two subjects.Both were "oscillators" (i.e. showed predominantly "10 second" rhythm during standing), but the subject in (a) had one large peak at the low frequency, whereas the subject in (b) had two peaks, one at the low frequency and a relatively smaller peak at the respiratory frequency.

Although the marked changes in heart rate pattern during maintained standing were noticeable by eye and very impressive, spectral analysis gave more insight of the different ways that this change can be achieved in different subjects. In some subjects as in Fig. (3 - 15) , there was one large peak at the respiratory frequency ($\sim$ 0.22 cycles/beat) during supine posture (a), while during maintained standing (b), the large peak was then at $\sim$ 0.1 cycles/beat and the respiratory peak ($\sim$ 0.21 cycles/beat) was relatively very small. The contrast in the heart rate patterns was very clear cut ; "RSA" during supine posture and "10 second" rhythm during maintained standing.

In other oscillators, there were two peaks in the heart rate spectrum during supine posture as in (a) of (Fig. 3 - 16) and (Fig. 3 - 17) and the predominant rhythm in heart rate was the "RSA". During maintained standing, both subjects showed prominent "10 second" rhythm, but they achieved this end result differently. In the subject depicted in Fig. (3 - 16), the size of the peak at $\sim$ 0.1 cycles/beat changed very little, but there was almost complete abolition of the peak at the respiratory frequency. On the other hand, in the subject of Fig (3 - 17), not only was there a marked decrease in the respiratory peak, but in addition, the peak at $\sim$ 0.1 cycles/beat was doubled in size.

So, it seems that the resulting heart rate pattern depends on the ratio between the the "RSA" and the "10 second" rhythm.

Sometimes it has been difficult to differentiate between the two rhythms. This happened in those subjects who spontaneously

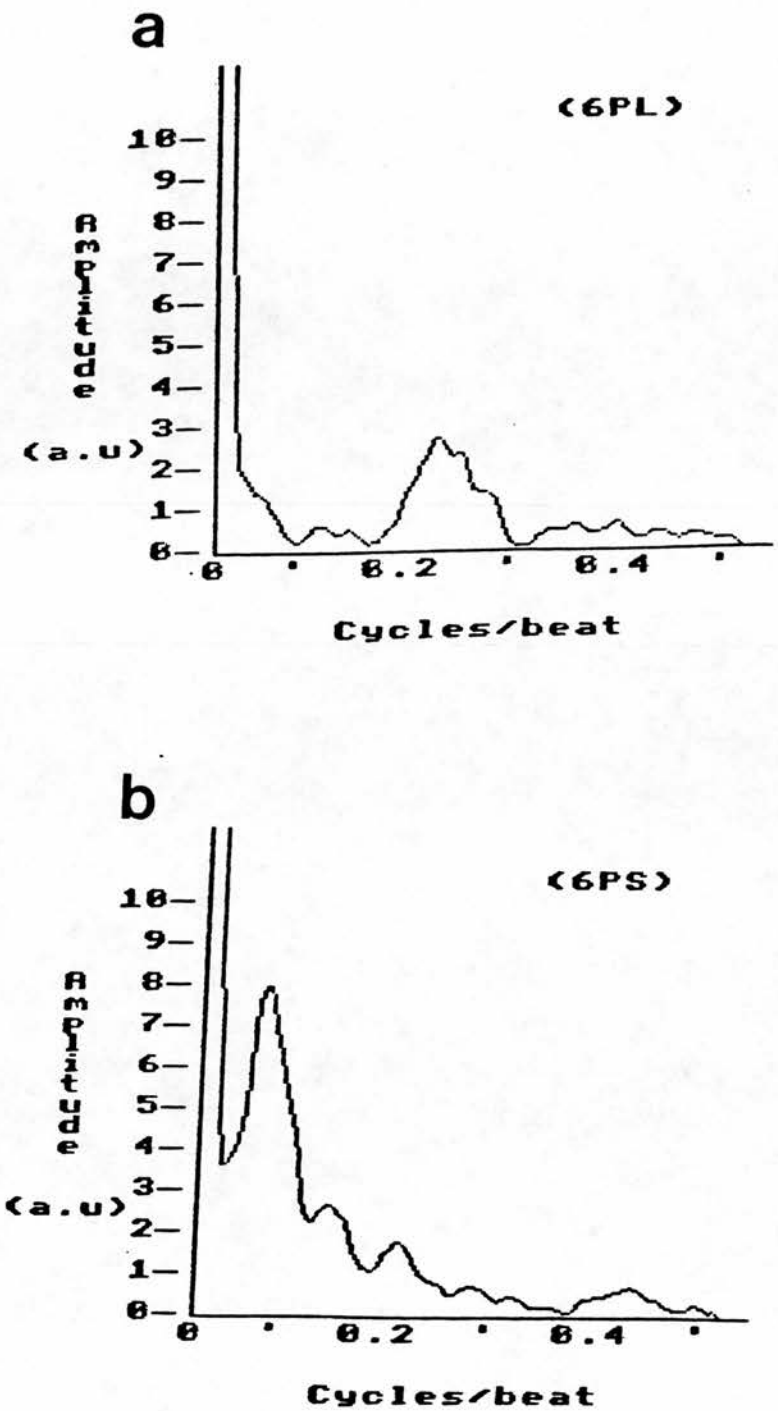


Fig.(3-15). The heart rate spectra of an "oscillator" with one large peak at the respiratory frequency during supine posture in (a) and one large peak at low frequency during standing in (b).

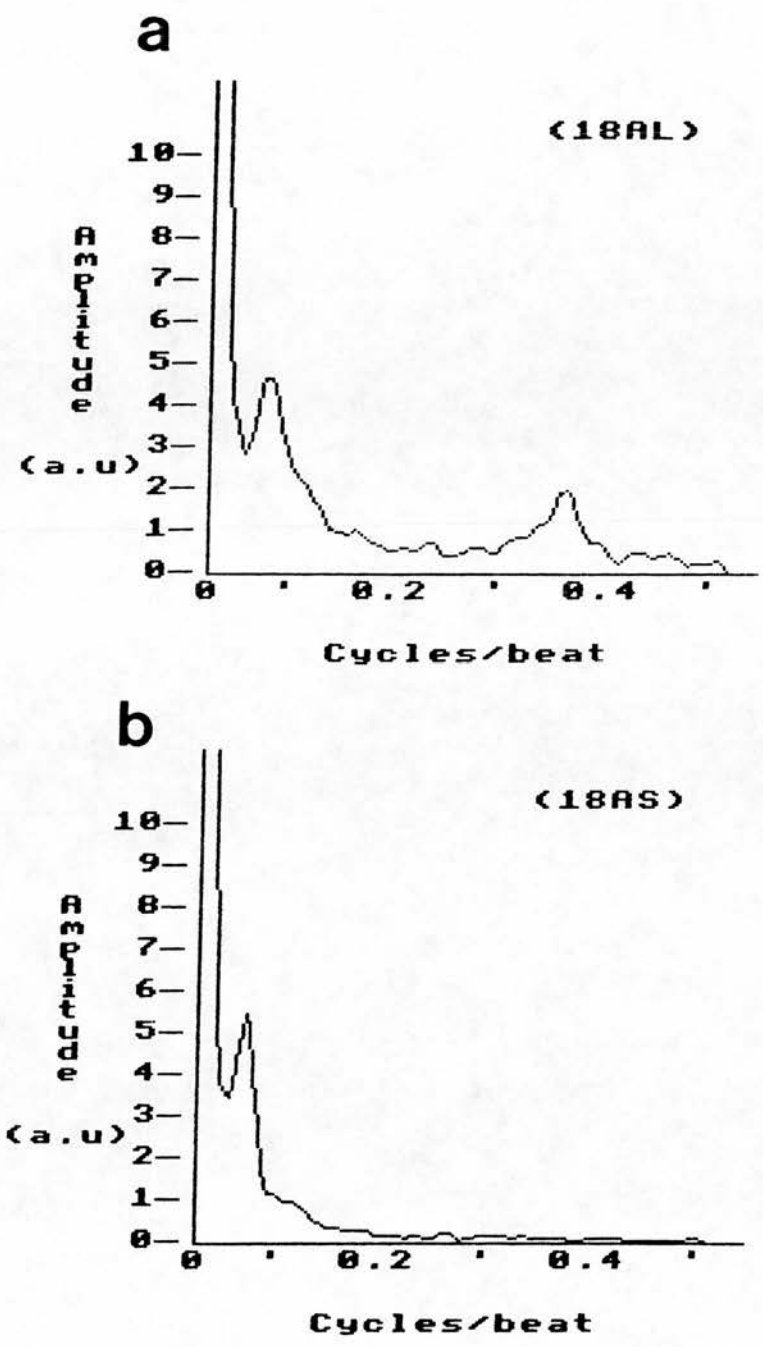
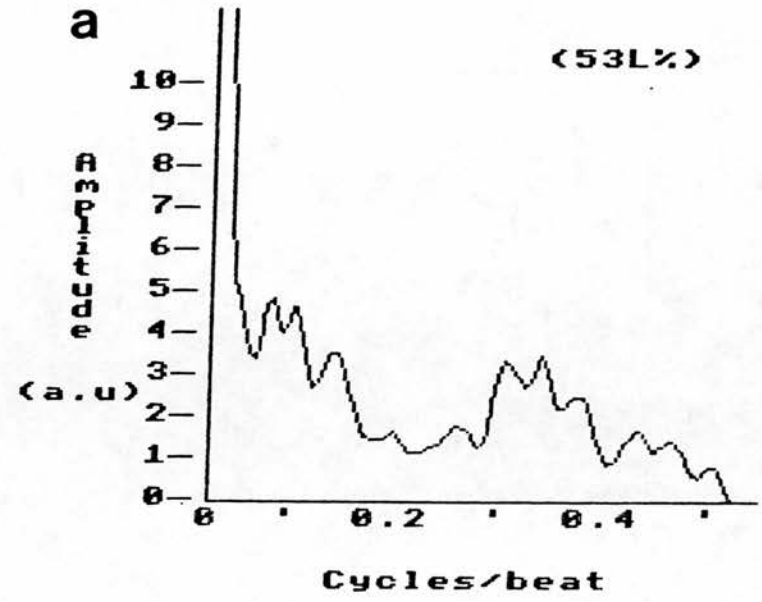


Fig.(3-16). The heart rate spectra of an "oscillator" showing two peaks during supine posture in (a). During standing (b), the amplitude of the peak at the low frequency increased slightly, but the peak at the respiratory frequency was almost abolished. Thus, the ratio between the two peaks increased several folds.



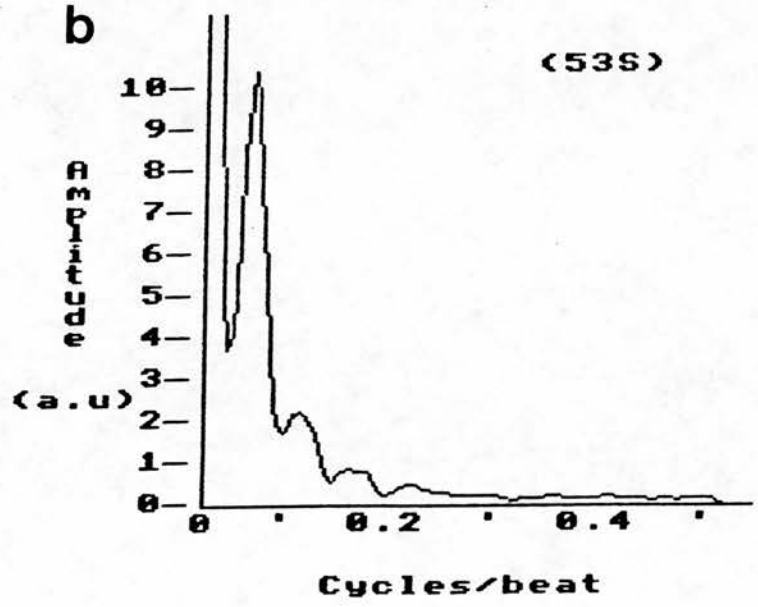


Fig.(3-17) shows two prominent peaks during supine posture in (a) as in the previous figure.However during standing, not only was there a marked reduction in the amplitude of the peak at the respiratory frequency, but the peak at the low frequency had doubled its size.

breathed slowly during the recordings. Fig. (3 - 18) shows that during supine posture (a), the heart rate spectrum (b) showed a tall peak at the respiratory frequency (7 /min.) which is in the same range as the "10 second" rhythm (6 /min.).However,during standing (c), the heart rate changes, though still related in a 1:1 ratio to respiration, are now smaller in amplitude and smoother. The heart rate spectrum in (d) showed a smaller peak at the same frequency.

Fast shallow breathing was performed and in Fig.(3-19b) it can be seen that the peak at the low frequency is still present though reduced in amplitude. Therefore it is likely that the peak in (a) is due to both "RSA" and the "10 second" rhythm.

The dominating role of posture on the "10 second" oscillations was again demonstrated in another subject when fast shallow breathing in both supine and standing postures led to similar increases in MHR ,but the slow "10 second" oscillations were only seen clearly during standing (Fig.3-20).

Reproducibility of the phenomenon

The duration of these oscillations varied between 7 and 15 seconds, but mostly 8.5 to 12 seconds (a frequency of 5 to 7 per minute). There was also a large variation in the amplitude (3 to 30 bpm). Both frequency and amplitude varied between subjects and in the same subject on different days. However, the striking difference in heart rate pattern on changing posture from supine to maintained standing was consistently found on repeating the act several times

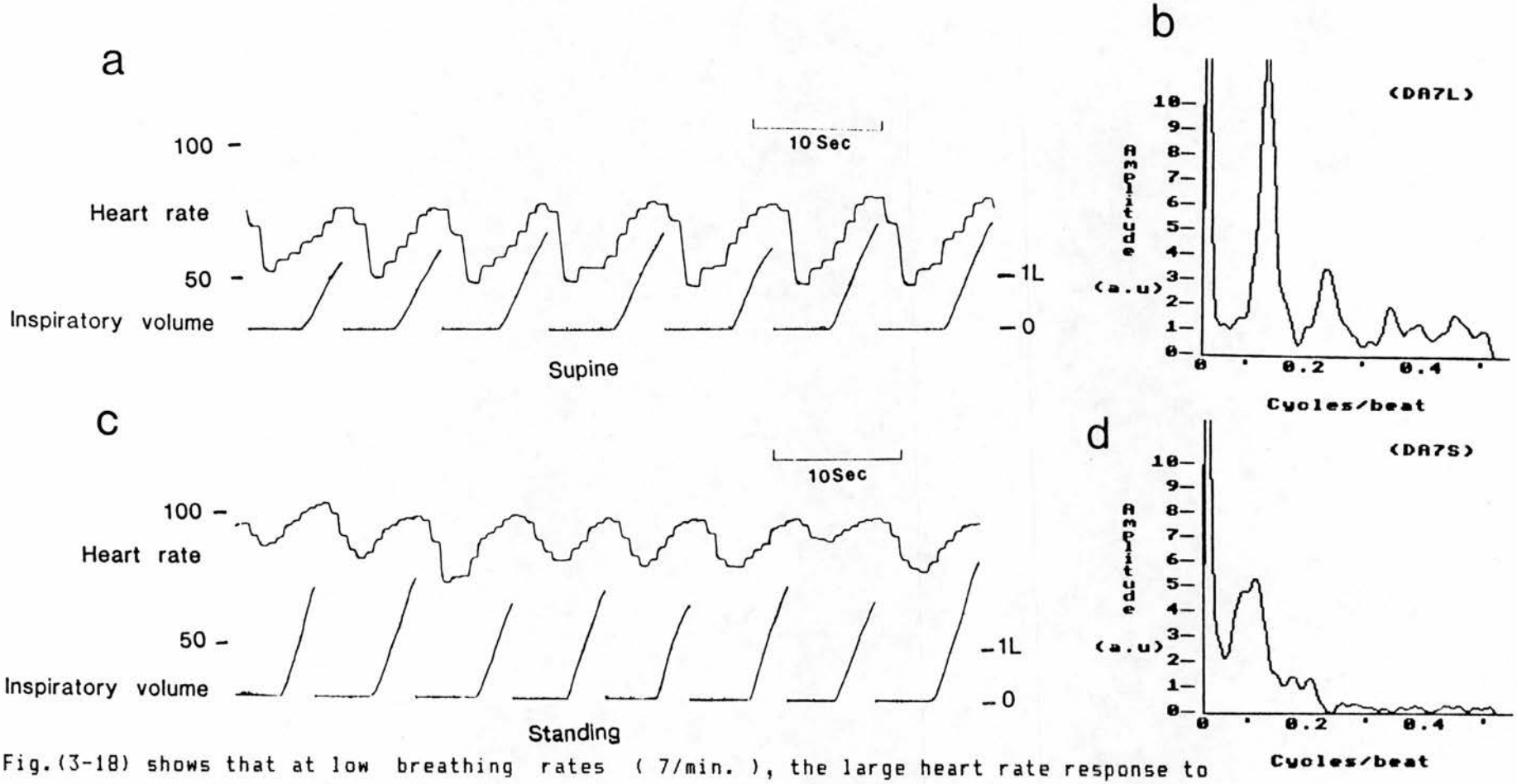


Fig.(3-18) shows that at low breathing rates (7/min.), the large heart rate response to respiration is probably due to the combination of both "RSA" and "10 second" rhythms. During standing the amplitude of the heart rate changes decreases, most likely due to the decrease in the "RSA" component.

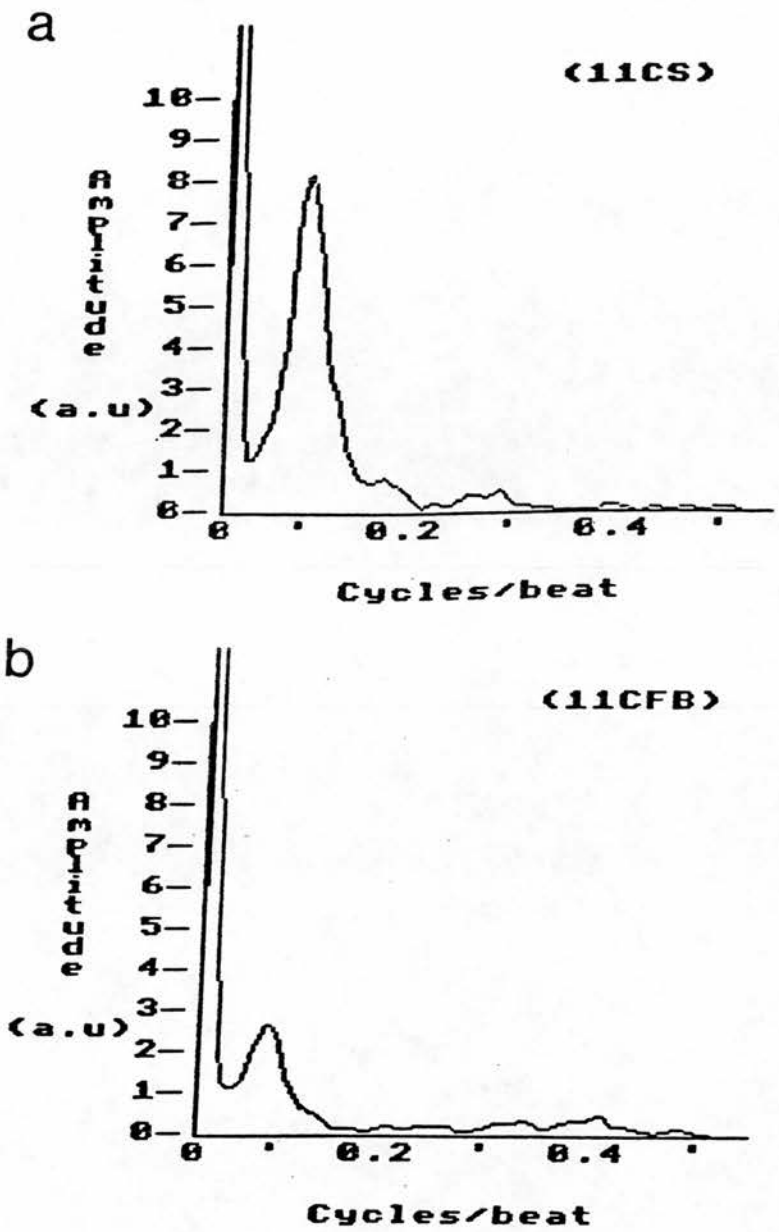


Fig.(3-19) shows a very large peak at low frequency during standing when the subject was breathing at 6/min. in (a). When the two components (i.e."RSA" and "10 second" rhythm) were disengaged by breathing faster and shallower in (b), the peak at the low frequency decreased in size as it represented then the "10 second" rhythm only.

N.B. The amplitudes of the spectra in this figure have been halved because of the extra-large size of the peak in (a).

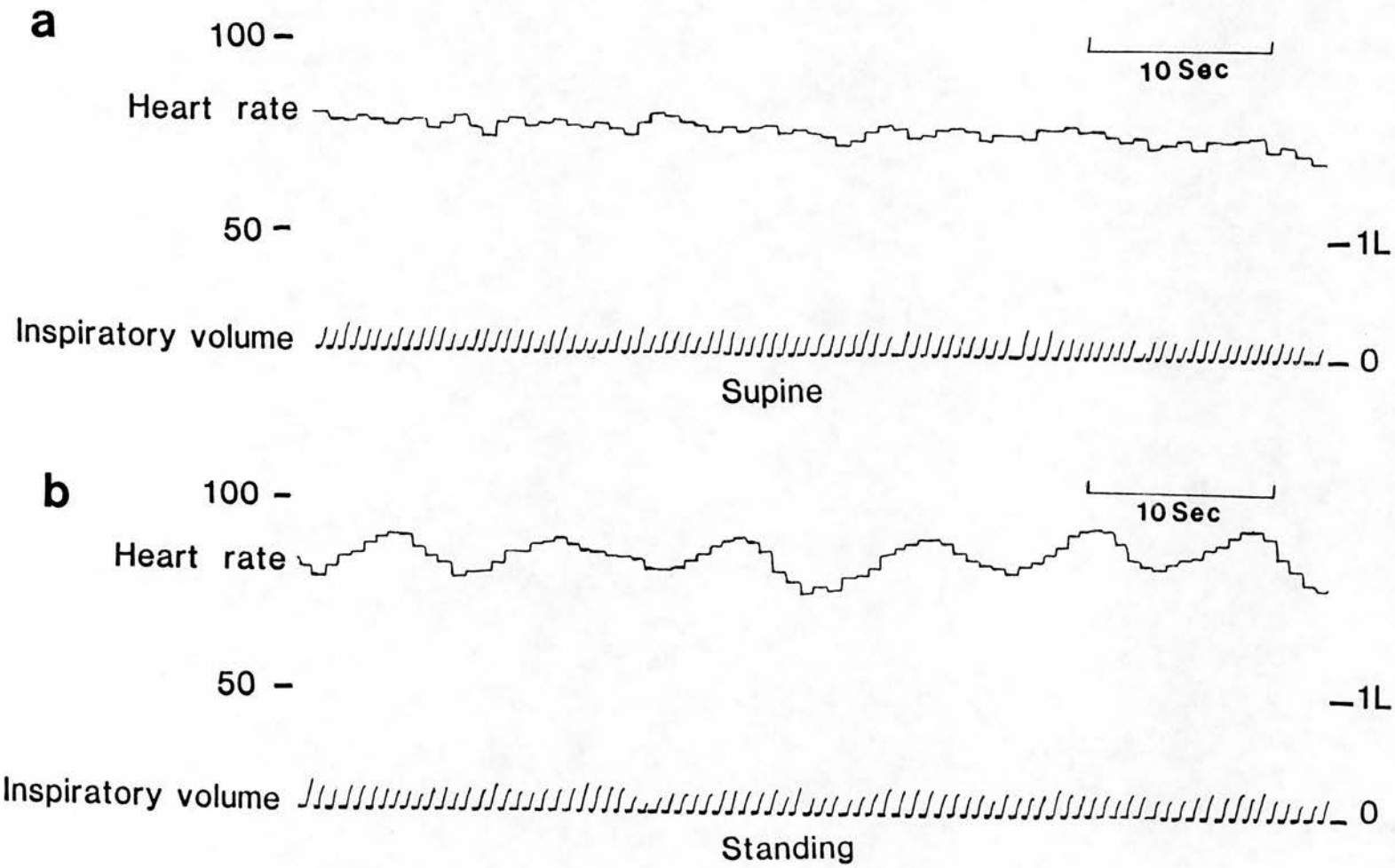


Fig.(3-20) shows that fast shallow breathing by itself could not induce the "10 second" rhythm during the supine posture in (a), while this rhythm was clearly seen during the same breathing manoeuvre in the standing posture in (b).

in the same day, or on different days .

The effect of change of posture from supine to maintained standing was repeated in 24 oscillators on the same session. The result in one subject is illustrated in Fig. (3 - 21). As can be seen from the figure, every time the subject was in the supine position (a and c), the heart rate spectrum was dominated by a large peak at the respiratory frequency ($\sim$ 0.2 cycles/beat), which reflected the prominent "RSA" rhythm. During maintained standing (b and d), however, the respiratory peak ($\sim$0.15 cycles/beat) was very small, and the peak at $\sim$ 0.1 cycles/beat, reflecting the "10 second" rhythm was the predominant one.

Fourteen oscillators with a prominant "10 second" rhythm during maintained standing, participated in experiments conducted on different days. The change in heart rate pattern between supine and maintained standing postures was consistent, even when the time lapse between the two days of experiments was up to 2 years.
Fig.(3 - 22) shows the heart rate pattern during maintained standing in three subjects on two different days (A and B). In all the subjects, the heart rate spectra were very similar on both days, with the peak at$\sim$0.1 cycles/beat clearly predominant.

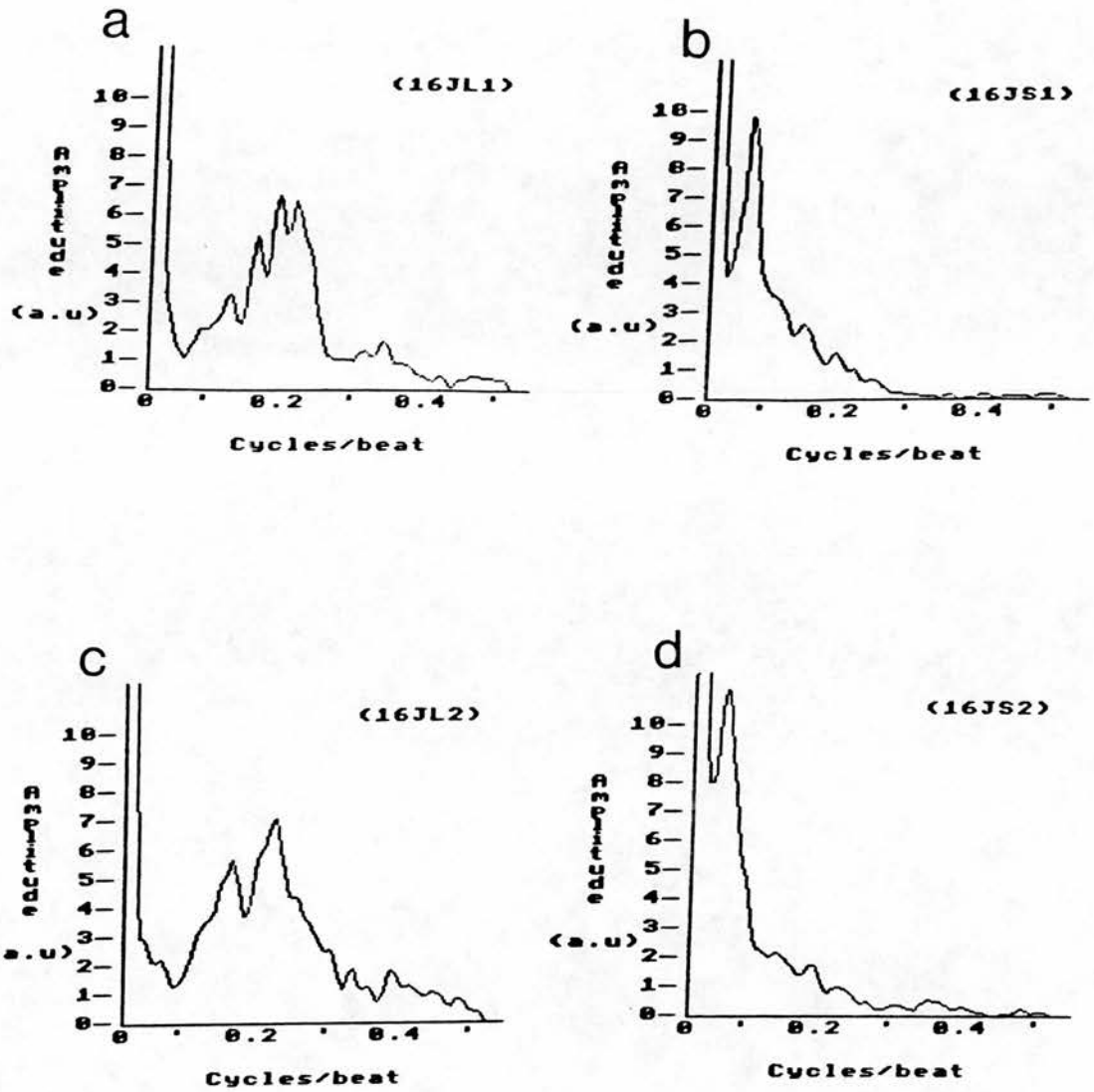


Fig.(3-21) shows the consistency of the phenomenon in one of the oscillators who repeated the act twice in the same session. In the supine posture (a & c), the large peak is at the respiratory frequency (~0.2 cycle/beat), while during standing (b & d), the large peak is at the lower frequency (~0.1 cycle/beat).

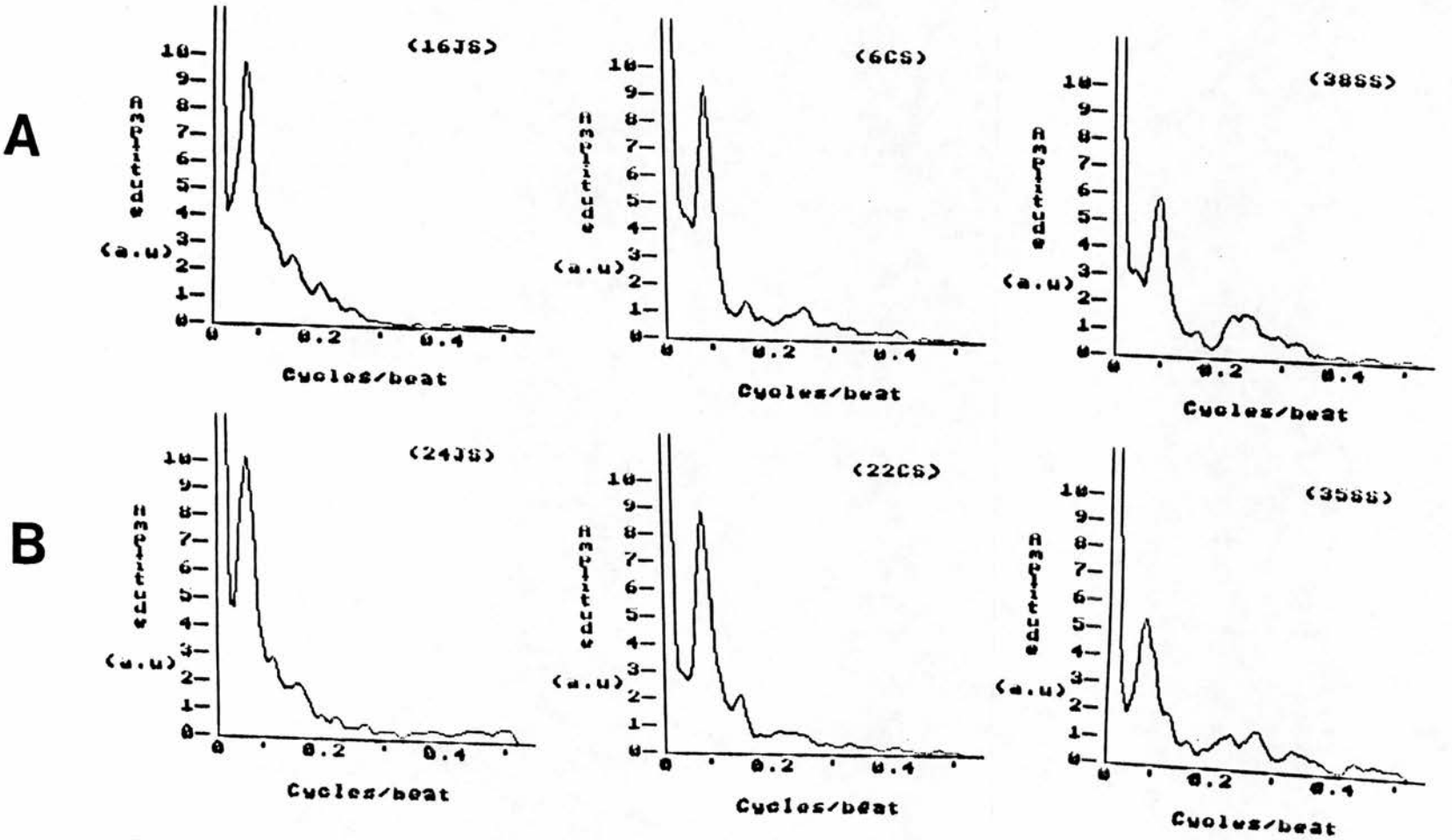


Fig.(3-22) shows the consistency of the phenomenon of repetition of the act of changing posture on different days. During standing, the heart rate spectra of three oscillators showed prominent peaks at the low frequency on both day A and B.

DISCUSSION

Effect of posture on MHR

When the supine-standing manoeuvre was repeated twice in the same session, it was found that the MHR during maintained standing was not significantly different between the two acts. But, Δ HR was significantly smaller in the first act because of the significantly higher supine MHR .

The significantly higher supine MHR in the first act was consistently found in all the 33 subjects who repeated the act twice . It might have been due to the excitement and worry in the beginning of the session, but this seems to be unlikely as subjects were informed of the simple, non-invasive nature of the experiment and allowed time to get accustomed to breathing through the pneumotachograph. Moreover, it was consistently found even in those subjects who repeated the manoeuvre several times on different days and were well aware of the nature of the experiment and the technique involved. Furthermore,the parts of the records chosen for analysis were the last few minutes during lying, when the heart rate was stabilised.

This effect of repeating the act of supine-standing manoeuvre on MHR during supine and maintained standing postures has not been described previously. However ,results of the effect of repetition of the act of standing up on the initial tachycardia have been reported. The increment in heart rate on standing was found to be not significantly different when the subjects repeated the act for a second and even a third time in quick succession (Ewing et al

1980). However, Wieling (1983) showed that a longer period of rest prior to standing, increased the increment in heart rate.

When comparison of MHR on two different days was made, it was found to be not significantly different either in the supine or standing posture. Moveover, the $\triangle$ HR, too, was not significantly different on the two occasions. This shows that intra-individual variation in these parameters is small in contrast to the large inter-individual variations.

In most subjects, the MHR during maintained standing was higher than supine MHR, however, in one subject the standing MHR was only 1 bpm higher, and in another subject it was 1 bpm lower than supine MHR .

Failure of the heart rate to increase adequately after standing is thought to be due to impaired sympathetic drive in patients with autonomic neuropathy, leading to postural hypotension (Bennett et al 1975). However, it is reported here, almost no change and even a decrease in MHR during maintained standing in healthy, young subjects, with no symptoms of postural hypotension. Earlier studies with large samples of volunteers (Schneider & Truesdell 1922 , Currens 1948) also reported "no change" and "decrease" in MHR during standing in normal people.

The increase in MHR during the change of posture ($\triangle$HR) was negatively correlated with supine MHR . A similar correlation was reported by Lindblad et al (1981).

Subjects with low heart rates in the supine posture have high levels of muscle sympathetic activity (MSA) (Bath et al 1981).

Thus, during standing, when there is increased sympathetic stimulation, these subjects would have had limited reserve to increase their MSA, instead, they increase their heart rate more to compensate for relatively smaller increase in TPR. Therefore, inter-individual differences in cardiac acceleration during postural stress are related to inter-individual differences in muscle sympathetic activity in the supine position (Lindblad et al 1981). This confirmed an earlier prediction that pre-existing background autonomic activity profoundly influences the baroreceptors - induced changes in heart rate (Robinson et al 1966).

Effect of posture on MAD & CV%

The combined results of statistical indices and spectral analysis showed that the changes in MAD followed very closly the changes in the amplitude of the peak at the respiratory frequency which represents "RSA". Therefore, although MAD measures the beat-by-beat differences, it also reflects the variation at high frequencies(i.e."RSA").

The significant negative correlation between MHR and MAD is in agreement with the results obtained using other indices of short term variability such as MSSD (Ewing et al 1981 a). The reduction in MAD during standing is in line with the general view that there is less vagal tone during head-up posture (Robinson et al 1966) as MAD was shown to be mediated largely by the parasympathetic system (chapter VIII, Dalton et al 1983).

It could be argued that the decrease in MAD was merely due to the increase in MHR during standing, but the finding of a significant

decrease in normalised MAD (MAD%) showed that there was a genuine reduction in MAD.

During standing, with the significant reduction in MAD and the significant positive correlation between MAD and CV%, one would anticipate a significant reduction in CV%, but that was not the case. The CV% during standing was only slightly lower than supine CV% .

The CV% was introduced by Yeh et al (1973) as a measure of LTV and others followed (Kariniemi & Hukkinen 1977, Laros et al 1977, Stallworth et al 1981, Kariniemi & Ammala 1981, Kariniemi et al 1982). LTV was defined as the changes in heart rate that occur at the rate of 3-5 cycles /min.(Yeh et al 1973).

Following other authors, initially it was decided to use the CV% as an index of the slow oscillations in heart rate that occur at the mean rate of 6 /min.("10 second" rhythm). However, the results of CV% failed to follow the changes in this rhythm. This is because CV% measures the total variability including long term variability (LTV) as well as short term variability (STV) rather than LTV alone.

On this basis and with the help of the schematic diagram shown in Fig.(3 - 23),an explanation of the changes in LTV and STV during changes of posture is given below.

In (a) of Fig. (3 - 23) the LTV and STV are almost equal in size. The CV% is the sum of the two, but the net result (the difference between the two) is zero, thus no slow oscillations in heart rate records (-). This occurs in the supine posture or during standing in the "non-oscillators".

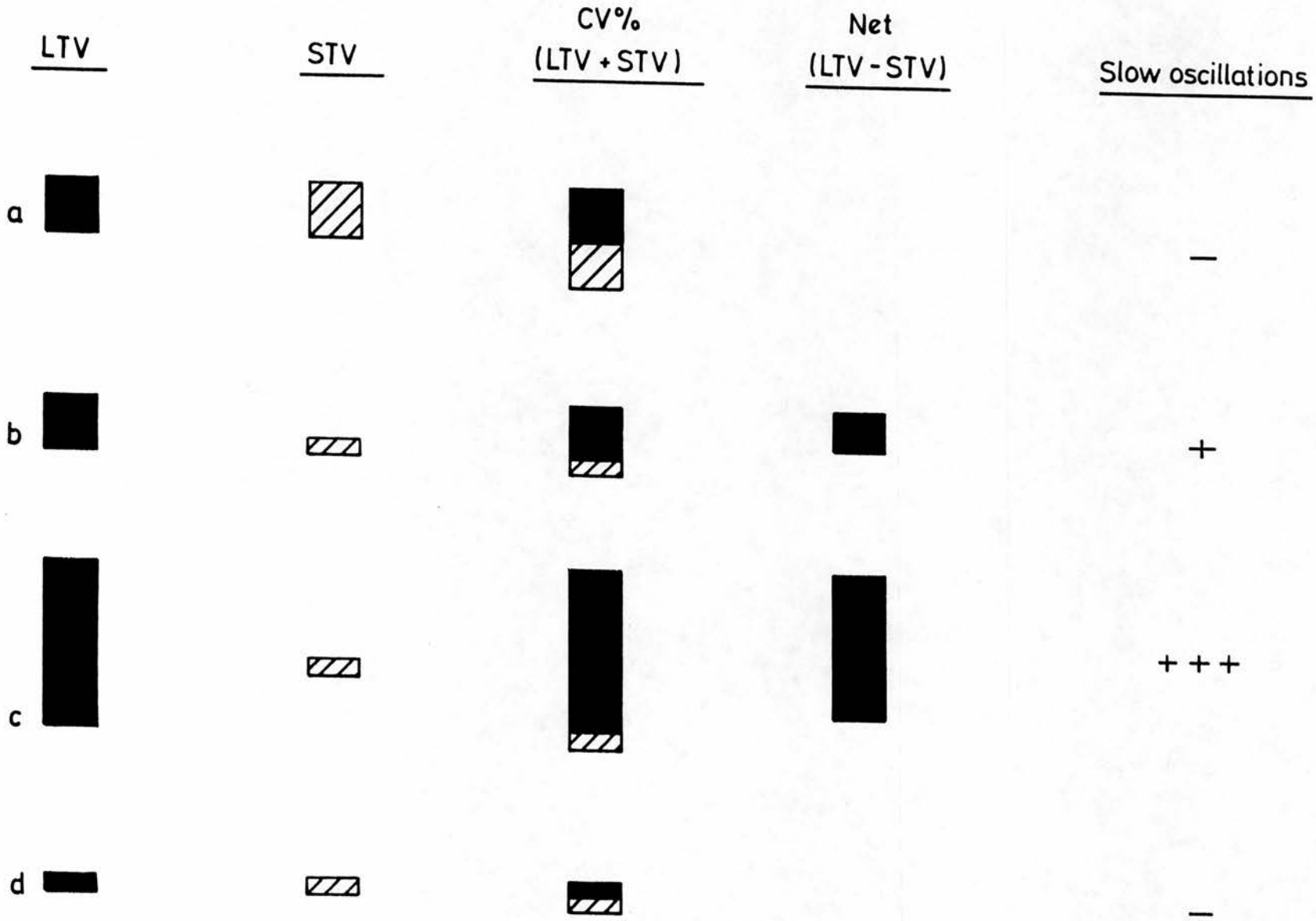
In (b), LTV stays the same, but STV decreases which leads to a

Fig.(3-23). This diagram illustrates schematically the changes in long term variability (LTV), short term variability (STV) and total variability (CV%) based on the assumption that CV% measures the sum of LTV and STV. The difference between the latter two (net) determines the amplitude of the slow "10 second" oscillations in the heart rate records.

- the "10 second" rhythm is absent.

+ the "10 second" rhyhthm is present.

+++ the "10 second" rhythm is present and of a large size.


LTV
STV
CV%
(LTV + STV)
Net
(LTV - STV)
Slow oscillations
a
b
c
d
—
+
+ + +
—

reduction in the total variability (CV%). However, the difference between LTV and STV is more than zero, and this is reflected by the positive sign in the slow oscillations column (+), which indicates a relative increase in LTV , as it occurs in some oscillators during standing.

In other oscillators,in addition to the decrease in STV during standing ,there is a concurrent increase in LTV as in (c) of Fig. (3 - 23). This leads to an increase in the total variability (CV%) and a bigger amplitude slow oscillations in heart rate records (+++), due to a larger difference between LTV and STV.

It is important to re-emphasize that CV% does not measure LTV alone. Conclusions about LTV can sometimes be drawn from the combined results of a total variability index such as CV% and an STV index such as MAD.

Effect of posture on HRV

It has been shown that the change of posture from supine to maintained standing can bring about a remarkable change in heart rate pattern (Sattar & Young 1983).

In the supine posture, the predominant rhythm was the respiratory sinus arrhythmia while during standing , slower "10 second" oscillations, that were not related to respiration in any fixed ratio, were predominant.

This dramatic change in heart rate pattern during maintained standing occurred only in about half the subjects studied (48%) and this held true even when young subjects only (<30 yr.) were considered (54%). The other half showed no change in rhythm and

the respiratory sinus arrhythmia was still predominant during standing with a smaller amplitude usually.

This seems to be at variance with a more recent report in which the effect of standing was described to be universal in all the subjects studied (Pomeranz et al 1985).

The discrepancy between the results probably stems from the fact that in this study a larger number of subjects (75 compared with only 8) of both sexes (rather than males only), were included. In addition, the subjects were breathing freely in contrast to those of Pomeranz et al (1985) who were breathing in synchrony with a metronome. The use of fixed breathing frequency was shown to cause enhancement in vagal tone (Pagani et al 1986) with a possible reciprocal reduction in sympathetic tone (Kollai & Koizumi 1979). This disturbance in the autonomic control of supine heart rate might have affected the response to the postural stress (Robinson et al 1966).

Moreover, in the present investigation, details of various combinations of rhythms in different subjects are given.

In the earlier report (Sattar & Young 1983), two types of oscillators during maintained standing were described. In some, the slow "10 second" oscillations has replaced the "RSA" completely for a considerable period, while in others there was a combination of both the "10 second" rhythm and "RSA".

Spectral analysis, later, confirmed this with the first group of oscillators showing a prominent single peak at the "10 second" rhythm frequency, whereas the second group who showed a combination of both rhythms, exhibited two peaks in their heart rate spectra; one at the "10 second" frequency and the other at the respiration

frequency with the former peak being larger in size.

Furthermore, it was recognised that in few subjects, the "10 second" rhythm could be seen in the supine posture, but became more prominent during standing (Sattar & Young 1983).
Spectral analysis showed that most subjects do exhibit a peak at the "10 second" frequency in the supine posture , but only in a few, this peak was of sufficient amplitude to make the "10 second" rhythm prominent. In addition, in the supine posture, most subjects had a sizeable peak at the respiratory frequency which overshadowed the other peak at the lower frequency.

The results showed that the switch in pattern from predominantly "RSA" rhythm in the supine posture to predominantly "10 second" rhythm during standing, can be achieved through different mechanisms.
Some subjects have a prominent single peak at the respiratory frequency in the supine posture, while during standing they have a prominent single peak at the "10 second" frequency .
In others, both peaks are present during both supine and standing postures, but it is the ratio between the two peaks that determines the predominant rhythm exhibited in the heart rate records. In the supine posture, usually the respiratory peak is large enough to make "RSA" rhythm predominate, while during standing this peak decreases and is often accompanied by an increase in the size of the "10 second" peak, thus leading to a ratio in favour of the "10 second" rhythm .
Pomeranz et al (1985) described the heart rate pattern in all the subjects as having a prominent respiratory peak in the supine

posture and a prominent peak at low frequency during standing. These results from eight highly selected subjects (all young men) did not show the different varieties of heart rate patterns observed in the present investigation. Furthermore, the switch in pattern with the change in posture was found to involve usually a quantitative change in the ratio between the two peaks, rather than a completely different peaks in each posture as was suggested by them.

When the MHR was compared between the "oscillators" and the "non-oscillators" in all the 75 subjects, the results confirmed the earlier observations on 59 subjects (Sattar & Young 1983). The supine MHR was not significantly different in the two groups, however, the MHR during standing and ΔHR in the "oscillators" were both significantly higher than in the "non-oscillators" in spite of a wide overlap.

So, it seemed that the presence of these slow oscillations was associated with a higher MHR during standing and a larger Δ HR. However, individual results did not conform to this rule. Notable examples were the two subjects shown in Fig (3 - 7) and (3 - 8). The subject in Fig (3 - 7) had a MHR of 82 bpm during standing and she showed "10 second" oscillations .In contrast, the subject in Fig. (3 - 8) showed no slow oscillations during standing in spite of having a higher MHR (91 bpm) and in the same age group (< 30 yr.) as the other subject.

Also, in those subjects who showed the "10 second" rhythm, it was found that this could temporarily disappear and be replaced by "RSA" without any change in mean heart rate (Fig. 3-24).

A similar phenomenon was seen with respect to "RSA" (Fig. 3-25). As

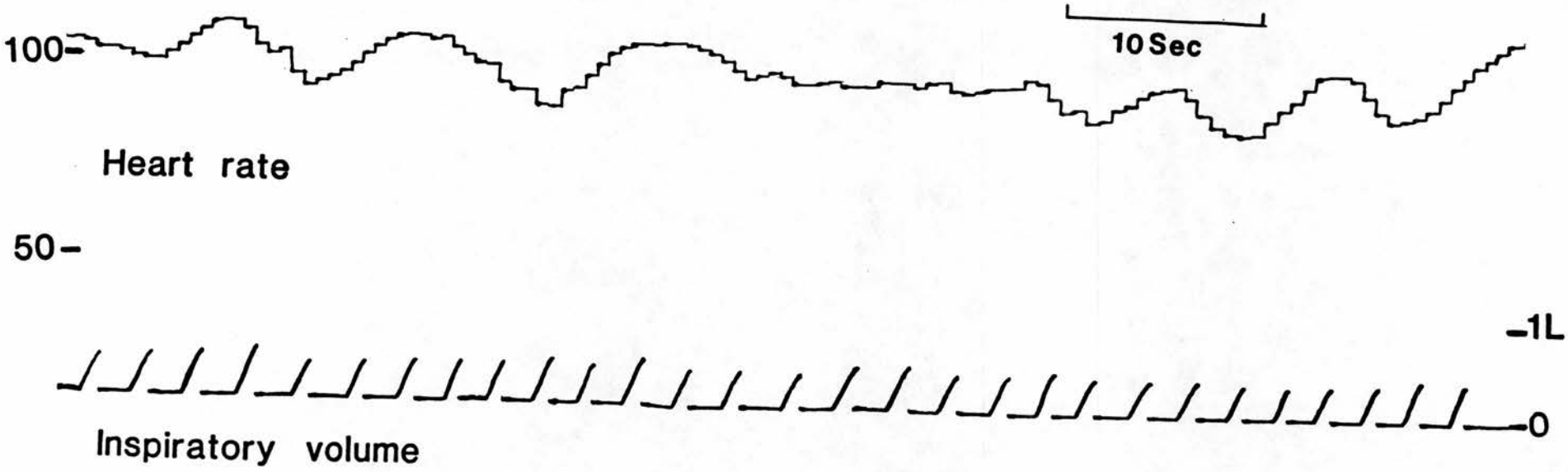


Fig.(3-24) shows the change in heart rate pattern from "10 second" rhythm to "RSA" then back to "10 second" rhythm without any change in mean heart rate over these three periods that lasted about half a minute each.

can be seen from the figure, only five out of the fourteen breaths are associated with prominent "RSA" in spite of fairly constant respiratory depth and mean heart rate.

Another example of the difference in heart rate pattern without an appreciable change in mean heart rate is shown in Fig (3 - 26). The subject in (a) had a slow MHR of 51 bpm, indicative of high vagal tone. In such a healthy young man in the supine position, a large amplitude "RSA" would be anticipated (Wheeler & Watkins 1973), but the heart rate was almost flat during normal breathing. In contrast, the subject in (b) had the same MHR but she showed a good size "RSA" inspite of the slightly smaller tidal volumes. The subject in (a) had an intact parasympathic pathway , as he was able to produce large heart rate variations in response to deep breathing .

Previously, it has been shown that the maximum response of heart rate to respiration occurs at a breathing rate of 5-7 per minute (Clynes 1960, Angelone & Coulter 1964, Kelman & Wann 1971).

Subsequently, many of the investigations that were carried out purpoting to study "RSA" (e.g. Melcher 1976) used slow breathing rates (6 / min.) to get the best response. However, conclusions about "RSA" from such studies were found to be in conflict with others (DeBoer 1985). This is probably due to the finding reported in this study that at these slow breathing rates the heart rate response is not purely due to the changes related to respiration, but most likely a combination of "RSA" and the "10 second"rhythm.

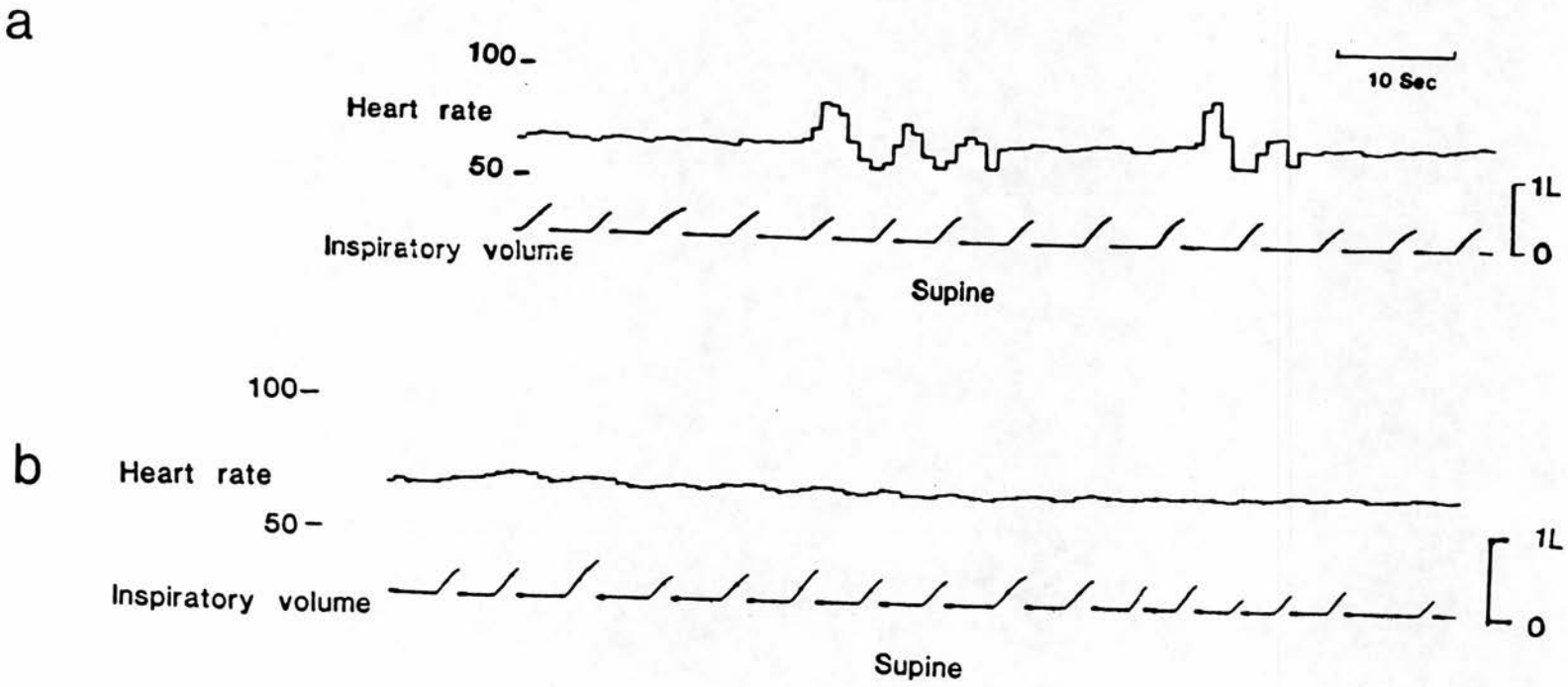


Fig.(3-25) shows the alternating heart rate pattern without any change in mean heart rate in (a). The big amplitude heart rate changes were abolished by 0.02 mg./kg. atropine in (b), suggesting that they were parasympathetically mediated.

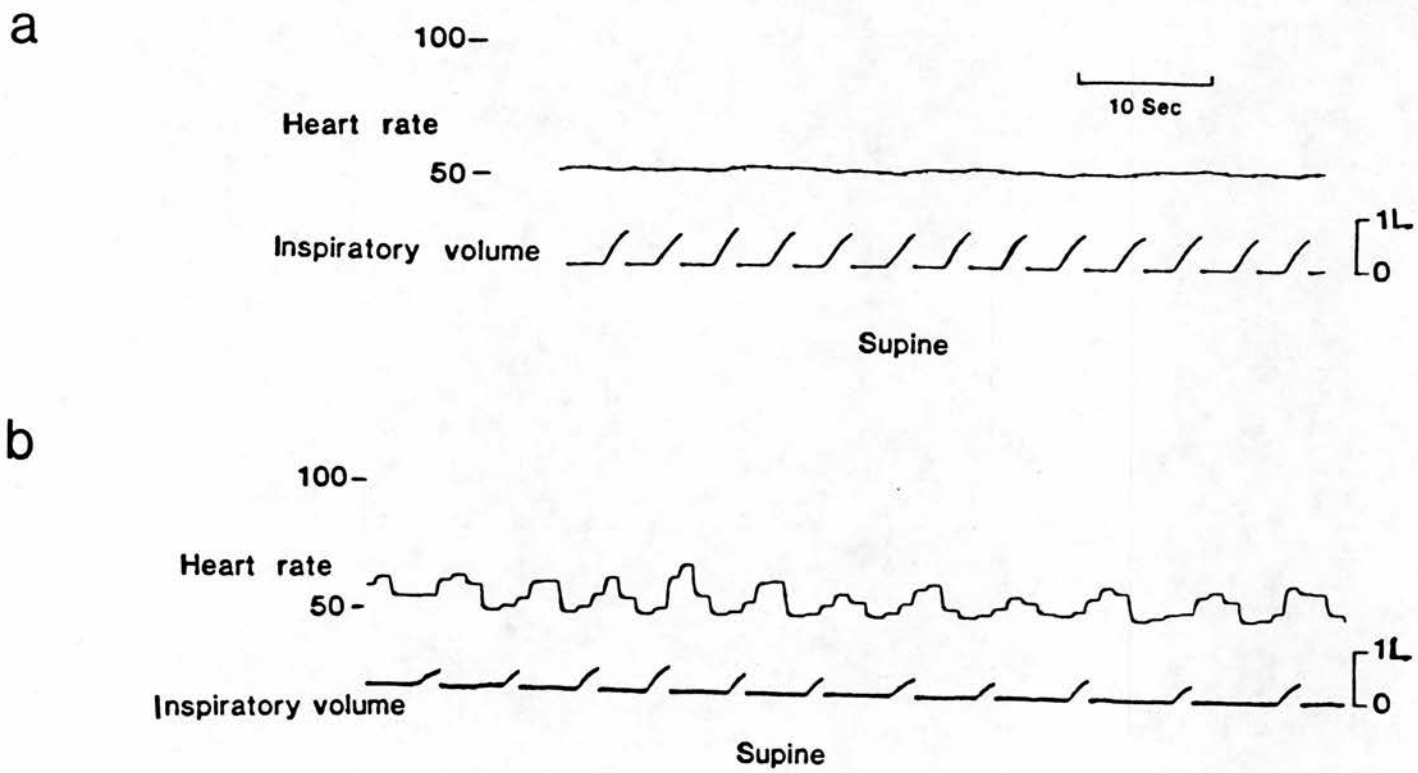


fig.(3-26) shows two young healthy subjects, both having the same MHR of 51 bpm, but the subject in (a) failed to show "RSA" despite having larger tidal volumes.

CHAPTER IV

RELATION OF AGE TO "HRV"

INTRODUCTION

It is often stated that cardiovascular responses diminish with advancing age, but this has been questioned recently. The cardiac output during resting supine position was shown to be reduced in old subjects (Brandfonbrener et al 1955, Strandell 1964, Lee et al 1966, Smith et al 1987). However, a significant reduction in cardiac output in the elderly subjects was not found in a recent study (Rodeheffer et al 1984).The difference in the results was attributed to the more sensitive method (i.e. radionuclide imaging) used to exclude those elderly subjects with occult coronary disease from the population study. Vargas & Lye (1982) also found no significant difference in cardiac output in the supine posture between the young and the old, but the response to postural change was significantly different. The decrease in cardiac output and stroke volume during 70° head up tilt was significantly less in the elderly. A similar finding was reported earlier by Strandell (1964) when the subjects changed their posture from supine to sitting.

The initial heart rate response to standing or tilting was also found to be significantly smaller in the old subjects (Norris et al 1953, Page & Watkins 1977, MacKay et al 1980, Wieling et al 1982, Persson & Solders 1983, O'Brien et al 1986, Dambrink & Wieling 1987, Shiraki et al 1987). Contrary to the others, Ewing et al 1978

found no significant relation of age to the 30/15 ratio (the ratio between the RR interval at 30th beat to the RR interval at 15th beat after standing up), but this could be due to the smaller number of subjects they studied (22) compared with the others [e.g. Wieling et al 1982 (133 subjects) , O'Brien et al 1986 (310 subjects)].

Although no significant correlation was found between supine MHR and age (Strandell 1964, Smith & Smith 1981, Sato et al 1981, Vargas & Lye 1982, Persson & Solders 1983, Vargas et al 1984, Rodeheffer et al 1984, Pagani et al 1986), the increase in MHR on changing posture from supine to sitting , standing or tilted upright ($\triangle$HR) was consistently less in the elderly (Strandell 1964, Sato et al 1981, Vargas & Lye 1982, Pagani et al 1986, Smith et al 1987, Dambrink & Wieling 1987).

The cardiovascular changes during exercise was thought also to be affected by the aging process . Earlier workers (Brandfonbrener et al 1955, Strandell 1964) reported a relatively smaller increase in cardiac output during exercise in the elderly, due to a decrease in stroke volume. However, recently this concept of "age limiting the physical capacity" has been questioned too as Rodeheffer et al (1984) showed that the increase in cardiac output during vigorous exercise was not significantly related to age, but the mechanisms involved in maintaining similar cardiac outputs were different. In the young, the increase in cardiac output was mainly through an increase in heart rate, whereas in the elderly, there was a relatively smaller increase in heart rate but this was compensated by an increase in the stroke volume. Mann et al (1986) were in

agreement with the above, except that they found there was an increase in heart rate in addition to the increase in stroke volume, which led to a greater increase in cardiac output during exercise. So, both studies found an increase in stroke volume in the elderly during exercise, in contrast to the finding by earlier workers. Rodeheffer et al (1984) explained the contradictory results on the basis of a better selection of their elderly subjects by the non-invasive method of screening for occult coronary disease. The increase in heart rate in Mann et al (1986) study was most probably due to the different posture adopted (i.e. supine), and the submaximal load of exercise used, because heart rate response to maximum exercise in the supine posture was shown to decline with age (Radice et al 1982).

Heart rate changes with respiration ("RSA") was shown to decrease with advancing age (Jennett & McKillop 1971,Wheeler & Watkins 1973, Hellman & Stacy 1976, Waddington et al 1979, Cicmir et al 1980, MacKay et al 1980, Sato et al 1981, Smith & Smith 1981, Chipps et al 1981, Hirsch & Bishop 1981, Weiling et al 1982, Smith 1982, Persson & Solders 1983, Pfeifer et al 1983, Masaoka et al 1985, O'Brien et al 1986). This was thought to be due to a decreased vagal tone (Wheeler & Watkins 1973), as atropine resulted in a smaller increase in heart rate in the elderly (Dauchot & Gravenstein 1971).

Since age was shown to affect the amplitude of the "RSA" and the initial response to standing or tilting, it could , also, affect the response of the heart rate pattern to change of posture. Therefore, it was decided to study the effect of change of posture in two different age groups.

METHODS

Subjects

Eight young subjects (18 - 21) years (4 male, 4 female) with a mean age of 19.3 ± 0.3 were compared with eight older subjects (40 - 65) years (2 male, 6 female) with a mean age of 47.9 ± 2.9. To exclude any bias in selecting the young subjects, the first 8 young subjects were chosen for this comparison. The physical characteristics of the two groups are shown in Tables (4 - 1) and (4 - 2).

Experimental protocol

As described in chapter III.

Analysis

As described in chapter II.

Statistical analysis

For the comparison of mean heart rate (MHR) between the two groups, unpaired -t-test was used ,while the paired-t-test was used for the comparison of MHR between different postures in each group.
For the comparison of mean absolute difference (MAD) and Interval Index (CV%) between the two groups, Mann-Whitney U test was used, while the Wilcoxon signed rank test was used for the comparison of MAD & CV% between different postures in each group.

	Sex	Age	Ht.(cm)	Wt.(kg)
1.	F	20	155	51
2.	F	19	160	55
3.	M	19	175	70
4.	M	21	176	79
5.	M	19	184	100
6.	F	19	163	61
7.	M	19	173	67
8.	F	18	163	58
Mean		19.3	168.6	67.6
± SEM		0.3	3.5	5.6

Table (4-1). Physical characteristics of the young subjects.

	Sex	Age	Ht.(cm)	Wt.(kg)
1.	M	52	174	67
2.	F	43	149	46
3.	M	51	168	64
4.	F	47	152	57
5.	F	40	165	56
6.	F	42	150	68
7.	F	65	151	65
8.	F	43	160	54
Mean		47.9	158.6	59.6
±SEM		2.9	3.4	2.8

Table (4-2). Physical characteristics of the older subjects .

RESULTS

MHR

The individual MHR for the two groups (the old and the young) in the supine and standing postures and the difference between the standing and the supine MHR ($\triangle$ HR) are shown in Table (4-3). In both groups, the MHR during standing was significantly ($P<0.001$) higher than the supine MHR (Fig. 4 - 1). In both supine and standing postures there was no statistically significant difference in MHR between the two groups (Fig.4-2), but supine MHR in the old group (71.5 $\pm$ 3.6) was slightly higher than the supine MHR in the younger group (69.5 $\pm$ 3.3). However, during maintained standing the MHR for the old (82.1 $\pm$ 2.6) was slightly lower than the MHR for the young (87.0 $\pm$ 5.6).

The real difference between the two age groups was in the amount of increase in MHR during maintained standing ($\triangle$ HR). The young group had a bigger $\triangle$ HR (17.5 $\pm$ 2.9) than the old (10.4 $\pm$ 1.5) ($P<0.05$) (Fig. 4-2).

MAD

Table (4 - 4) shows the individual MAD for all the subjects in both age groups in the supine and standing postures, and also the difference between standing and supine MAD ($\triangle$ MAD).

The MAD in the standing posture was significantly ($P<0.01$) lower than the supine MAD in both age groups (Fig. 4 - 1).

The MAD of the old group was not significantly different from the MAD of the younger group but it tended to be lower in both supine

	Supine		Standing		△ H.R.	
	Old	Young	Old	Young	Old	Young
1.	69	76	84	108	15	32
2.	88.5	67	93	82	4.5	15
3.	59	69	73	87	14	18
4.	72	66	83	88	11	22
5.	58	59	70	69	12	10
6.	80	68	85	76	5	8
7.	74	62	82	73	8	11
8.	71.5	89	86.5	113	14	24
Mean	71.5	69.5	82.1	87.0	10.4	17.5
±SEM	3.6	3.3	2.6	5.6	1.5	2.9

Table (4-3). The MHR during supine and standing postures and the difference between the two (ΔHR) compared between the two age groups.

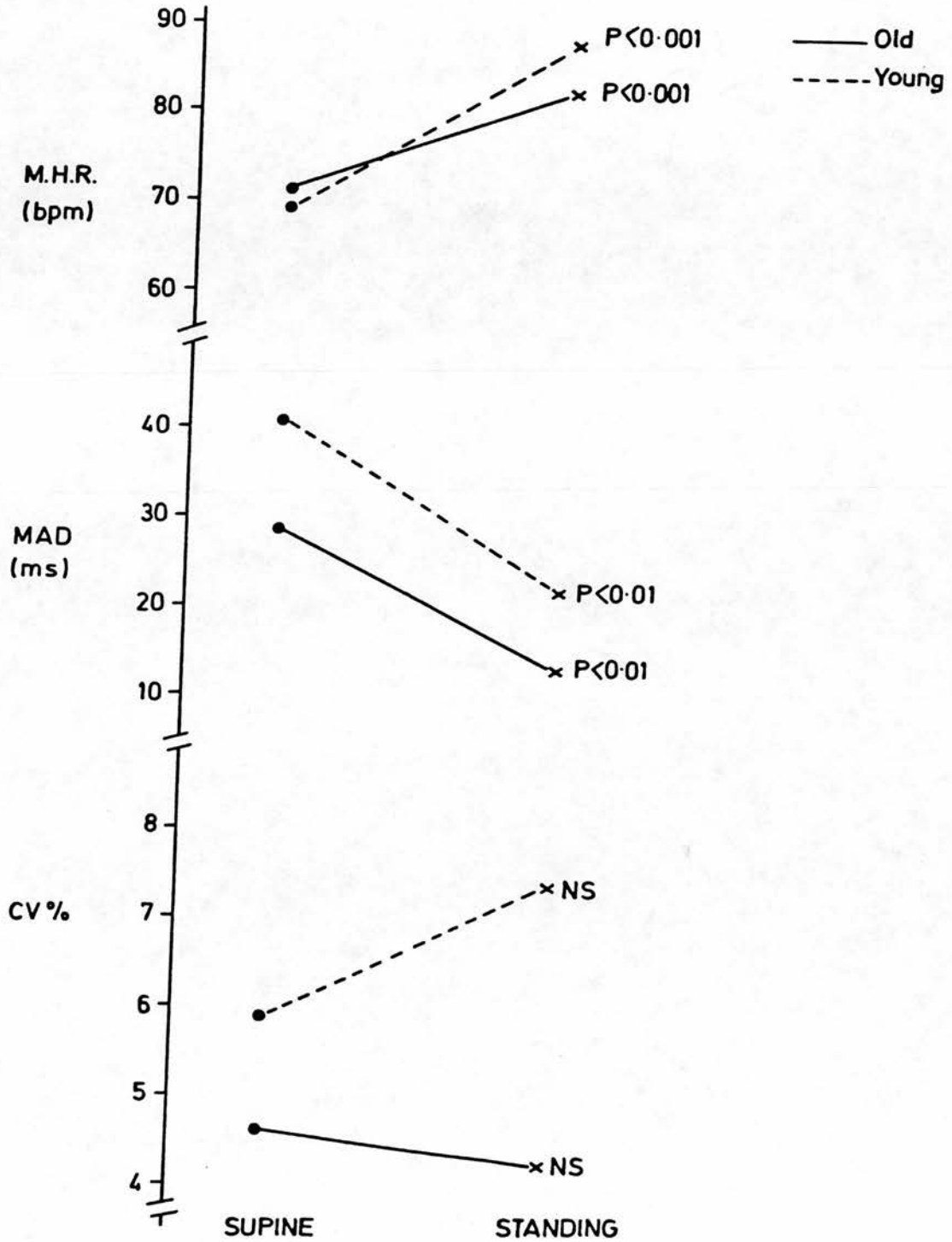


Fig.(4-1) compares the response of MHR, MAD and CV% to the change of posture, in the two age groups. The statistical significance refers to the difference between supine and standing values.

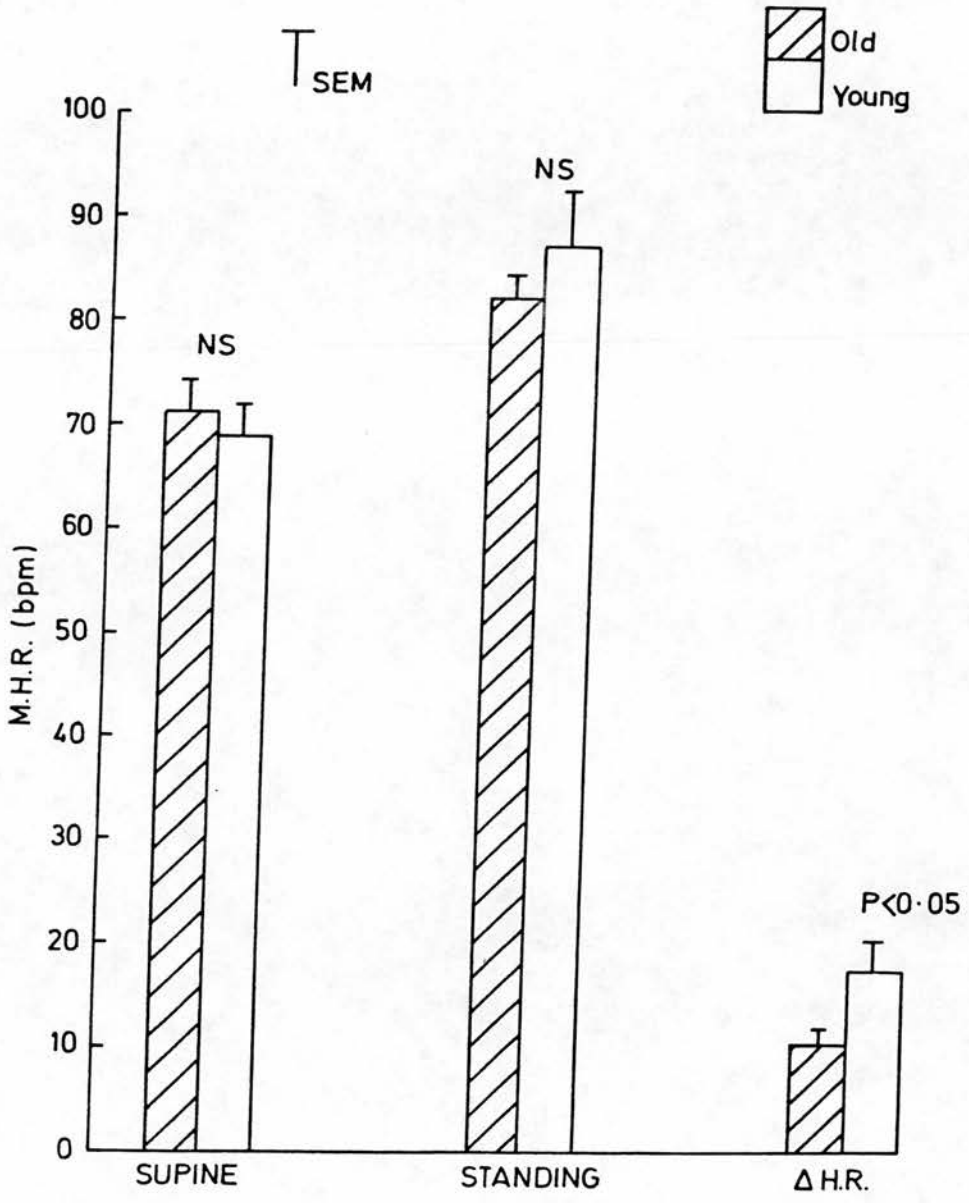


Fig.(4-2) compares between the means of MHR during supine and standing postures and also ΔHR (the difference between standing and supine MHR) in the two age groups.

	Supine		Standing		△ M.A.D.	
	Old	Young	Old	Young	Old	Young
1.	14.7	56.1	9.3	11.5	– 5.5	– 44.6
2.	25.7	43.1	8.3	21.3	– 17.3	– 21.8
3.	69.0	56.8	9.2	21.2	– 59.8	– 35.6
4.	13.8	36.6	12.8	10.3	– 1.0	– 26.3
5.	29.2	48.7	11.2	35.1	– 17.9	– 13.6
6.	28.6	43.6	17.9	39	– 10.7	– 4.6
7.	20.9	29.4	10.0	24.3	– 11.0	– 5.0
8.	26.6	8.6	21.1	5	– 5.4	– 3.6
Mean	28.6	40.4	12.5	21.0	– 16.1	– 19.4
± SEM	6.2	5.6	1.6	4.3	6.6	5.5

Table (4-4). The MAD during supine and standing postures and the difference between the two (△MAD) compared between the two age groups.

and standing postures. Also, the decrease in MAD during standing ($\triangle$ MAD) was slightly lower in the old group (-16.1 $\pm$ 6.6) than MAD of the younger group (-19.4 $\pm$ 5.5) but the difference was not statistically significant (Fig 4 - 3).

CV%

Table (4 - 5) shows the CV% for the individual subjects in both age groups in the supine and standing postures, and also the difference between standing and supine CV% ($\triangle$ CV%).

In the supine posture, the CV% was not significantly different between the two age groups, but standing CV% of the young (7.3 $\pm$ 0.6) was significantly ($P<0.1$) higher than CV% of the old (4.2 $\pm$ 0.6) (Fig. 4 - 4).

This was as a result of the different responses of the two age groups to the stimulus (i.e. standing). Although the change in CV% with the change of posture from supine to maintained standing was not statistically significant in both groups (Fig. 4-1), nevertheless they were in opposite directions. The older subjects decreased their CV% from (4.6 $\pm$ 0.5) during supine posture to (4.2 $\pm$ 0.6) during maintained standing, while the young subjects increased their CV% from (5.9 $\pm$ 1.0) during supine posture to (7.3 $\pm$ 0.6) during maintained standing (Fig. 4 - 1).

The $\triangle$ CV% was also not significantly different in the two age groups, but on the whole, it was positive (1.4 $\pm$ 0.9) in the young group while the mean of CV% for the older group was negative (-0.4 $\pm$ 0.6) (Fig. 4 - 4).

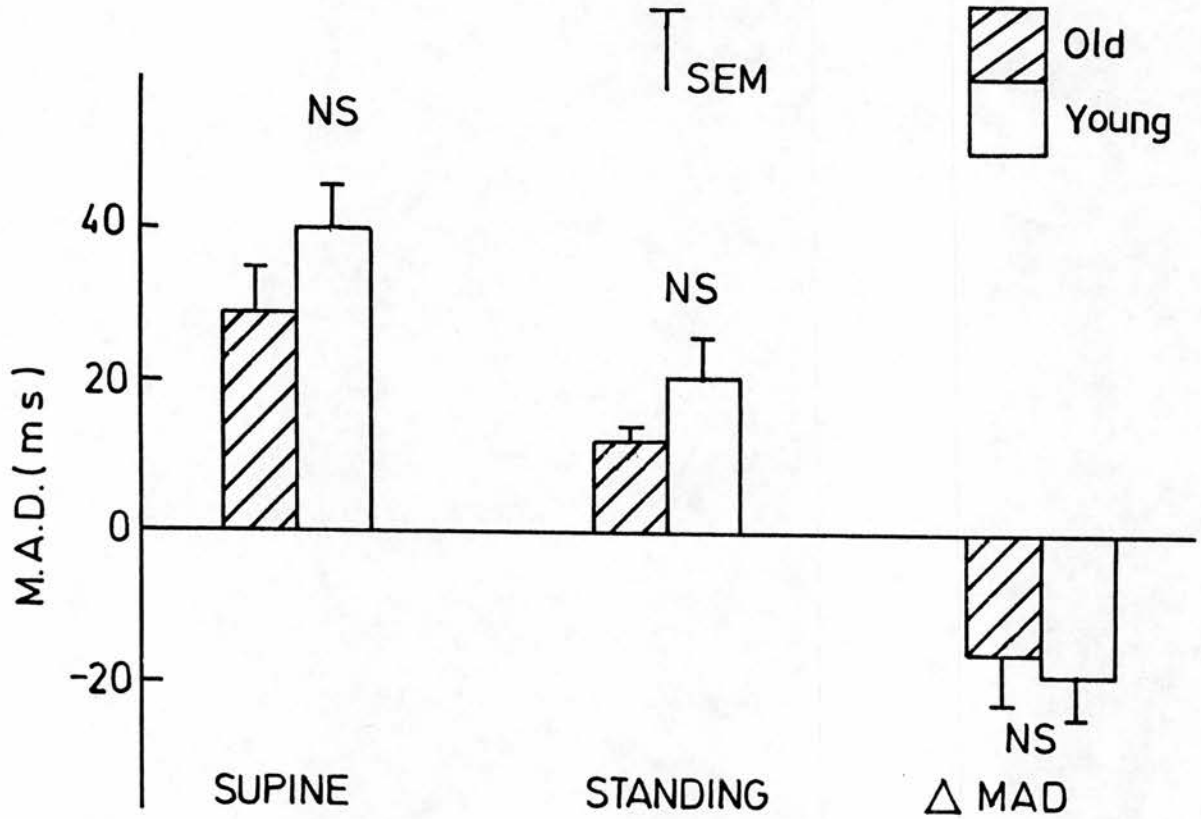


Fig.(4-3) compares between the means of MAD during supine and standing postures and also △MAD (the difference between standing and supine MAD) in the two age groups.

	Supine		Standing		△CV%	
	Old	Young	Old	Young	Old	Young
1.	2.9	11.3	3.6	8.9	0.7	−2.4
2.	5.9	5.2	2.8	9.9	−3.2	4.7
3.	6.5	8.8	3.7	7.0	−2.8	−1.8
4.	3.5	4.3	4.4	5.6	0.9	1.3
5.	4.6	5.5	3.2	7.6	−1.4	2.1
6.	3.8	5.5	4.3	8.0	0.6	2.5
7.	3.5	3.3	3.3	7.1	−0.3	3.8
8.	5.9	3.3	7.9	4.1	2.0	0.7
Mean	4.6	5.9	4.2	7.3	−0.4	1.4
±SEM	0.5	1.0	0.6	0.6	0.6	0.9

Table (4-5). The CV% during supine and standing postures and the difference between the two (△CV%) compared between the two age groups.

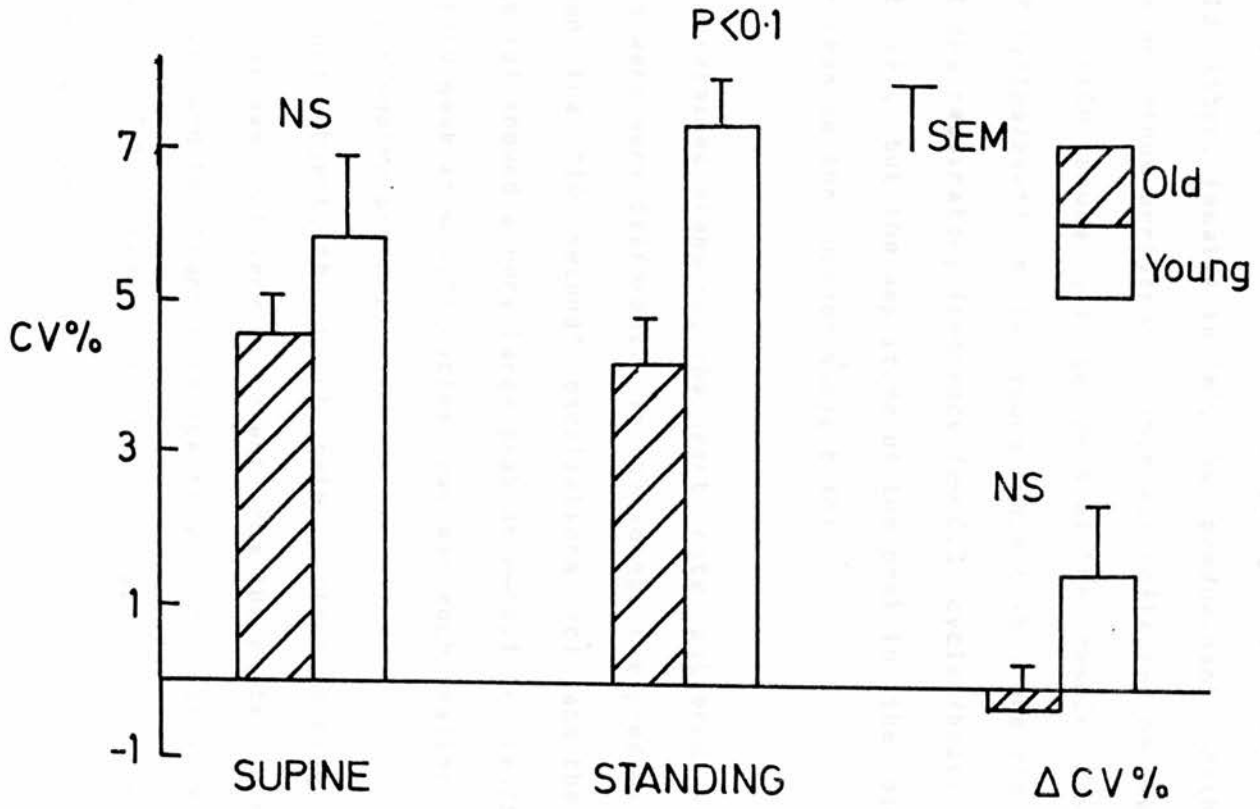


Fig.(4-4) compares between the means of CV% during supine and standing postures and also ΔCV% (the difference between standing and supine CV%) in the two age groups.

HRV

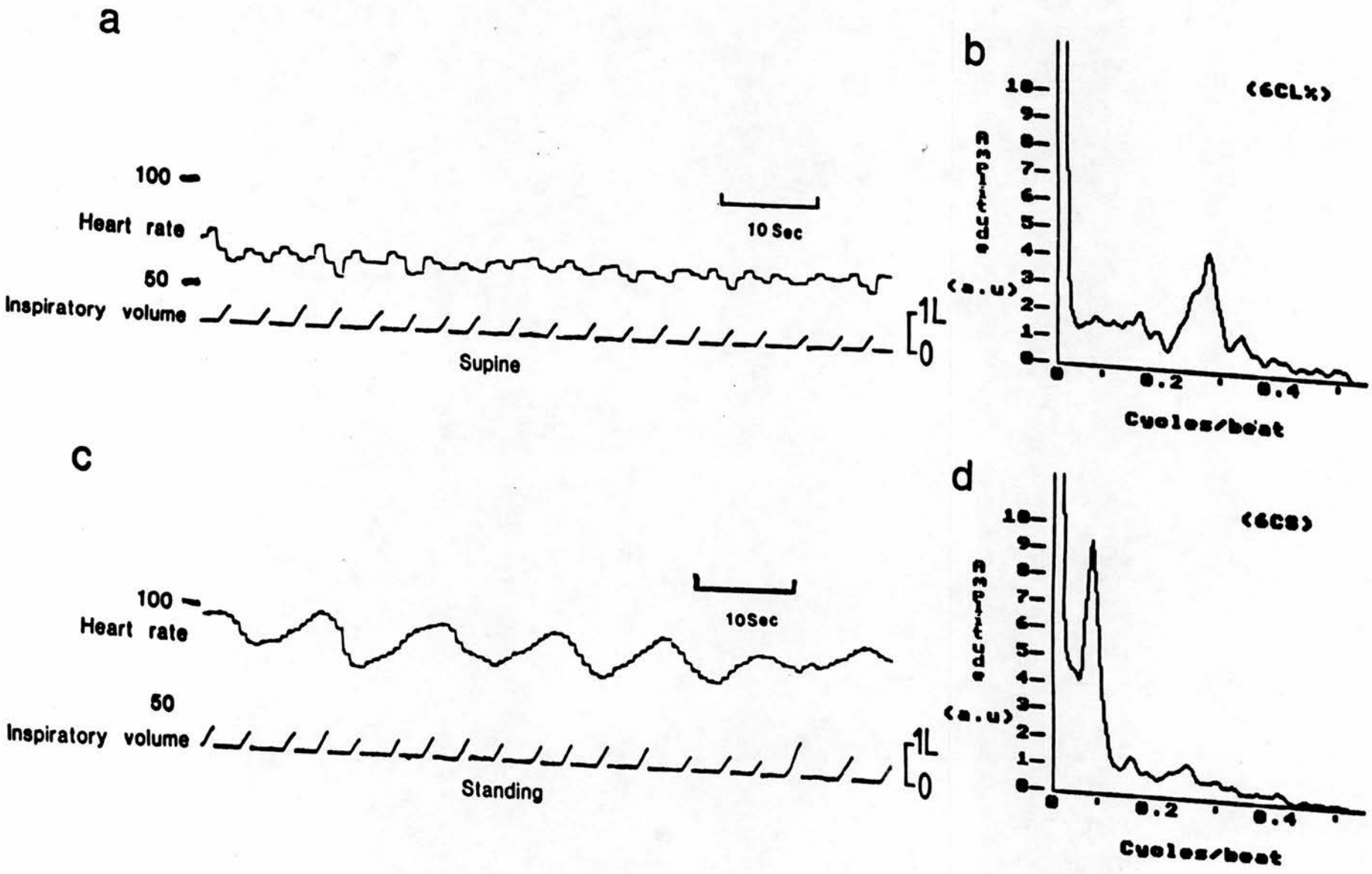
The different heart rate patterns during the change of posture from supine to maintained standing in the two age groups are illustrated in Fig (4 - 5).

During supine posture in both the young (19yr. female) in (a) and the old (65yr. female) in (e), the predominant rhythm was the respiratory sinus arrhythmia. This was reflected on the heart rate spectra which showed a large peak at the respiratory frequency ($\sim$0.27 cycles/beat) in the young subject (b), and also a definite peak at the respiratory frequency ($\sim$ 0.3 cycles/beat) in the old subject (f), but the amplitude of the peak in the old (f) was smaller than in the younger subject (b).

During maintained standing, the heart rate patterns in the two subjects were very different. In the young, the predominant rhythm was then the "10 second" oscillations (c) and the heart rate spectrum (d) showed a very large peak at $\sim$ 0.1 cycles/beat. The respiratory peak at $\sim$ 0.24 cycles/beat was much smaller than it had been during supine posture.

In the old subject, the heart rate pattern during maintained standing (g) was not very different from the pattern during supine posture (e), and the heart rate spectrum in (f) was very similar to the one in (h) except that the respiratory peak at $\sim$ 0.26 cycles/beat was slightly smaller.

So, the dramatic change in pattern from "RSA" during supine posture to "10 second" rhythm during maintained standing in the young subject was completely absent in the older subject. The older


a
100
Heart rate
50
Inspiratory volume
10 Sec
1L
0
Supine
b
(6CLx)
(a.u)
0
0.2
0.4
Cycles/beat
c
100
Heart rate
50
Inspiratory volume
10Sec
1L
0
Standing
d
(6CS)
(a.u)
0
0.2
0.4
Cycles/beat

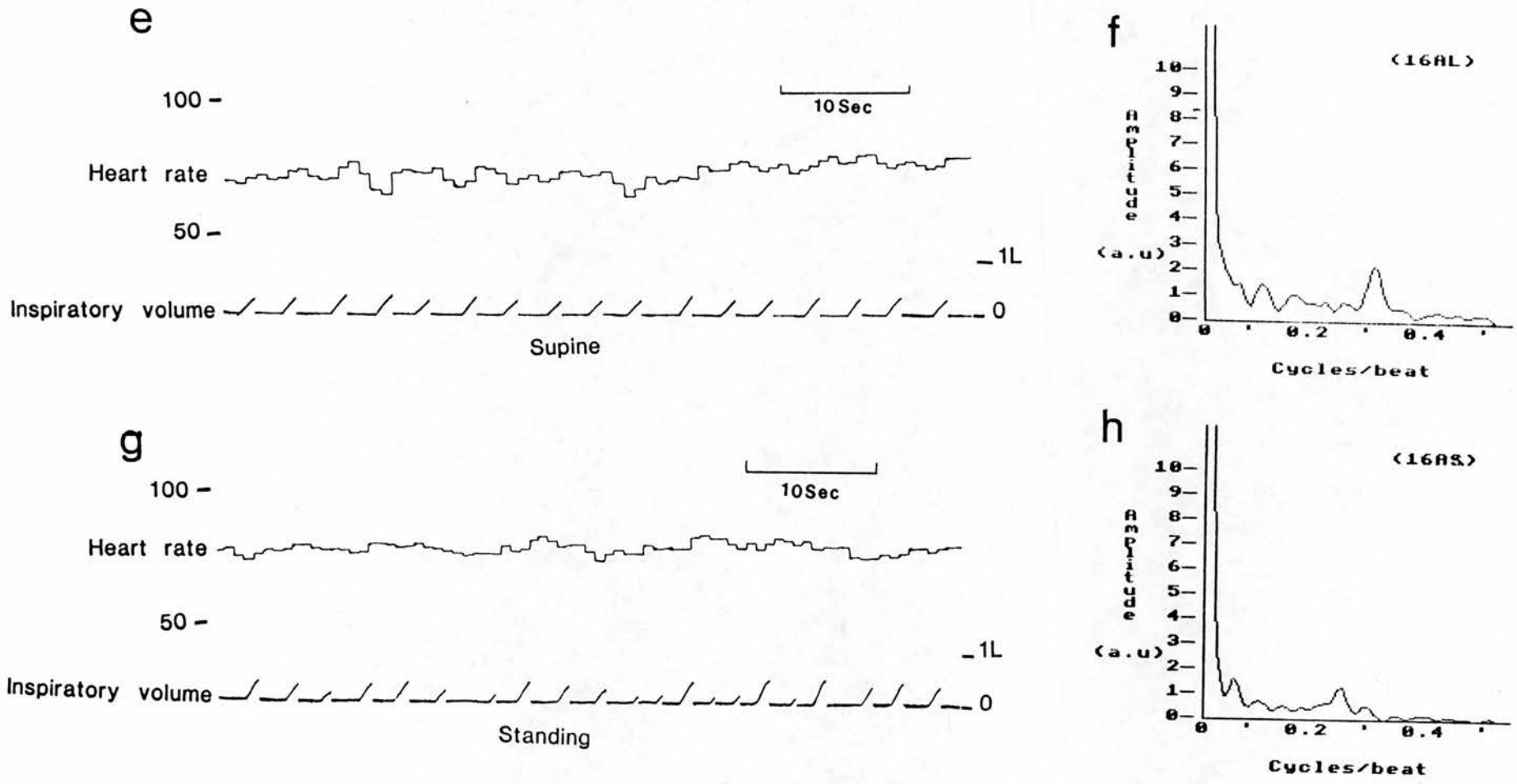


Fig.(4-5) compares the heart rate patterns in a young subject (a & c) with the heart rate patterns in an older subject (e & g). See text for details.

subject showed no difference in pattern between the two different postures apart from a slight decrease in the amplitude of the "RSA" during maintained standing.

The heart rate patterns during maintained standing for all the subjects in the two age groups are shown in Fig. (4 - 6) and (4 - 7).

In the young group (Fig. 4 - 6), five subjects (a,b,d,g & h) showed a large peak at $\sim$ 0.1 cycles/beat and a small, if any, peak at the respiratory frequency, so the ratio between the two peaks ("10 second" / "RSA") was very large , and this was reflected on the heart rate records which exhibited prominent "10 second" oscillations similar to the one shown in (c) of Fig (4 - 5).

In the other three subjects (c,e & f) the peak at $\sim$ 0.1 cycles/beat was not big and in addition the peak at the respiratory frequency was relatively large and that made the ratio between the two peaks to be very small. This large amplitude "RSA" apparently obscured the "10 second" rhythm which was reltatively small in these subjects and the net result was a predominant "RSA" rhythm .

In the older group (Fig. 4 - 7), 6 subjects (b,c,d,e,f & g) did not show a definite large peak at $\sim$ 0.1 cycles/beat and there was an equally small peak at the respiratory frequency, so the ratio between the two peaks was small. In addition, the absolute amplitudes of both peaks were smaller compared with the younger subjects. In these 6 subjects the predominant rhythm during standing was the "RSA" similar to the one shown in (g) of Fig (4 - 5). Subject (a) (male, 52yr.) showed a peak at $\sim$ 0.1 cycles/beat but of small size and therefore the ratio between this and the

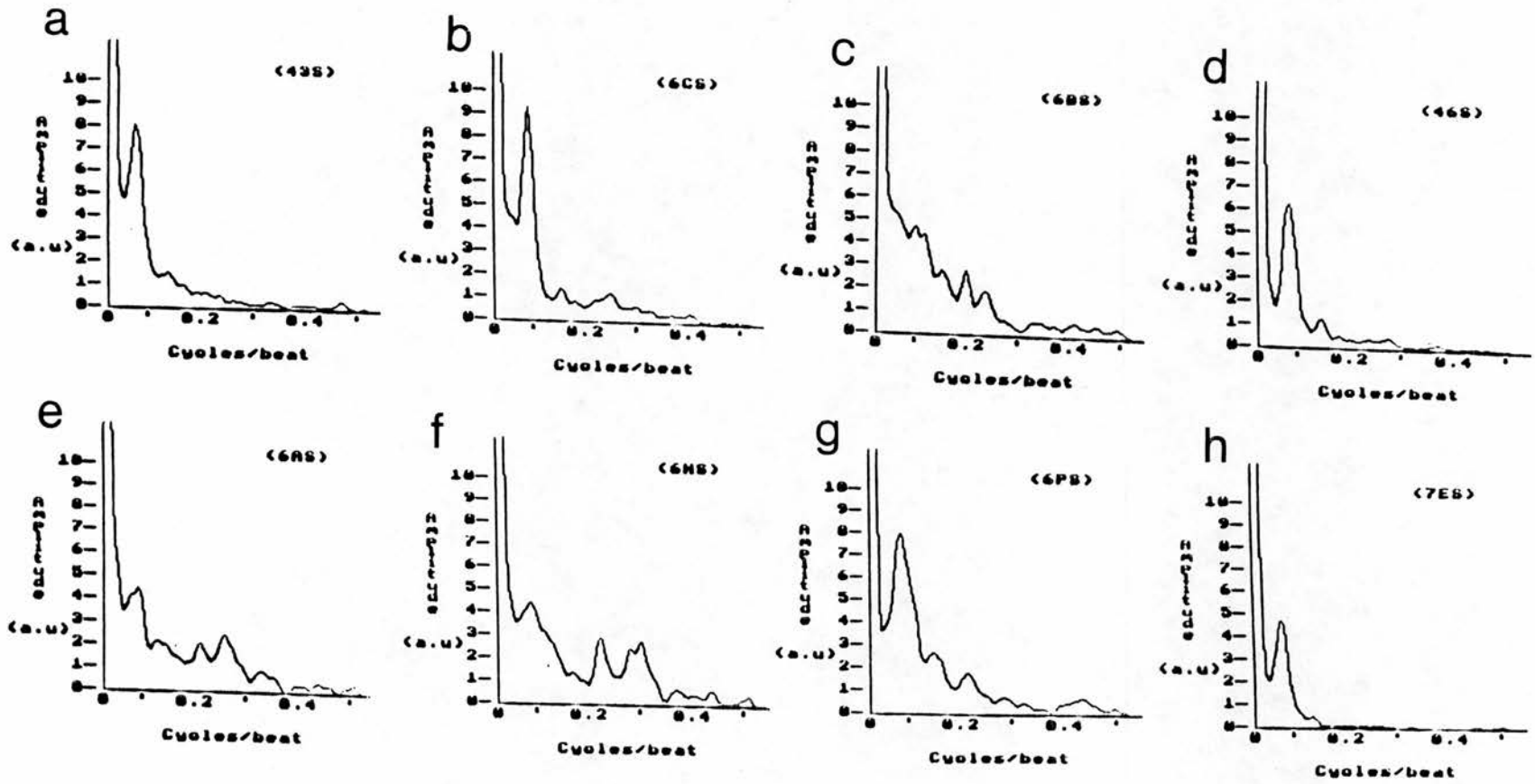


Fig.(4-6). The heart rate spectra during maintained standing for all the young subjects.

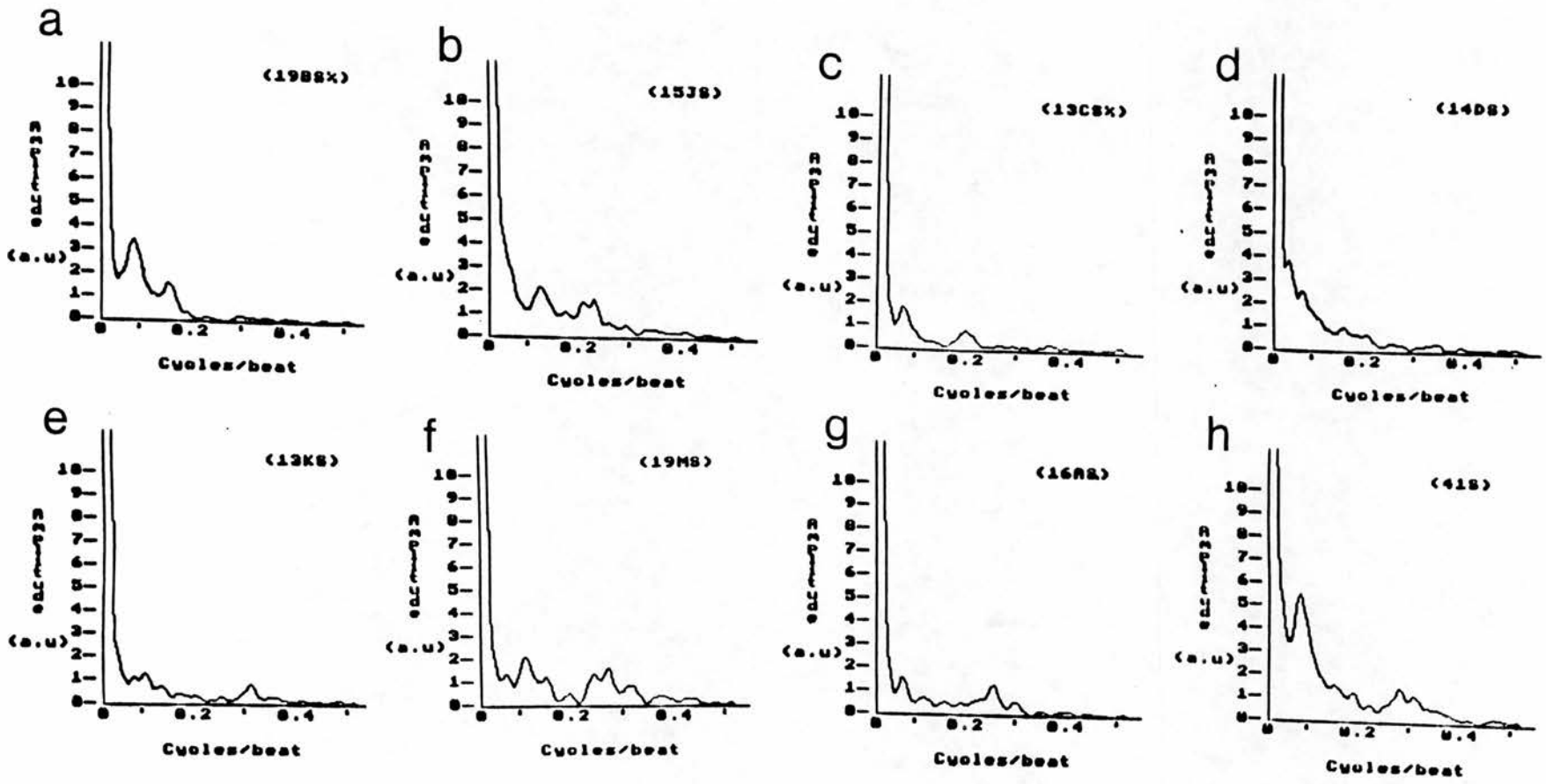


Fig.(4-7). The heart rate spectra during maintained standing for all the subjects in the older age group.

respiratory peak at ~ 0.15 cycles/beat was not very big. This was reflected on his heart rate record which showed infrequent, small amplitude "10 second" oscillations. The eighth subject (h) (female, 43yr.) showed a peak at ~ 0.1 cycles/beat of considerable size and a smaller one at the respiratory frequency (~ 0.28 cycles/beat). The ratio between the two peaks was large enough to make the "10 second" rhythm predominant during standing in this subject, although on a previous occasion the peak at ~ 0.1 cycles/beat was not so large and thus she was, initially, thought to be a non-oscillator.

Both subjects (a) and (h) are physically more fit than the others, as they cycle daily to and from work.

In summary, five out of eight young subjects (62.5%) were good oscillators, while only one subject (h) from the older age group (12.5%) showed good oscillations on standing similar to the younger oscillators.

DISCUSSION

The results suggest that age does seem to play a part in the response of heart rate rhythm to change of posture from supine to maintained standing.

The changes in MHR with the change of posture from supine to maintained standing, were in the same direction in both age groups, but they differed quantitatively.

The finding of a non-significant difference in supine MHR between the two different age groups , was in accordance with others (Strandell 1964, Smith & Smith 1981, Sato et al 1981, Vargas & Lye

1982, Persson & Solders 1983, Vargas et al 1984, Rodeheffer et al 1984, Pagani et al 1986).

The slightly higher supine MHR was thought to be due to a lower vagal tone in old age (Pfeifer et al 1983).A higher sympathetic tone could be another explanation with the consistent finding of a higher plasma norepinephrine (PNE) level in the older subjects during supine rest (Christensen 1973, Ziegler et al 1976, Sever et al 1977, Vargas et al 1984). However, this increase in PNE level may be partially due to the reported decrease in beta-adrenoceptors sensitivity with age (Vestal et al 1979).

The slightly lower MHR during maintained standing and the significantly smaller $\triangle$ HR in the older subjects was also in agreement with the others (Strandell 1964, Vargas & Lye 1982, Pagani et al 1986, Smith et al 1987, Sato et al 1981).

It is known that in the elderly, there is a greater and more sustained increase in PNE level in response to change of posture (Rowe & Troen 1980). The lack of correlation between the apparent increase in sympathetic activity (higher PNE level) in response to postural change and the heart rate responses (i.e. standing MHR and $\triangle$ HR) in the older subjects, might be due to a decreased baroreflex sensitivity with age (Gribbin et al 1971), or the above mentioned decrease in beta- adrenoceptors sensitivity to circulating catecholamines (Vestal et al 1979) or both.

The changes in MAD were also in the same direction in both age groups, however, the MAD was slightly, but not significantly, lower in the older subjects in both supine and maintained standing postures .

The MAD reflects the variability at high frequencies i.e. "RSA"

(chapter III). So "RSA" was smaller in older group but not significantly so. A larger sample might have brought the difference to a statistical significance, but it is also possible that "RSA" was not significantly reduced. Many of the studies that reported a decrease in "RSA" with age, measured it at slow breathing rates (Wheeler & Watkins 1973, Hellman & Stacy 1976, Mackay et al 1980, Smith & Smith 1981, Smith 1982, Wieling et al 1982, Pfeifer et al 1983, Masaoka et al 1985, O'Brien et al 1986). However, at these slow rates, the changes in heart rate are not pure "RSA" but rather a combination of both the "RSA" and the "10 second" rhythm (chapter III). Other studies have used an index that measures the total variability rather than "RSA" alone (Waddington et al 1978, Cicmir et al 1980, Chipps et al 1981, O'Brien et al 1986). In this study, the results from spectral analysis suggested that the decrease in the total amplitude with age could be due to a larger decrease in the "10 second" rhythm component. Jennings & Mack 1984 using the same type of analysis, independently reached the same conclusion.

The CV% was not significantly different between the two groups in the supine posture, however, the response to change of posture was completely different. In the older subjects, the CV% tended to decrease during maintained standing, while in the young it tended to increase in spite of a slightly larger decrease in MAD . This led to a widening of the gap in CV% during maintained standing which was then significantly higher in the younger group .
The increase in total variability (CV%) in spite of decreased short term variability (MAD) during maintained standing in the younger subjects, could only be explained by a marked increase in the long term variability (chapter III , Fig. 3 - 23 c). This was confirmed

by spectral analysis results which showed increased "10 second"/"RSA" ratios during standing.

To attribute the difference in heart rate patterns during maintained standing between the two age groups, to the difference in MHR seems to be invalid. Both the young as well as the old subjects in Fig (4 - 7) had a MHR of 82 bpm during maintained standing, but the heart rate patterns were completely different in the two subjects, as explained in detail in the results.

So, age does seem to play a part in the response of heart rate rhythm to the change in posture, however, it is not the only factor that determines that response. Three out of the eight randomly selected young subjects, and 31 out of the total population of young subjects studied (67), did not show slow oscillations during maintained standing. On the other hand, one subject in the older group, did show some oscillations during maintained standing.

Chapter V

EFFECTS OF SUPINE EXERCISE ON "HRV"

INTRODUCTION

The change in heart rate pattern from a predominantly "RSA" rhythm in the supine posture to a predominantly "10 second" rhythm during maintained standing was associated with a significantly higher MHR during maintained standing (chapter III).

The possibility that the MHR is the factor that determines the heart rate pattern was raised, but individual results(chapters III & IV) did not support this contention. Therefore, it was decided to systematically study the effect of increasing the MHR per se on the heart rate pattern, excluding the effect of standing.

METHODS

Subjects

The subjects chosen for this experiment were 12 young oscillators (7 male, 5 female), who showed prominent "10 second" rhythm during maintained standing. The age ranged between 18 and 30 years with a mean of 21.6 $\pm$ 0.9 . The physical characteristics of the subjects are shown in Table (5 - 1).

Experimental protocol

A control supine-standing manoeuvre was carried out as described

	Sex	Age	Ht.(cm)	Wt.(kg)
1.	M	30	183	77
2.	F	18	163	58
3.	F	20	155	51
4.	M	21	176	79
5.	M	20	173	73
6.	M	22	178	75.5
7.	M	18	180	70
8.	M	19	176	64
9.	M	24	183	67
10.	F	22	165	59
11.	F	24	164	58
12.	F	21	169	67.5
Mean		21.6	172.1	66.9
± SEM		0.9	2.5	2.6

Table (5-1). Physical characterstics of the subjects.

before (chapter III). Then, another supine control was recorded before the subjects started to pedal a bicycle ergometer (Siemens-Elema 380B). The start load was 20W, then it was increased, in steps of 5W, until the heart rate, monitered on the cardio tachometer was estimated to be the same as it had been during maintained standing. The work load was maintained at this level, which ranged between 20 and 60W for several minutes.

Analysis

As described in detail in chapter II. However, in 8 files (marked with an asterisk in table 5-2), the arrays consisted of 128 RR intervals because the records were not long enough to have 256 intervals.

Statistical analysis

The paired -t-test was used for the comparison of MHR, while the Wilcoxon signed-rank test was used for MAD and CV% comparison.

RESULTS

MHR

The MHR for the individual subjects during the first supine control and maintained standing, and also during the second supine control and supine exercise are shown in Table (5 - 2).

The MHR during maintained standing (90.8 $\pm$ 2.1) and during supine exercise (93.7 $\pm$ 1.7) were both significantly ($P<0.001$) higher than

	Supine I	Standing	Supine II	Ex.
1.	68	99	67	101
2.	81	95	78.5	100
3.	74	84	69*	93
4.	79	93	67	96
5.	78	85	72*	95
6.	65	96	59	94
7.	62.5	84	67*	86
8.	61	91	58*	89
9.	73	105.5	78*	102
10.	70	90.5	68	94
11.	70*	85	58	92
12.	54*	81	54*	82
Mean	69.6	90.8	66.3	93.7
± SEM	2.3	2.1	2.2	1.7

Table (5-2). The MHR during the first and second supine postures (I & II), standing, and during supine exercise (Ex.).

the respective supine controls (69.6 ± 2.3, 66.3 ± 2.2) (Fig. 5 - 1).

Although it was intended to have the same mean heart rates during both maintained standing and supine exercise, it was difficult to acheive exactly the same level because of the different patterns of heart rate variations in the two conditions. Consequently, there was a small difference between the MHR during supine exercise (93.7 ± 1.7) and maintained standing (90.8 ± 2.1) which was significant ($P<0.05$).However,the percentage difference (3.2%) was very small compared with the percentage difference (41.3%) between second supine MHR (66.3 ± 2.2) and the MHR during supine exercise (93.7 ± 1.7).

MAD

Table (5 - 3) shows the MAD for the individual subjects during the first supine control and maintained standing, and also during the second supine control and supine exercise.

There was no significant difference in MAD between the two supine controls.However,the MAD during both maintained standing (13.6 ± 1.8) and supine exercise (9.7 ± 1.3) were significantly ($P<0.01$) lower than the respective supine controls (49.1 ± 9.8, 58.2 ± 10.8) (Fig. 5 - 1).

Moreover, the MAD during supine exercise was not only significantly lower than its supine control but it was even significantly ($P<0.05$) lower than the MAD during maintained standing.

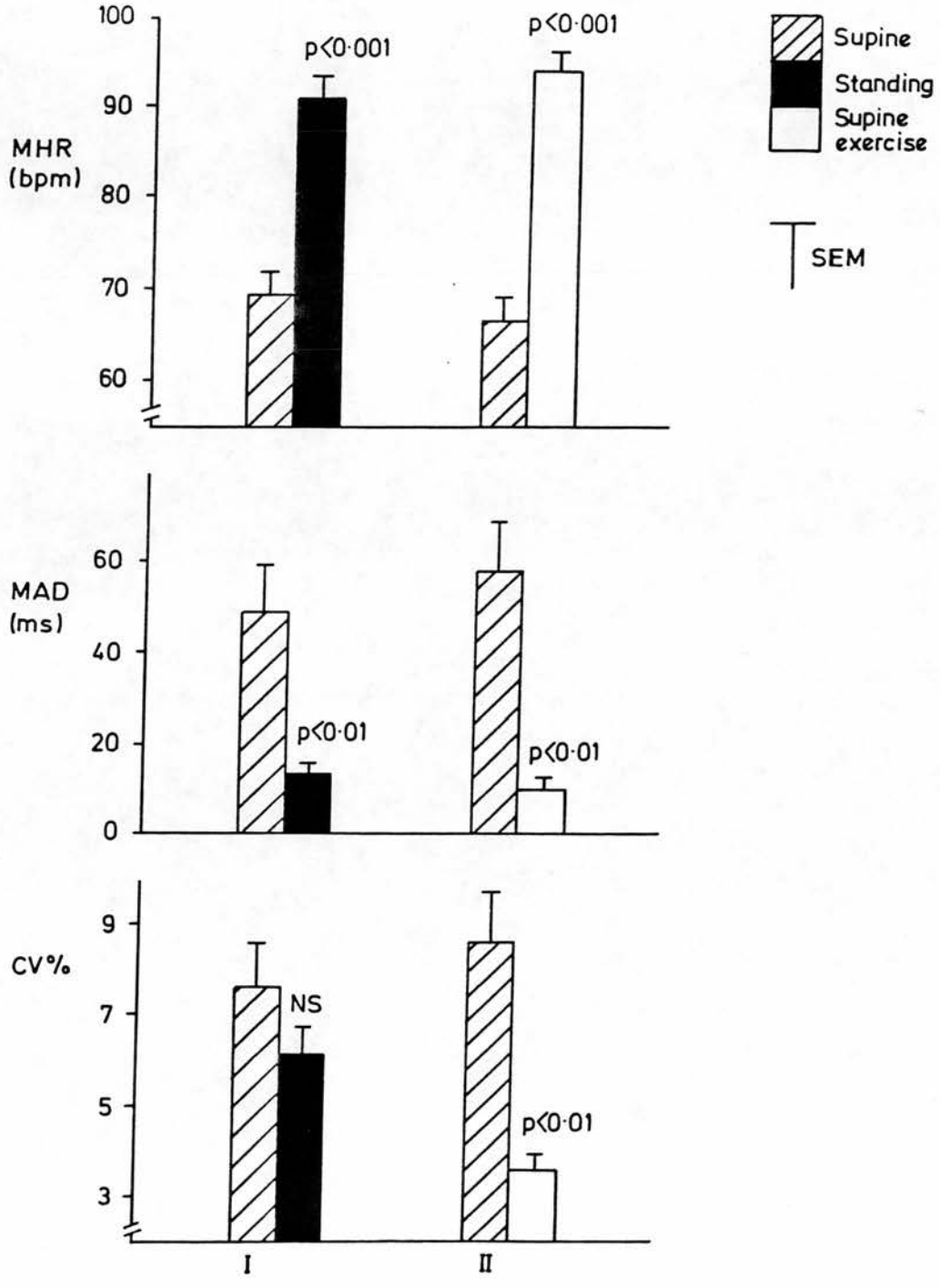


Fig. (5.1) The means of MHR, MAD and CV% for all subjects during the first and second supine postures (I & II), standing and during supine exercise.

	Supine I	Standing	Supine II	Ex.
1.	27.1	6.0	26.7	4.1
2.	18.6	7.8	17.7	5.5
3.	34.0	23.5	57.0	13.6
4.	17.2	7.7	49.9	9.1
5.	32.3	15.6	40.4	6.4
6.	62.3	13.4	73.2	8.1
7.	46.3	11.3	32.7	7.5
8.	38.6	13.3	61.4	18.1
9.	27.4	8.2	18.8	3.6
10.	52.5	13.5	67.1	11.1
11.	122.0	27.2	145.2	12.9
12.	111.4	16.0	108.6	16.1
Mean	49.1	13.6	58.2	9.7
± SEM	9.8	1.8	10.8	1.3

Table (5-3). The MAD during the first and second supine postures (I & II), standing, and supine exercise (Ex.).

CV%

Table (5 - 4) shows the CV% for the individual subjects during the first supine control, maintained standing, the second supine control, and also during supine exercise.

The mean of CV% for all the subjects during maintained standing (6.1 $\pm$ 0.5) was not significantly different from the CV% during supine control (7.6 $\pm$ 1.0) (Fig. 5 - 1).

Although there was no statistically significant difference in CV% between the two supine controls , the CV% during supine exercise (3.6 $\pm$ 0.4) was significantly ($P<0.01$) lower than its supine control (8.6 $\pm$ 1.1) (Fig. 5 - 1) and even significantly ($P<0.01$) lower than the CV% during maintained standing.

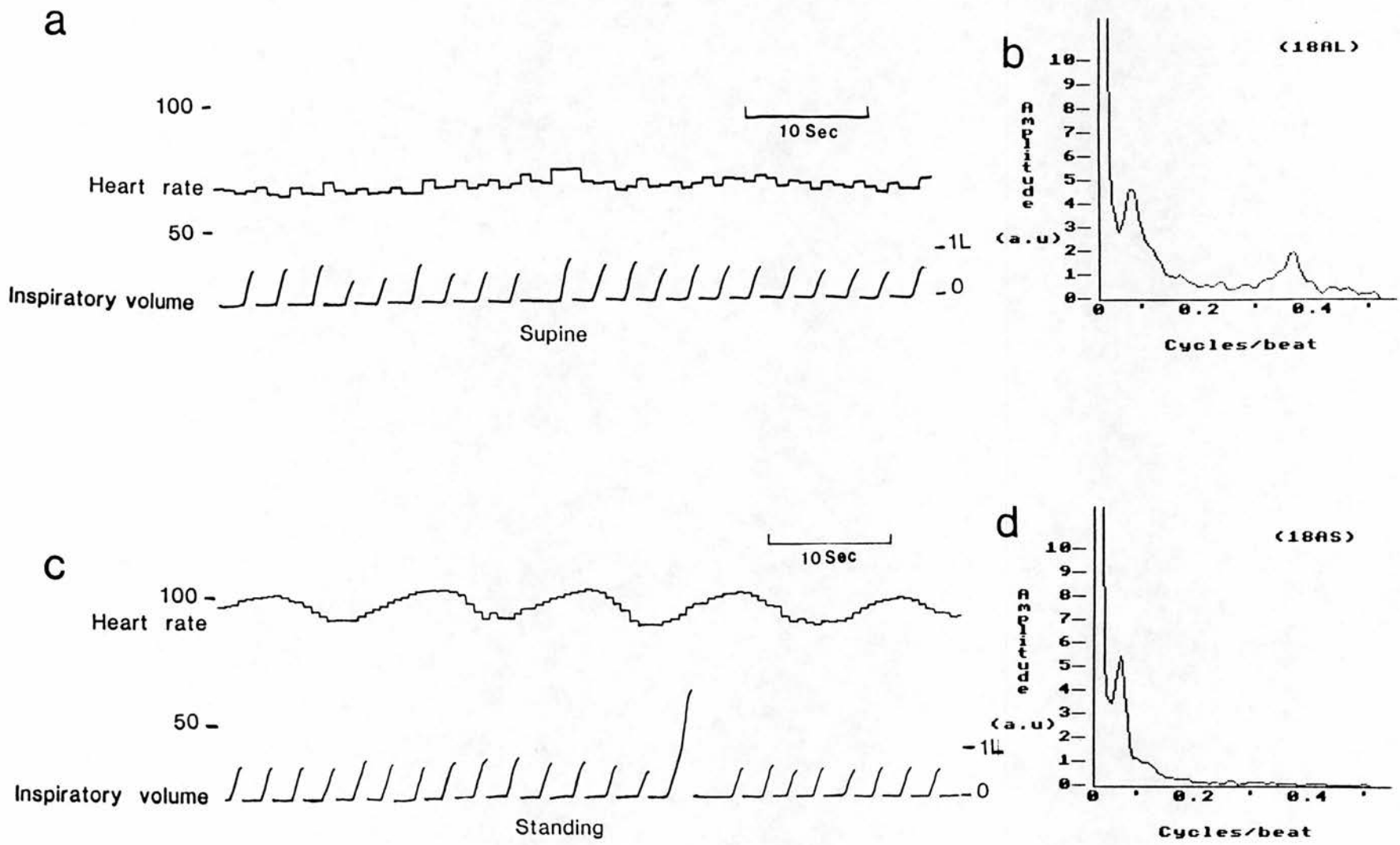
HRV

The heart rate pattern during a change of posture compared to the pattern during supine exercise in one subject is illustrated in Fig (5 - 2). During the supine posture, there are two peaks in the heart rate spectrum (b) and the predominant rhythm is the respiratory sinus arrhythmia (a). However during maintained standing, there is only one peak at $\sim$0.1 cycles/beat (d), and the predominant rhythm is the slow "10 second" oscillations (c).

The pattern during the second supine control (e) & (f) is very similar to the first supine control (a) & (b), but during supine exercise it is very different. In spite of a similar mean heart rate during both maintained standing and supine exercise, the heart rate patterns are completely different. The "10 second" rhythm

	Supine I	Standing	Supine II	Ex.
1.	4.8	4.1	4.5	2.1
2.	5.4	4.4	5.1	2.5
3.	7.9	9.1	13.5	5.3
4.	2.9	4.4	6.6	3.0
5.	8.1	6.9	5.8	3.0
6.	7.8	6.9	8.0	3.7
7.	6.9	4.3	4.4	2.6
8.	9.5	7.2	14.3	4.7
9.	4.1	7.6	7.7	1.8
10.	9.7	5.0	11.5	3.3
11.	16.1	8.8	15.1	6.1
12.	7.7	4.3	7.1	4.7
Mean	7.6	6.1	8.6	3.6
± SEM	1.0	0.5	1.1	0.4

Table (5-4). The CV% during the first and second supine postures (I & II), standing, and during supine exercise (Ex.).


a
100 -
10 Sec
Heart rate
50 -
1L
Inspiratory volume
0
Supine
b
(18AL)
Amplitude
(a.u)
10
9
8
7
6
5
4
3
2
1
0
0
0.2
0.4
Cycles/beat
c
10 Sec
100 -
Heart rate
50 -
1L
Inspiratory volume
0
Standing
d
(18AS)
Amplitude
(a.u)
10
9
8
7
6
5
4
3
2
1
0
0
0.2
0.4
Cycles/beat

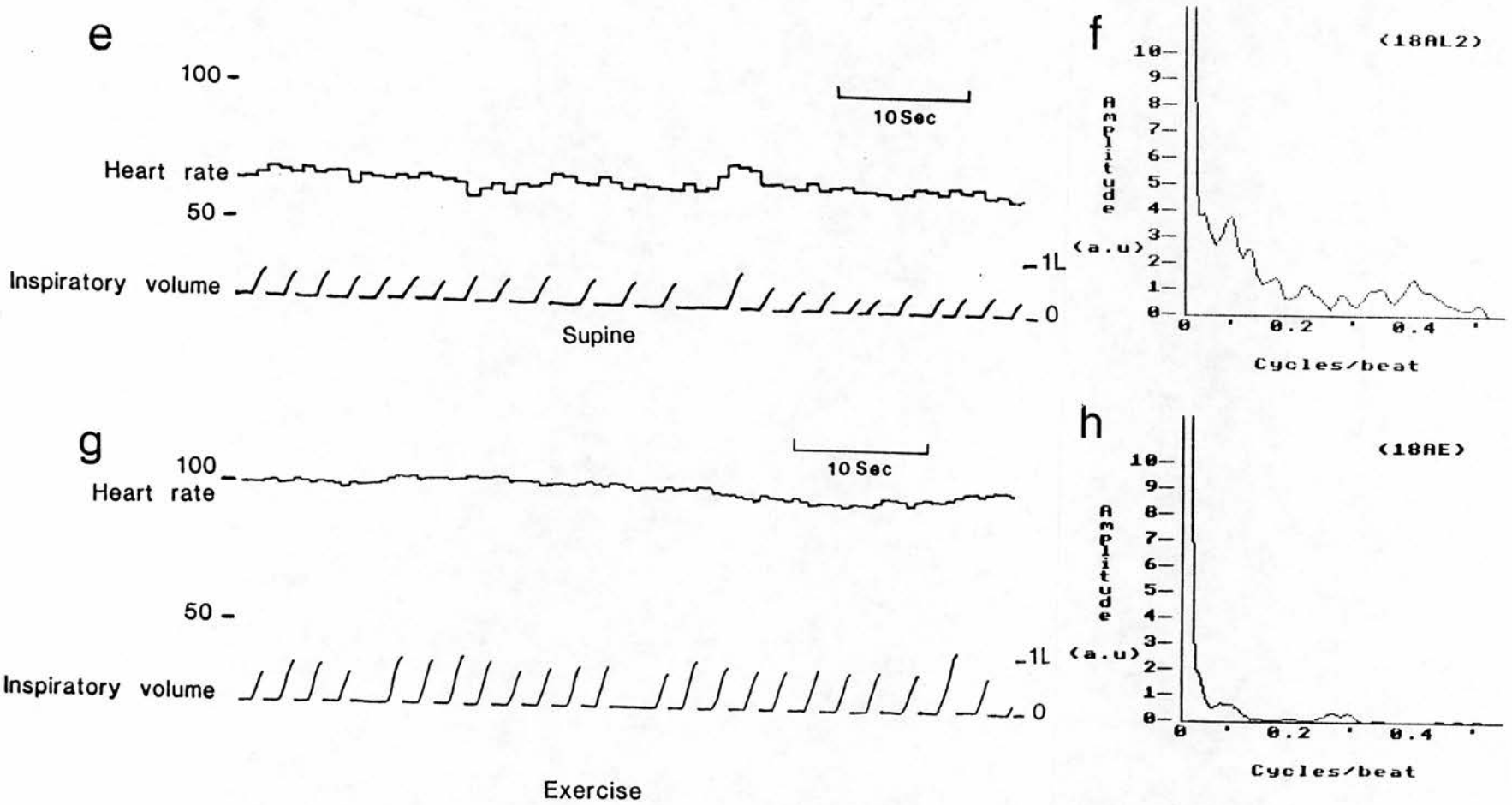
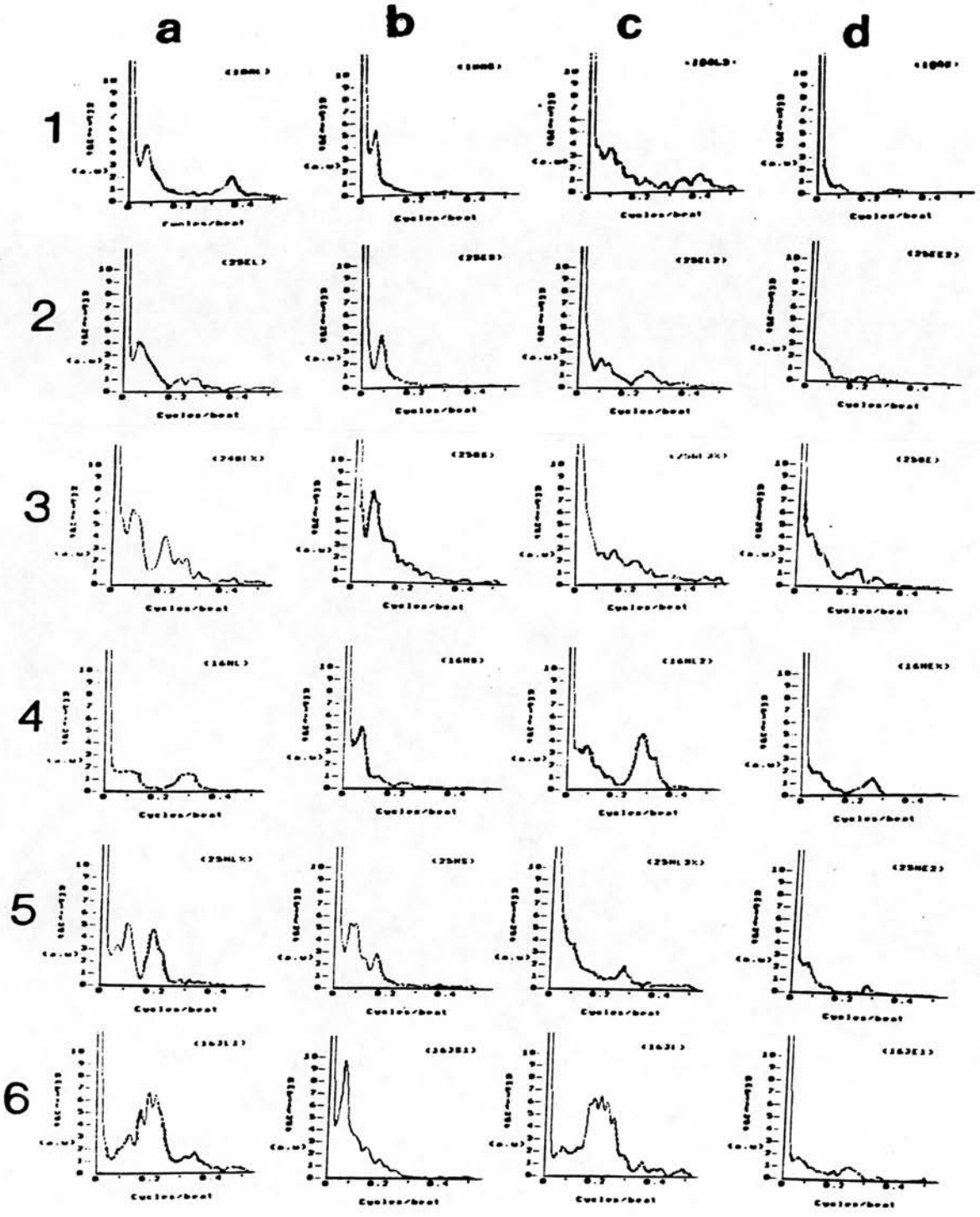


Fig.(5-2) shows the difference in heart rate pattern between maintained standing and supine exercise. See text for details.

which was very prominent during maintained standing (c) has almost disappeared during supine exercise (g). This change in pattern is reflected on the heart rate spectra, as the large peak at $\sim$ 0.1 cycles/beat during maintained standing (d) has been reduced to one tenth its size during supine exercise (h). The respiratory sinus arrythmia which was of moderate amplitude during supine controls (a) & (e) has also been reduced markedly during supine exercise (g), and the heart rate spectrum (h) now shows a very small peak at the respiratory frequency ($\sim$ 0.25 cycles/beat).

These contrasting heart rate patterns in the two conditions (maintained standing versus supine exercise) in spite of similar mean heart rates, in the above subject, were also shown by all the other twelve subjects. Their heart rate spectra in the four conditions i.e. first supine (a), maintained standing (b), second supine (c) and supine exercise (d) are illustrated in Fig (5 - 3). They all showed a large peak at $\sim$ 0.1 cycles/beat during maintained standing (b) which was markedly reduced in size during supine exercise (d). This was also apparent in the heart rate records even at milder work loads with relatively lower MHR.

So,although the mean heart rate during supine exercise was similar to the mean heart rate during maintained standing, the heart rate patterns were not the same.During supine exercise, both the "10 second" rhythm and the "RSA" were markedly reduced in amplitude, and the heart rate was almost flat, in contrast with the large slow oscillations during maintained standing.


a
b
c
d
1
2
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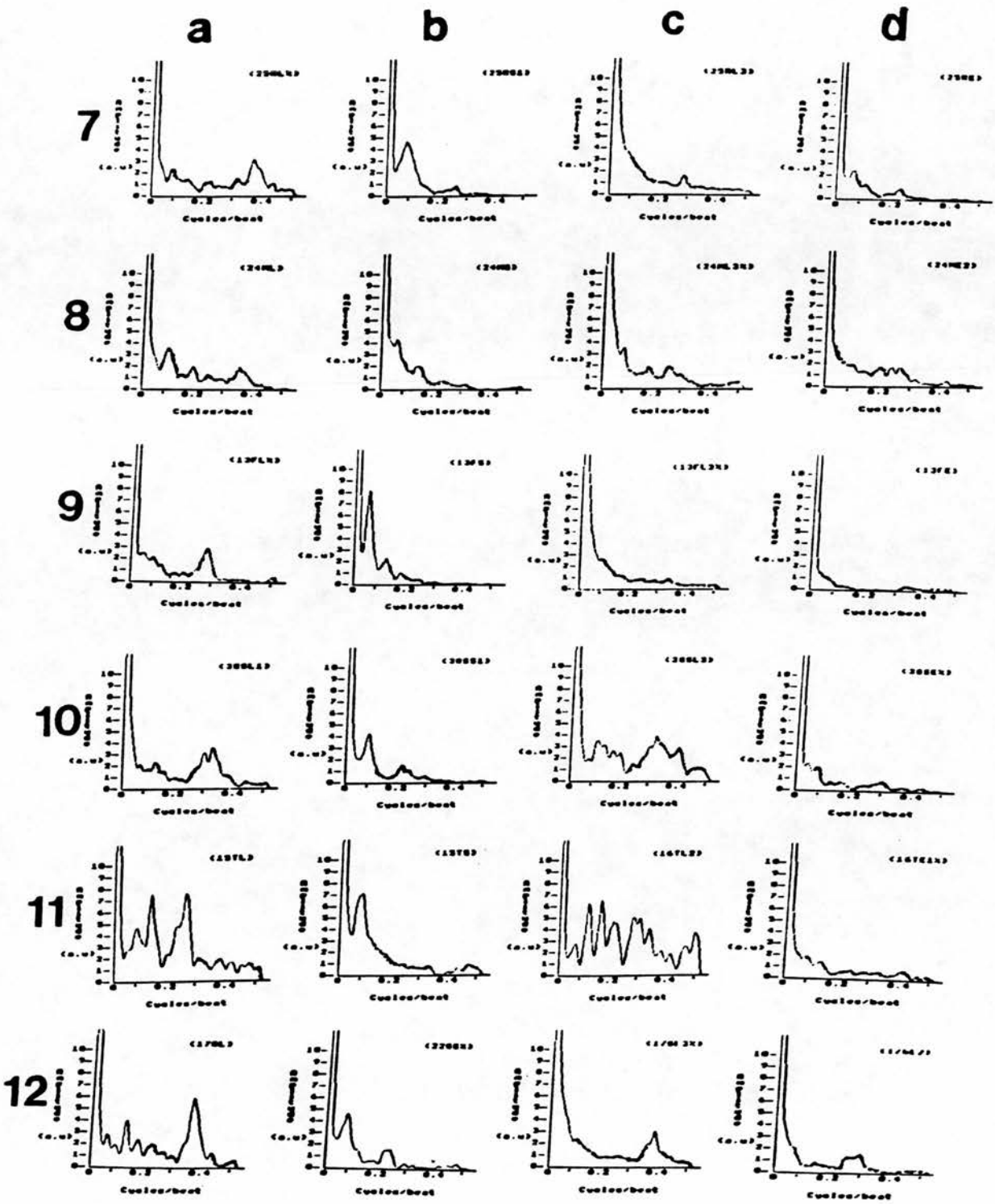


Fig.(5-3). The heart rate spectra for all the subjects during the first supine posture (a), standing (b), the second supine posture (c) and during supine exercise (d).

DISCUSSION

The significantly higher MHR during maintained standing than supine MHR (Chapter III), suggested that the difference in the heart rate patterns between the two postures might be due to the difference in the MHR.

This study was conducted on 12 young "oscillators" who showed prominent "10 second" rhythm during maintained standing and had high standing MHR . The MHR was increased to a similar level by exercising in the supine position to exclude other changes in the cardiovascular system induced by the standing posture. The work loads needed to raise the MHR were mild, ranging between 20 and 60 Watts.

The significant decrease in short term variability (MAD) during both supine exercise and maintained standing was probably due to a lower vagal tone in both conditions (Robinson et al 1966), as the MAD was shown to be markedly reduced by atropine (chapter VIII, Dalton et al 1983).

The change in CV% was different. During maintained standing, the significant decrease in STV (MAD) was compensated by an increase in LTV which resulted in a total variability (CV%) being not significantly different from supine CV% . In contrast, the CV% during supine exercise was significantly reduced, and this was due to a marked reduction in both STV and LTV (chapter III, Fig. 3 - 23 d).

Spectral analysis confirmed this by showing a marked reduction in

the size of both the "10 second" and the "RSA" peaks during supine exercise in all the twelve subjects .

So the results seem to support the previous observations (Chapter III & IV) that the MHR was not the important factor that determines the heart rate pattern. During the mild supine exercise, in spite of a significantly higher MHR than its supine control , the "10 second" rhythm was almost absent, in contrast to the pattern during maintained standing in these subjects.

Robinson et al (1966) showed that attainment of an equivalent heart rate, by mild supine exercise or change of posture, involved a different balance of autonomic activity. The increase in MHR in response to mild supine exercise depended predominantly on parasympathetic withdrawal, whereas that produced by change of posture involved a relatively greater degree of sympathetic stimulation. This could explain, in part, the difference in heart rate pattern, although differences in receptors input and venous return in the two conditions are other possibilities.

Chapter VI

EFFECTS OF TILTING UP ON "HRV"

INTRODUCTION

During maintained tilt toward the upright posture, the MHR was found to be significantly higher than supine MHR (Tuckman & Shillingford 1966, Marin-Neto et al 1980, Amorim et al 1982). However, the initial heart rate response to the passive change in posture, was found to be different from the response to active standing (Ewing et al 1980, Borst et al 1982). The initial heart rate increased more gradually and there was no secondary bradycardia in head up tilt.

These initial changes were excluded and the heart rate pattern, during head up posture maintained passively, was compared with that during maintained standing.

METHODS

Subjects

Seven subjects (4 male, 3 female) participated in this study. The age ranged between 25 and 45 years with a mean of 29.9 $\pm$ 2.6. The physical characteristics of the subjects are shown in Table (6 - 1).

	Sex	Age	Ht (cm)	Wt (Kg)
1.	F	25	164	58
2.	M	25	183	67
3.	M	31	183	77
4.	M	28	169	66
5.	F	45	160	59
6.	F	30	159	61
7.	M	25	172	69
Mean		29.9	170	65.3
± SEM		2.6	3.7	2.5

Table (6-1). Physical characteristics of the subjects.

Experimental protocol

A control supine-standing manoeuvre was carried out as described before (chapter III). Then, a second supine control was recorded before the subjects were tilted and kept at 70° for 10 minutes. The subjects were strapped to the tilting table and their feet were supported.

Analysis

As described in detail in chapter II.
In one subject due to a faulty recording during the first supine control, no file could be made and the MHR was calculated manually from the heart rate record.

Statistical analysis

For the comparison of MHR, the paired -t-test was used, while the Wilcoxon's signed rank test was used for the comparison of MAD and CV%.

RESULTS

MHR

The MHR for the individual subjects during the first supine control, maintained standing, the second supine control and tilting are shown in Table (6 - 2).

	Supine I	Standing	Supine II	Tilting
1.	67	84	62	81
2.	70	89	62	93
3.	84	105	75	89
4.	79	108	71	93
5.	93	100	75	88
6.	81	91	78	94
7.	70	87	67	90
Mean	77.7	94.9	70.0	89.7
± SEM	3.5	3.6	2.5	1.7

Table (6-2). The MHR during the first and second supine postures (I & II), standing, and during 70° tilt.

There was no signficant difference beween MHR during tilting (89.7 ± 1.7) and maintained standing (94.9 ± 3.6). The MHR during both, were significantly ($p<0.001$) higher than their respective supine controls (70.0 ± 2.5 , 77.7 ± 3.5) (Fig. 6-1).

MAD

The MAD for the individual subjects during the first supine control, maintained standing , the second supine control and tilting are shown in Table (6-3).

There was no significant difference between MAD during tilting (14.2 ± 2.5) and maintained standing (11.9 ± 2.3).The MAD during both , were significantly ($P<0.02$, $P<0.05$) lower than their respective supine controls (41.0 ± 13.4, 24.7 ± 8.2) (Fig. 6 - 1).

CV%

The CV% for the individual subjects during the first supine control, maintained standing, the second supine control and tilting are shown in Table (6-4).

There was no significant difference between CV% during tilting (5.9 ± 0.7) and maintained standing (5.2 ± 0.7) and the slight decrease during tilting relative to its supine control (6.5 ±1.0) was also not significant (Fig. 6 - 1).

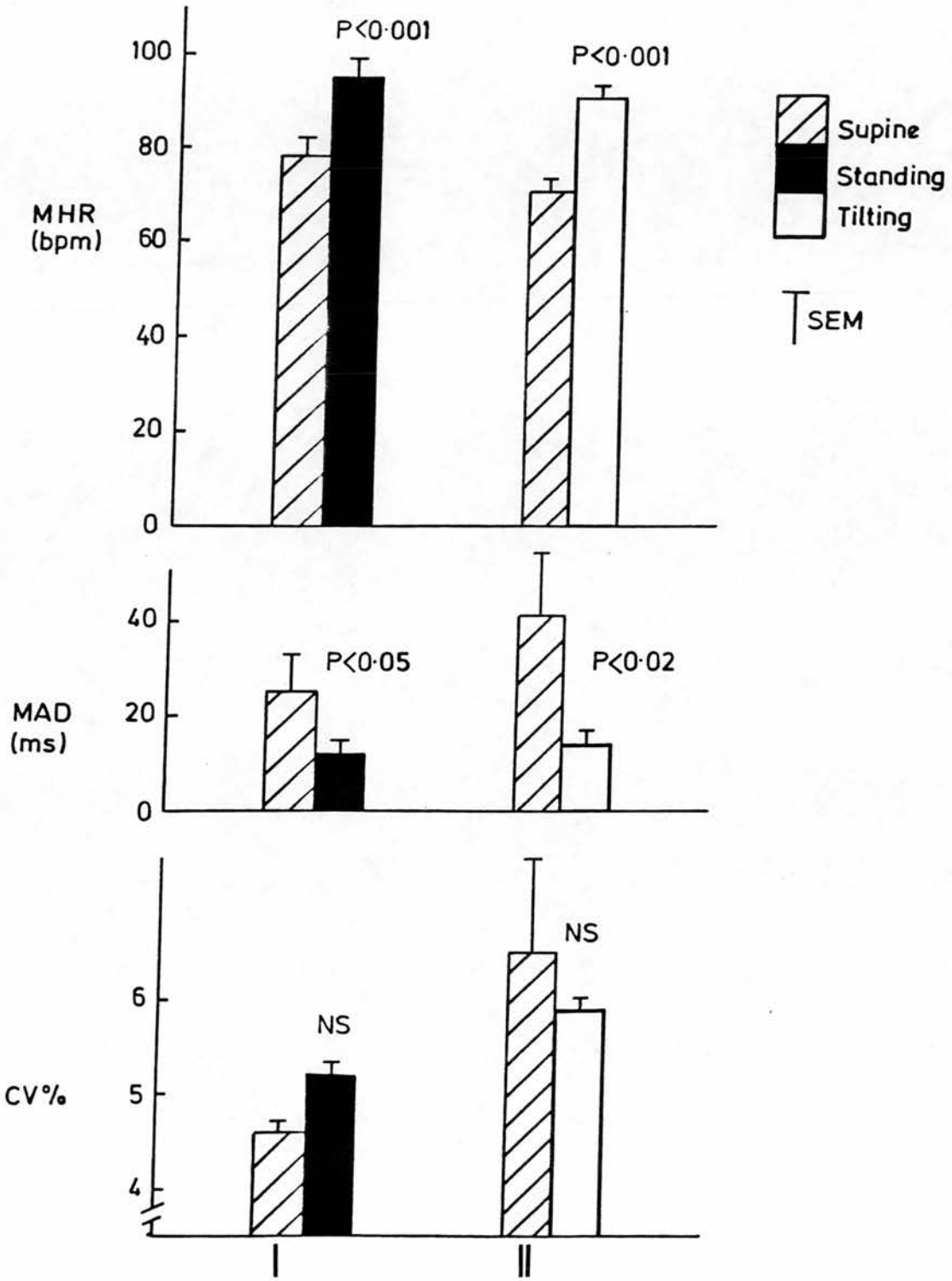


Fig.(6-1). The means of MHR, MAD and CV% for all the subjects during the first and second supine postures (I & II), standing, and during 70° tilt.

	Supine I	Standing	Supine II	Tilting
1.	59.3	20.9	111.1	27.1
2.	38.0	14.2	65.1	13.9
3.	6.8	3.2	13.0	6.9
4.	11.1	5.2	14.7	10.9
5.	11.2	10.1	30.4	14.6
6.	21.7	13.6	21.9	10.1
7.	–	16.4	30.9	15.6
Mean	24.7	11.9	41.0	14.2
± SEM	8.2	2.3	13.4	2.5

Table (6-3). The MAD during the first and second supine postures (I & II), standing, and during 70° tilt.

	Supine I	Standing	Supine II	Tilting
1.	7.1	6.6	11.2	8.2
2.	5.3	6.1	8.4	7.4
3.	2.9	3.1	4.2	3.6
4.	3.0	4.8	3.7	6.3
5.	3.8	4.8	6.7	5.0
6.	5.3	3.3	4.6	4.0
7.	–	7.9	6.8	7.1
Mean	4.6	5.2	6.5	5.9
± SEM	0.6	0.7	1.0	0.7

Table (6-4). The CV% during the first and second supine postures (I & II), standing, and during 70° tilt.

HRV

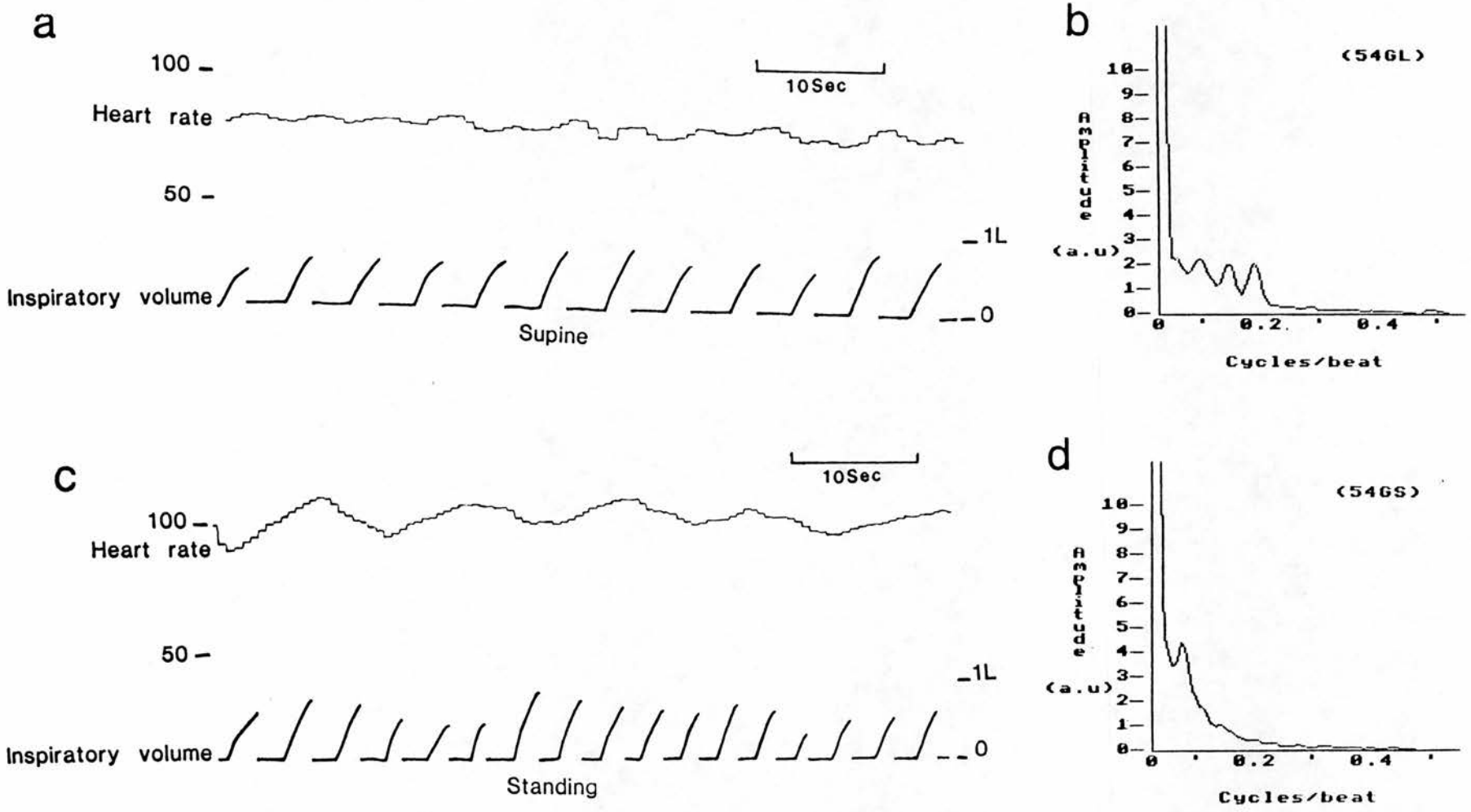
The effect on heart rate pattern of the passive change of posture (tilting) compared with the active change of posture (standing) in one subject is illustrated in Fig.(6 - 2).

During the first supine control, the heart rate spectrum in (b) showed a small peak at ~0.1 cycles/beat. The peak at the respiratory frequency (~0.19 cycles/beat) was almost the same size as the peak at ~0.1 cycles/beat. Consequently the ratio between the two was small and therefore the predominant rhythm in (a) was the "RSA".

During maintained standing, the heart rate spectrum in (d) showed an increase in the size of the peak at ~0.1 cycles/beat with marked decrease in the peak at the respiratory frequency (~0.17 cycles/beat), Consequently, the ratio between the two peaks was large, and therefore the predominant rhythm during maintained standing (c) was the "10 second" oscillations.

During the second supine control, both the heart rate spectrum (f) with its two small almost equal size peaks, and the predominant "RSA" rhythm in the heart rate in (e), were very similar to (b) and (a) of the first supine control.

During tilting, the changes in heart rate pattern were very similar to the changes that occurred during mintained standing. The peak at ~0.1 cycle/beat has increased in size several folds in (h) compared with (f), while the peak at the respiratory frequency


a
100
Heart rate
50
10Sec
1L
0
Inspiratory volume
Supine
b
(54GL)
Amplitude
(a.u)
Cycles/beat
c
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Heart rate
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d
(54GS)
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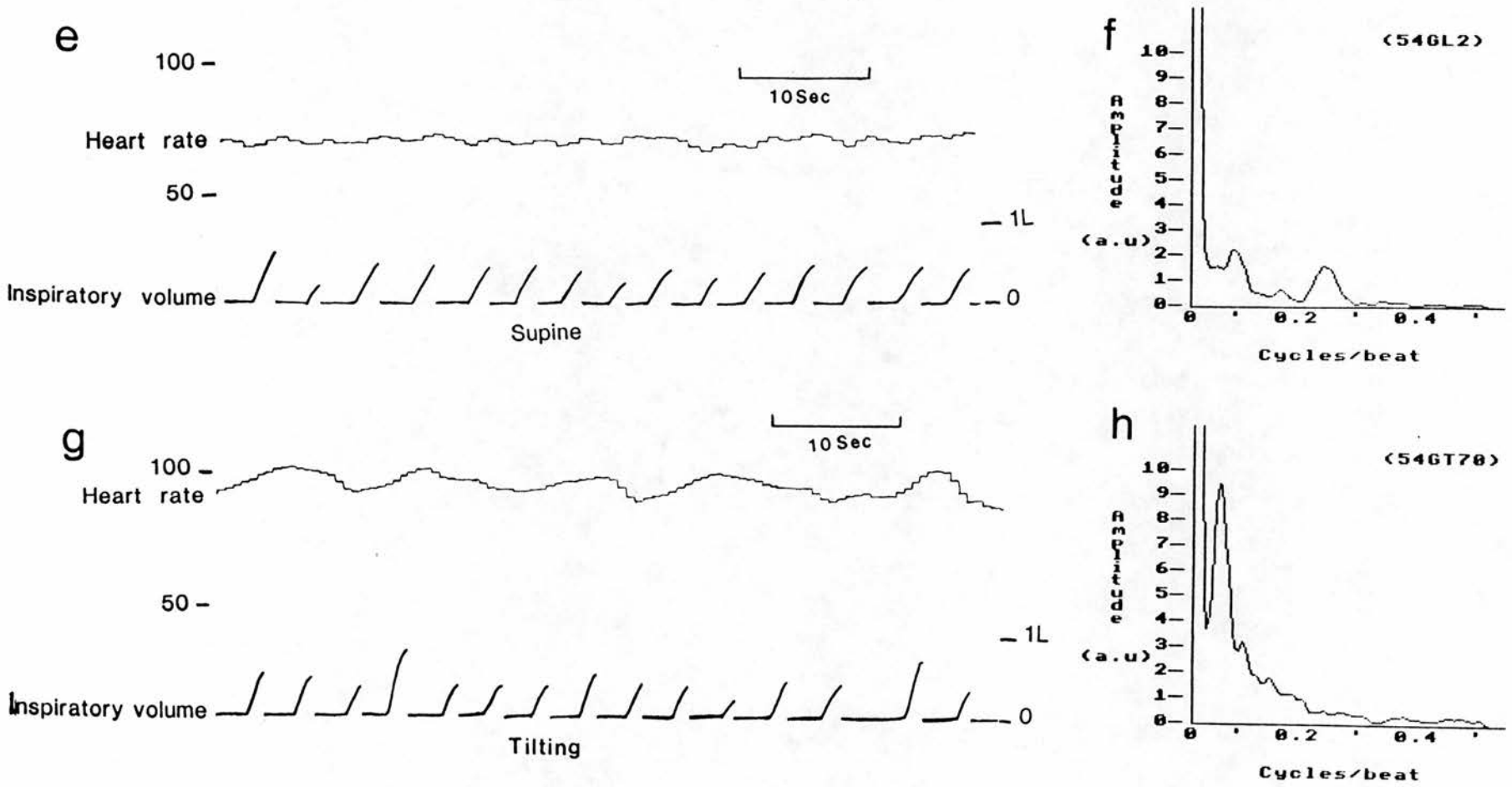


Fig.(6-2) shows the similarity of heart rate pattern during maintained standing and tilting to 70° from horizontal. See text for details.

(~0.17 cycles/beat) in (h) was smaller than the respiratory peak at ~0.25 cycles/beat in (f). The increase in the size of the peak at ~0.1 cycles/beat with the concurrent decrease in the size of the peak at the respiratory frequency led to an increase in the ratio between the two and consequently the predominant rhythm during tilting (g) was the "10 second" oscillations.

As it is clear from Fig.(6 -2), the heart rate pattern (g) and spectrum (h) during tilting were very similar to the heart rate pattern (c) and spectrum (d) during maintained standing.

The effect of the passive change of posture on the heart rate pattern in all the seven subjects is shown in Fig.(6 -3). During tilting (d), the heart rate spectra showed large peaks at ~0.1 cycles/beat in subjects No. 2, 4 & 7. While in the other four subjects, the peak at ~0.1 cycles/beat was not very large but the peak at the respiratory frequency was relatively small. In both cases, the ratio between the two peaks was large and consequently, the predominant rhythm in heart rate was the "10 second" oscillations, similar to the heart rate rhythm during maintained standing.

To summarise, in these seven subjects, the passive change of posture has markedly changed the heart rate pattern in a very similar way to the effect induced by the active change of posture.

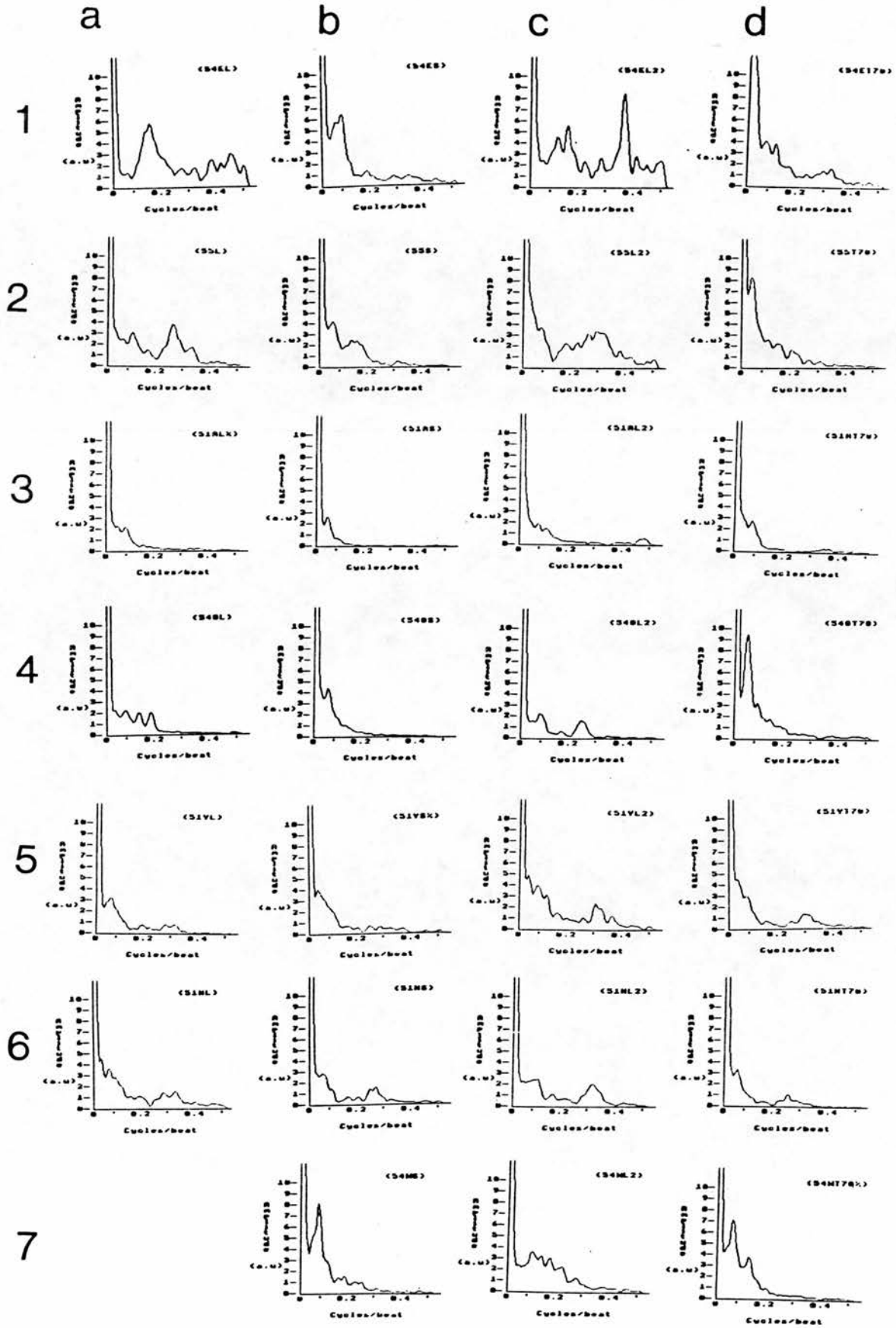


Fig.(6-3). The heart rate spectra for all the subjects during the first supine posture (a), standing (b), the second supine posture (c) and during 70° tilt (d).

DISCUSSION

During passive change of posture, the hemodynamic changes induced by gravity depends upon the sine function of the tilting angle (Gauer & Thron 1965). Therefore,during the 70° tilt that was used, the gravitational influence on the circulation was almost identical to the one at fully erect posture (sine 70° = 0.94). This may explain, at least in part, the non-significant difference in MHR, MAD and CV% results between active standing and passive tilting.

The CV% did not decrease significantly during tilting compared with the supine posture in spite of the signifiant decrease in MAD. This was most likely due to an increase in the LTV (chapter III, Fig. 3-23).

Spectral analysis results confirmed this by showing an increase in the "10 second" peak during tilting .
This result seemed to be in conflict with the reported decrease in the mid-frequency peak during a non-hypotensive tilt (no angle was specified) (Pagani et al 1984). However, more recently Pagani et al (1986) reported a similar increase in the $\sim$0.1 Hz. peak in response to 90° tilt.

The results also showed that the change in heart rate pattern during tilt was brought about by varying the ratio between the two peaks i.e "10 second" rhythm and "RSA" without necessarily a marked increase in the "10 second" peak in all the subjects.

Chapter VII

"HRV" DURING STANDING IMMERSED IN WATER

INTRODUCTION

It was shown in chapter III and VI that both maintained standing and 70° tilt caused an increased prominence of the "10 second" rhythm. In both, there was a significant increase in MHR compared with the supine posture. However, the results from chapter V showed that increasing the MHR per se, by exercise in the supine position, could not induce the "10 second" rhythm.

The change from supine to upright posture in both standing and 70° tilt causes changes in vestibular input and in blood distribution. It has been shown that vestibular and cerebellar mechanisms play an important part in modulating the autonomic response to tilt in cats (Doba and Reis 1974, Koyama et al 1981), but whether this holds true in humans and to what extent is, as yet, not clear.

The change in blood distribution during the assumption of the upright posture is more established. There is a shift of approximately 500 ml. of blood from the thorax to the lower parts of the body (Gauer and Thron 1965).

To determine the relative contribution of the two factors mentioned above (i.e. pooling of blood and change in vestibular input),recordings were made while the subjects were standing immersed in thermo-neutral water up to the level of the diaphragm

so that vestibular input remained the same but venous pooling was prevented. The immersion of upright subjects to the hydrostatic indifference point (xiphoid) prevents venous pooling by the counteracting pressure of the water column. This leads to a blood distribution very similar to that in the supine posture (Gauer & Thron 1965, Risch et al 1978).

Increasing the water level up to the neck causes a shift of blood to the thorax with a consequent increase in stroke volume and cardiac output (Arborelius et al 1972, Farhi & Linnarsson 1977, Lollgen et al 1981).

METHODS

Subjects

Fourteen subjects (7 male, 7 female) were chosen for this study. They all showed prominent "10 second" oscillations during maintained standing. The age ranged between 18 and 44 years with a mean of 23.0 $\pm$ 1.8. The physical characteristics of the subjects are shown in Table (7 - 1). ECG examination was made prior to these experiments and it was normal in all the subjects.

Experimental Protocol

The tank (1.35 X 1.35 X 1.85 m.) was filled with warm water prior to the experiment and the water temperature was maintained between 35 and 37° C.

Initially, the recordings (chapter II) were made for 10 minutes with the subjects standing outside the tank (air temperature was

	Sex	Age	Ht.(cm)	Wt.(kg)
1.	M	30	183	77
2.	F	19	160	55
3.	F	18	163	58
4.	F	20	155	51
5.	M	21	176	79
6.	M	20	173	73
7.	M	22	178	75.5
8.	M	18	180	70
9.	M	19	176	64
10.	M	24	183	67
11.	F	22	165	59
12.	F	24	164	58
13.	F	21	169	67.5
14.	F	44	160	54
Mean		23.0	170.4	65.1
± SEM		1.8	2.5	2.6

Table (7-1). Physical characteristics of the subjects.

24- 29° C) and then for 10 minutes with the subjects immersed in water to the level of the diaphragm (xiphoid), and then for a further 10 minutes with the subjects immersed to the level of the neck (C7) (Fig. 7 - 1).

Analysis

As described in detail in chapter II .

Statistical analysis

The two way analysis of variance followed by Newman-Keuls test was used for comparison of MHR, MAD, and CV% during the different conditions. A comparison was also made with the supine values recorded on a different day. The difference would be either significant at the 5% level ($P<0.05$) or not significant (NS).

RESULTS

MHR.

Table (7 - 2) shows the MHR for the individual subjects when they were supine, standing in air, standing immersed in water to the level of the diaphragm, and when they were immersed to the level of the neck.

There was no significant difference in MHR during immersion to the level of the diaphragm (74.8 $\pm$ 2.8) and immersion up to the level of the neck (76.7 $\pm$ 3.0). However, the MHR during both levels of immersion were significantly lower than the MHR during standing in air (96.5 $\pm$ 3.8) (Fig. 7-2).

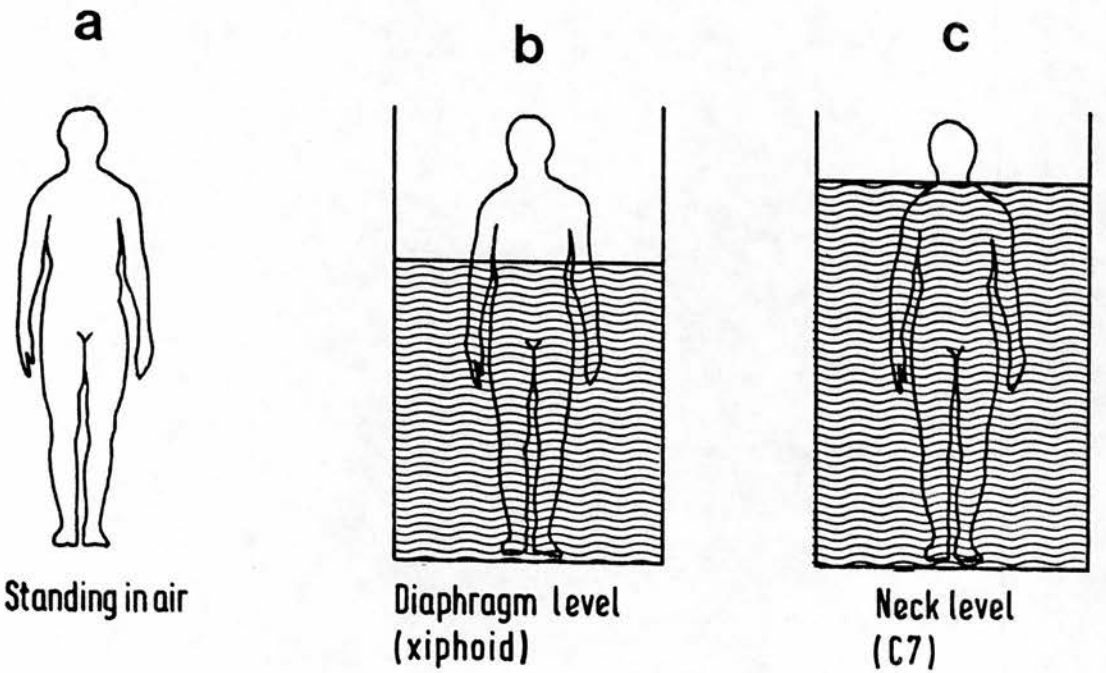


Fig.(7-1). The subjects were standing in air (control) in (a), standing immersed in thermoneutral water up to the level of the diaphragm in (b) and then they were immersed further up to the level of the neck in (c). The recordings were made in each of the three conditions for at least 10 minutes after stabilisation in the new water level.

	Supine	Standing in water diaphragm level	Standing in water neck level	Standing in air
1.	84	81	84	106
2.	82	76	84.5	89
3.	81	85	84	108
4.	74	67	71	89
5.	79	76	79	94
6.	69	78	83	98.5
7.	57.5	68	67	95
8.	62.5	59	64	110.5
9.	61	56	56	66
10.	73	84	85	97
11.	70	88	96	92
12.	67	80	85	100
13.	54	64.5	66.5	81
14.	81	84	69	125.5
Mean	71.1	74.8	76.7	96.5
± SEM	2.6	2.8	3.0	3.8

Table (7-2). The MHR during standing in air and standing immersed in water to the two different levels on the same day. The supine MHR was recorded on a different day.

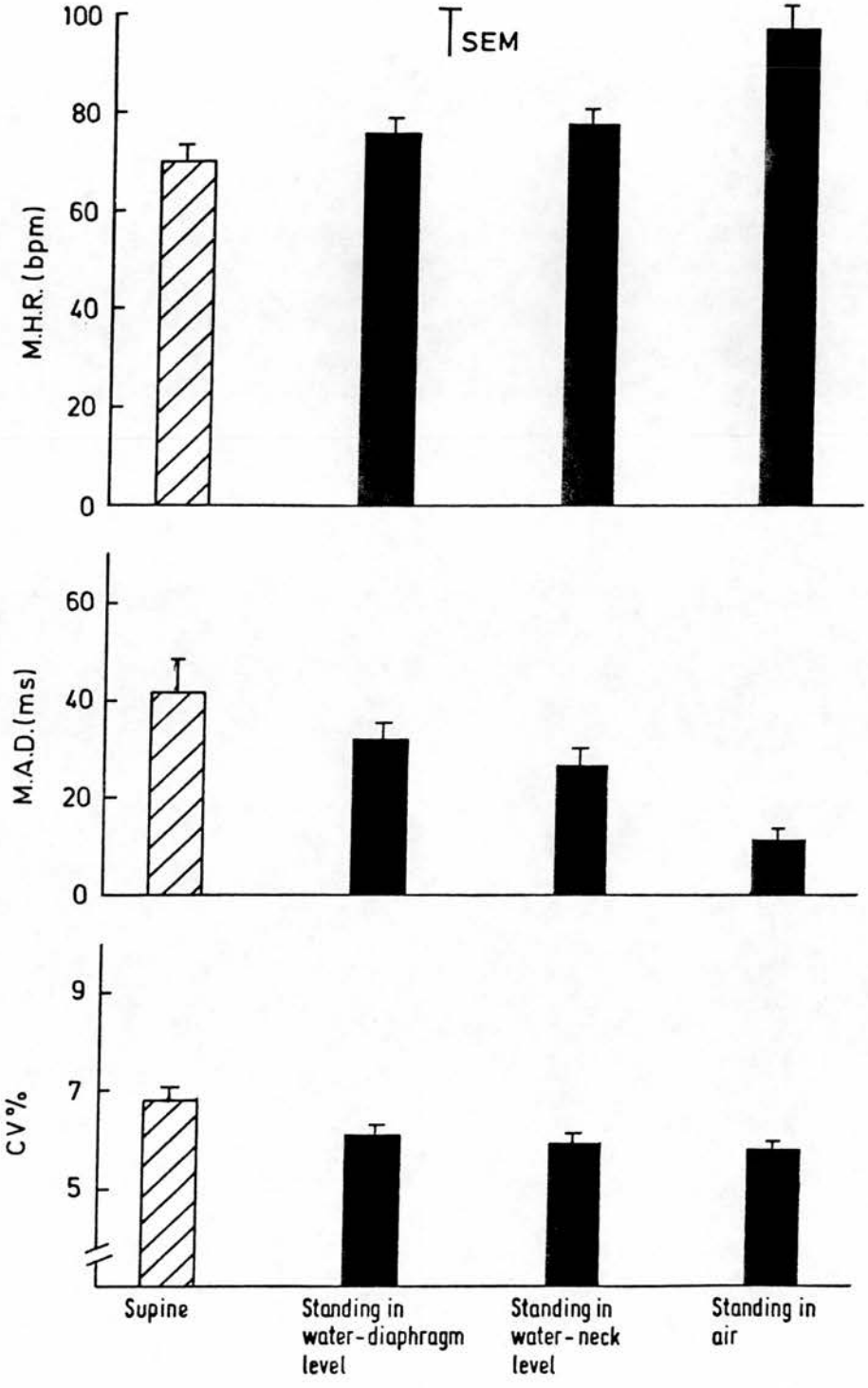


Fig.(7-2). The means of MHR, MAD and CV% for all the subjects during standing immersed in water up to the two different levels (diaphragm and neck). The supine values were recorded on a different day.

Similarly, the MHR during supine posture (71.1 ± 2.6) was not significantly different from the MHR during both levels of immersion , but it was significantly lower than the MHR during standing in air (96.5 ± 3.8) (Fig.7-2).

MAD

The MAD for the individual subjects during the three experimental conditions and also during supine posture are all shown in Table (7 - 3).

The MAD during standing in air (11.3 ± 1.5) was significantly lower than the MAD during immersion in water to the level of the diaphragm (32.0 ± 3.4) and also during immersion to the level of the neck (26.1 ± 3.7) (Fig. 7 - 2).

In 10 subjects out of the total of 14, the MAD during immersion to the level of the neck was lower than the MAD during immersion to the level of the diaphragm (Table 7 - 3). The mean for all the subjects during neck immersion (26.1 ± 3.7) was not significantly different from the mean during diaphragm immersion (32.0 ± 3.4), but it was lower.

The MAD during supine posture (40.8 ± 7.6) was not significantly different from the MAD during immersion to the level of the diaphragm (32.0 ± 3.4), but it was significantly higher than the MAD during immersion to the level of the neck (26.1 ± 3.7) and the MAD during standing outside the tank (11.3 ± 1.5) (Fig. 7 - 2).

	Supine	Standing in water diaphragm level	Standing in water neck level	Standing in air
1.	6.8	15.1	8.2	3.9
2.	21.3	24.1	12.3	15.7
3.	18.6	25.6	22.7	5.5
4.	34.0	49.0	28.9	12.5
5.	17.2	30.9	31.1	6.6
6.	41.5	35.4	25.5	10.2
7.	79.4	49.0	41.4	14.5
8.	46.3	36.7	44.6	6.0
9.	38.6	43.1	50.7	21.0
10.	27.4	17.3	11.5	11.8
11.	52.5	15.8	6.3	16.3
12.	59.3	37.0	23.4	15.2
13.	111.4	48.5	35.2	16.0
14.	17.5	20.7	23.5	3.0
Mean	40.8	32.0	26.1	11.3
± SEM	7.6	3.4	3.7	1.5

Table (7-3). The MAD during standing in air and standing immersed in water to the two different levels on the same day. The supine MAD was recorded on a different day.

CV%

Table (7 - 4) shows the individual CV% during the three different experimental conditions and also during supine posture. The means of the CV% for all the subjects were not significantly different from each other in all the four conditions (Fig. 7 - 2).

HRV

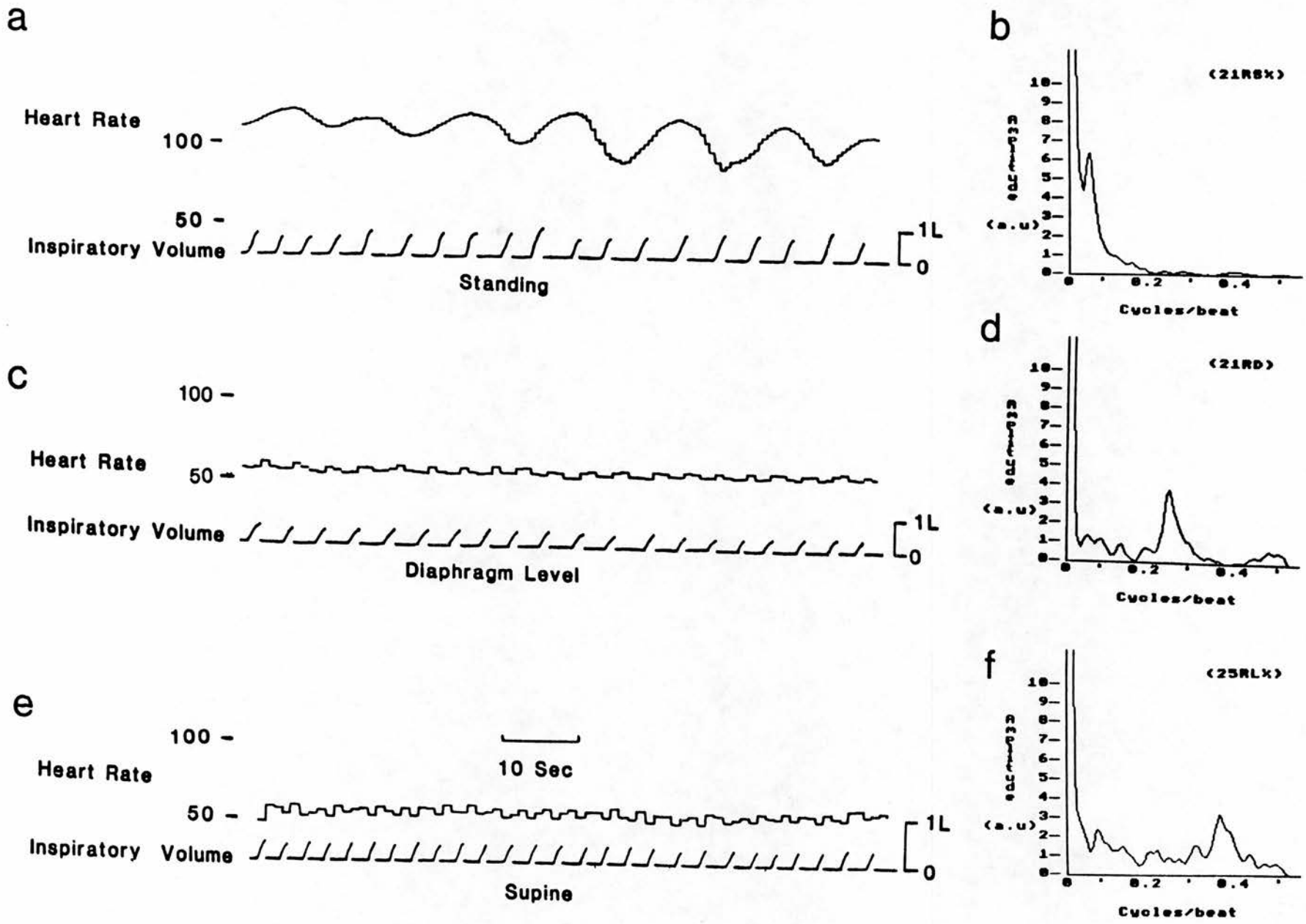
The effect of immersion in water to the level of the diaphragm on the heart rate pattern in one subject is illustrated in (Fig.7-3). When the subject was standing outside the tank, the heart rate spectrum (b) showed a single large peak at $\sim$0.1 cycles/beat, and the "10 second" oscillations were very prominent in the heart rate (a). Then the subject was immersed in water up to the level of the diaphragm and although he was standing, the heart rate pattern was completely different from the control standing in air. The heart rate spectrum (d) showed a large peak at the respiratory frequency ($\sim$ 0.26 cycles/beat), while the peak at $\sim$0.1 cycles/beat which had been very prominent during standing in air (b) was hardly visible. Consequently the predominant rhythm in heart rate (c) was the respiratory sinus arrhythmia. This pattern was very similar to the heart rate pattern during supine posture. The heart rate spectrum (f) showed a prominent peak at the respiratory frequency ($\sim$0.36 cycles/beat) and the "RSA" was the predominant rhythm in the heart rate (e) as it was during immersion in (c).

This remarkable change in heart rate pattern from "10 second" rhythm during standing in air to "RSA" during standing in water

	Supine	Standing in water diaphragm level	Standing in water neck level	Standing in air
1.	2.9	2.9	3.6	3.0
2.	9.9	6.0	5.9	6.3
3.	5.4	5.6	6.0	4.5
4.	7.9	9.9	7.9	7.2
5.	2.9	4.8	5.4	3.7
6.	6.7	6.8	7.3	6.4
7.	8.9	11.0	8.3	8.4
8.	6.9	3.9	5.6	5.5
9.	9.5	6.2	5.8	6.3
10.	4.1	3.7	4.8	6.8
11.	9.7	5.1	3.2	5.5
12.	7.1	7.2	8.4	8.4
13.	7.7	6.1	4.8	4.3
14.	5.2	5.1	6.1	4.5
Mean	6.8	6.0	5.9	5.8
± SEM	0.7	0.6	0.4	0.5

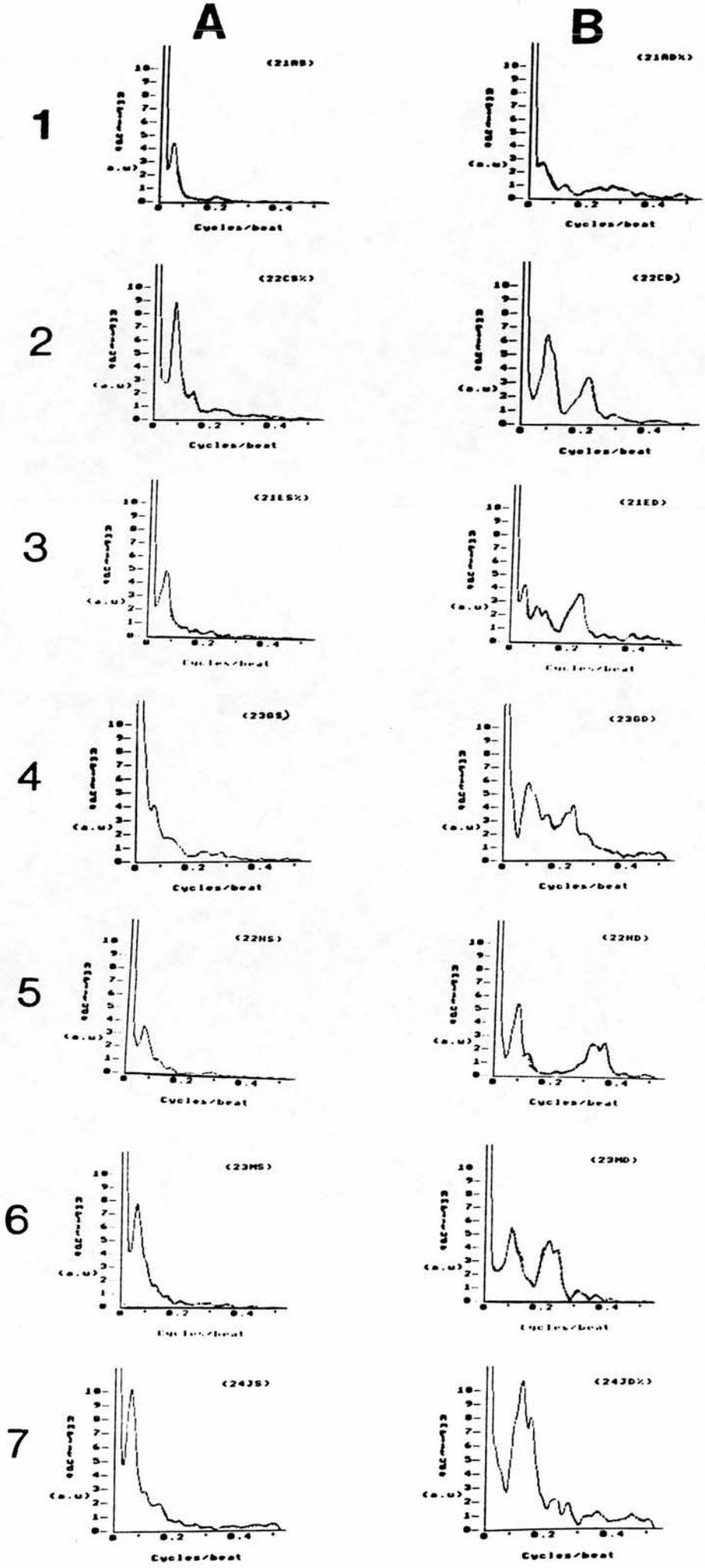
Table (7-4). The CV% during standing in air and standing immersed in water to the two different levels on the same day. The supine CV% was recorded on a different day.

Fig.(7-3) shows the change in heart rate pattern from predominantly "10 second" rhythm during standing in air (a) to predominantly "RSA" rhythm during standing immersed in water up to the level of the diaphragm in (c) which was very similar to the heart rate pattern during supine posture recorded on a different day in (e).


a
Heart Rate
100 -
50 -
Inspiratory Volume
1L
0
Standing
b
(21RSX)
(a.u)
Cycles/beat
c
100 -
Heart Rate
50 -
Inspiratory Volume
1L
0
Diaphragm Level
d
(21RD)
(a.u)
Cycles/beat
e
100 -
10 Sec
Heart Rate
50 -
Inspiratory Volume
1L
0
Supine
f
(25RLX)
(a.u)
Cycles/beat

immersed to the level of the diaphragm, has been consistent in all the 14 subjects studied. The heart rate spectra for all the subjects during standing in air (A) and standing immersed in water to the level of the diaphragm (B) are shown in Fig.(7-4). During standing outside the tank (A), all the subjects showed a large peak at $\sim$0.1 cycles/beat with a much smaller peak, if any, at the respiratory frequency. Therefore, the ratio between the two peaks was high and the predominant rhythm was the "10 second" oscillations as in (a) of Fig.(7 - 3). When the subjects were immersed in water to the level of the diaphragm, the heart rate pattern became very similar to the heart rate pattern of these subjects during supine posture, with the "RSA" being the predominant rhythm. However, the detailed changes in the two major rhythms i.e. the "10 second" oscillatios and "RSA" were not the same in all the subjects.

In seven subjects (No. 1,7,8,9,10,11 & 13) there was a marked decrease in the size of the peak at $\sim$0.1 cycles/beat with a concurrent increase in the size of the respiratory peak. While in the other seven subjects (No. 2,3,4,5,6,12 & 14), there was no or slight decrease in the size of the peak at $\sim$0.1 cycles / beat, but the marked increase in the size of the respiratory peak led to a considerable decrease in the ratio between the two peaks. Consequently the "RSA" was predominant and the "10 second" rhythm was infrequent and of apparently smaller amplitude. The spectra of these subjects also showed a similar peak at $\sim$0.1 cycles / beat when they were supine.


A
B
1
2
3
4
5
6
7
Cycles/beat

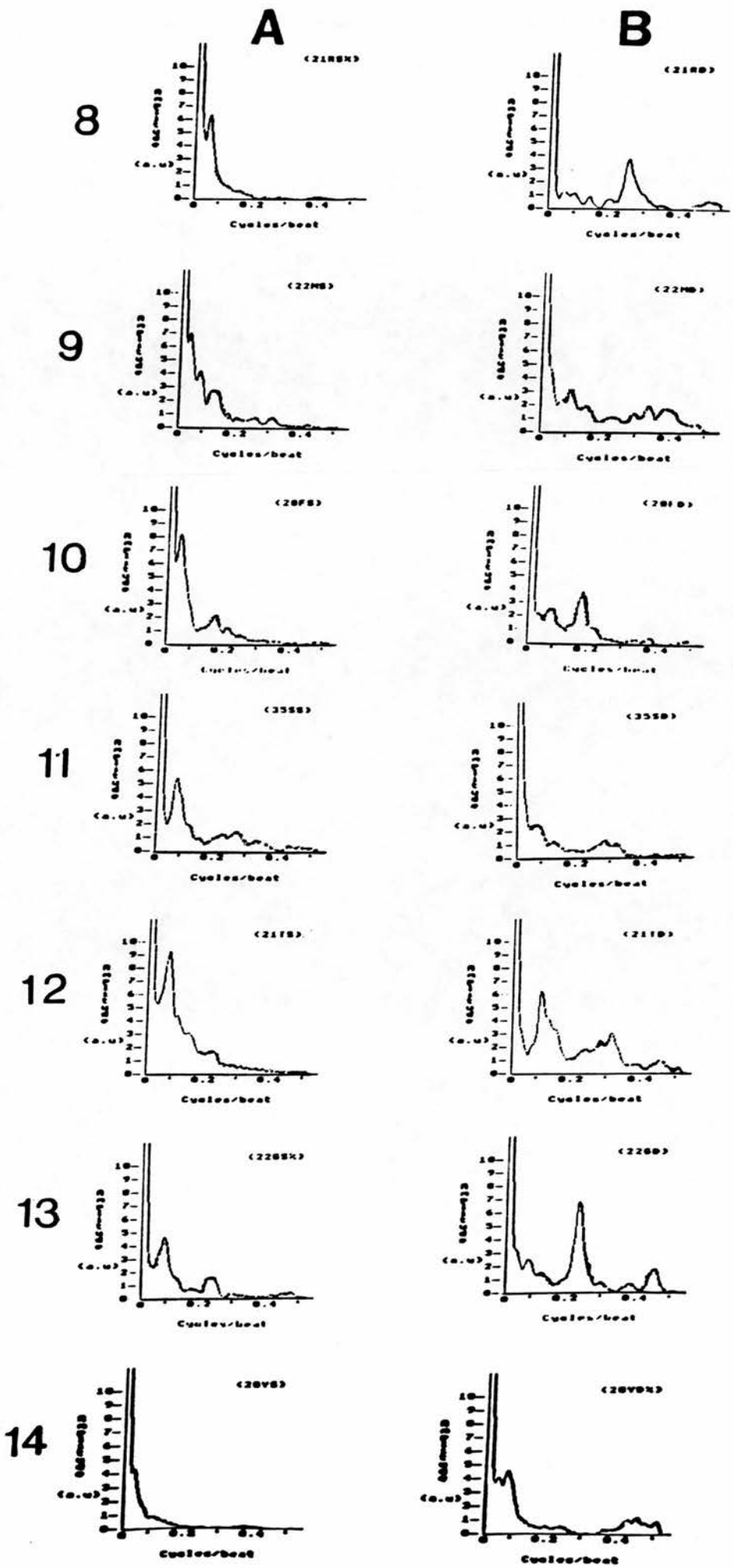


Fig.(7-4).The heart rate spectra for all the subjects during standing in air(A) and standing immersed in water up to the level of the diaphragm(B).

The heart rate patterns during the two levels of immersion in one subject is illustrated in Fig.(7-5). During both, immersion to the level of the diaphragm (a) and to the level of the neck (c), the predominant rhythm in heart rate was the respiratory sinus arrhythmia, however the amplitude of "RSA" during immersion to the level of the neck seemed to be smaller. The heart rate spectra showed clearly that the peak at the respiratory frequency ($\sim$0.28 cycles/beat) during immersion to the level of the neck (d) was indeed smaller than the respiratory peak at $\sim$ 0.23 cycles/beat during immersion to the level of the diaphragm (b).

In 10 out of 14 subjects, the increase in water level from the diaphragm to the neck caused a reduction in the size of the peak at the respiratory frequency with a consequent decrease in the amplitude of the respiratory sinus arrhythmia .

DISCUSSION

The non-significant difference in the results of MHR, MAD and CV% between standing immersed to the level of the diaphragm and supine posture is most likely due to the similarity of blood distribution in both conditions (Risch et al 1978).

Both the MHR and MAD during standing immersed to the level of the diaphragm were significantly different from that during standing in air. It is likely that the increased venous return during immersion which leads to an increase in right atrial pressure (Arborelius et al 1972, Lollgen et al 1981), causes stimulation of the mechanoreceptors in the low pressure side of the circulation

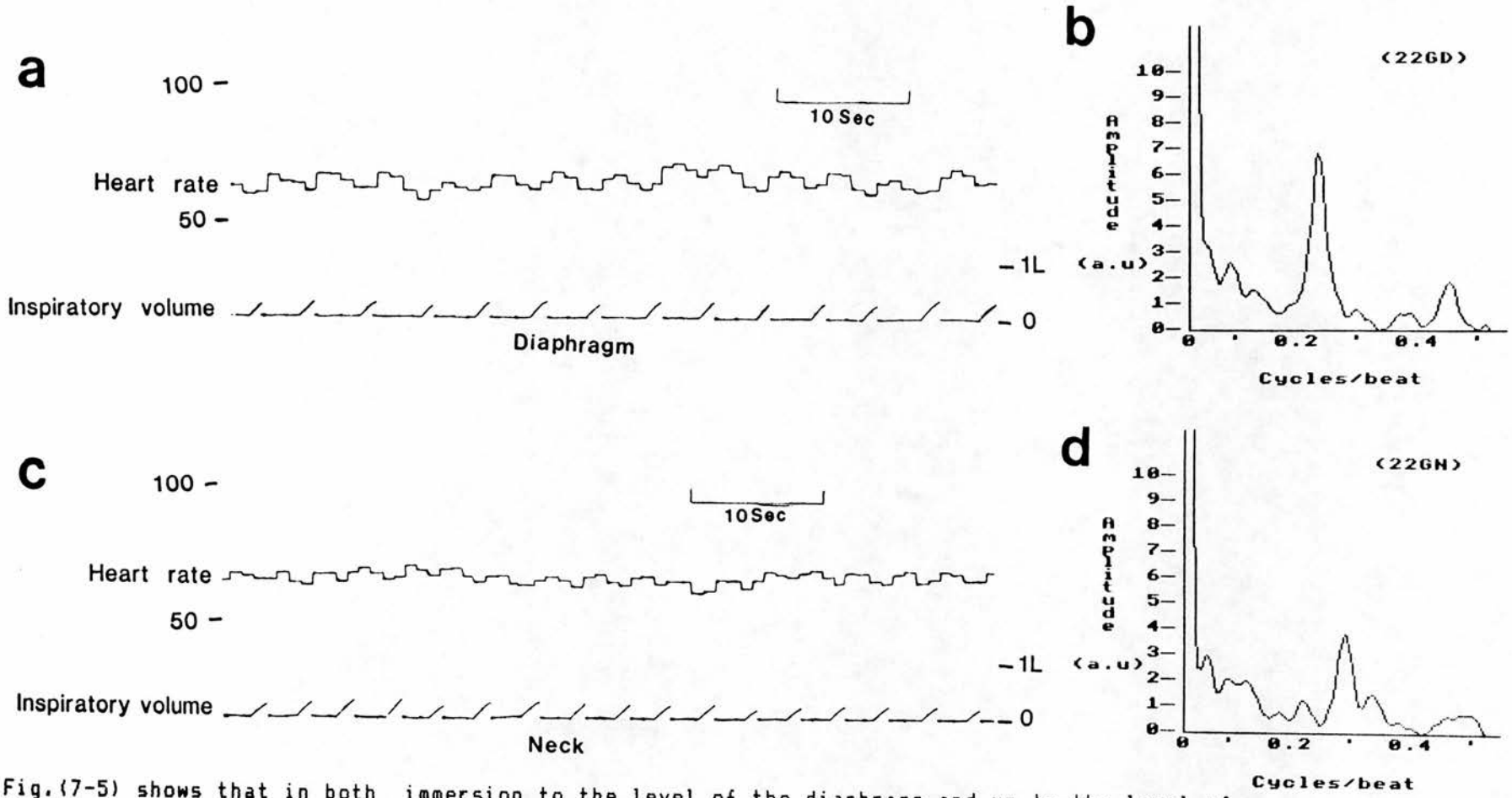


Fig.(7-5) shows that in both immersion to the level of the diaphragm and up to the level of the neck, the respiratory sinus arrhythmia was the predominant rhythm, but the amplitude of "RSA" was smaller during the latter level.

(Donald and Shepherd 1978, Shepherd 1981). Reflexes from these cardiopulmonary receptors were shown to play a far more important role in the regulation of heart rate than reflexes from arterial baroreceptors (Zanchetti et al 1976, Mancia et al 1977). An increased stimulation of the low pressure receptors could have caused the decrease in MHR and the increase in MAD by reflexly increasing the vagal activity.

In spite of the significant increase in MAD during immersion, the CV% was not significantly different from that during standing in air. This was most likely due to the decrease in LTV during immersion (Chapter III, Fig.3-23). This was clearly the case as was shown by the change in heart rate pattern. The "10 second" oscillations almost disappeared during immersion.

The disappearance of the "10 second" oscillations with the prevention of venous pooling and the similarity of this pattern to the one during supine posture when blood distribution is similar (Risch et al 1978) suggests that the shift of blood to the lower parts of the body during the erect posture (Gauer and Thron 1965) has an important contribution to the appearance of these oscillations.

The change in heart rate pattern occured even though the vestibular input must have been the same as the subjects were in the standing posture in both conditions. Thus it seems that although vestibular input was shown to participate in the rapid neural reflex to orthostatic stimulus in the anaesthetised paralysed cats (Doba and Reis 1974, Koyama et al 1981), it is not the dominant factor

controlling the increase in MHR and the change in pattern observed during maintained standing in conscious man.

During immersion to the level of the neck, the MHR, MAD and CV% were not significantly different from those during immersion to the level of the diaphragm. This was reflected in similar heart rate patterns with the "RSA" being predominant during both levels of immersion. However, in 10 subjects out of the total of 14, the MAD and the "RSA" peak were smaller during immersion to the level of the neck.

The increased work of breathing during immersion to the level of the neck (Hong et al 1969) should have increased the amplitude of the "RSA" by increasing the spill-over of activity from the respiratory to the cardiovascular centre (Heymans 1928). However, a decrease in "RSA" occured and it is likely that this may have been caused by the decrease in expiratory reserve volume (Hong et al 1969). This would have caused a decrease in the stimulation of the pulmonary stretch receptors which is one of the mechanisms proposed for the genesis of "RSA" (Hering 1871, Clynes 1960).

Chapter VIII

MECHANISMS OF AUTONOMIC CONTROL OF "HRV"

INTRODUCTION

In mammalian species including man, the heart begins beating rhythmically before innervation is developed (cf.Zugaib et al. 1980a). However, this spontaneous rhythmogenicity is modulated by various neuronal and humoral mechanisms. The principle mechanism involved in short term heart rate regulation is the autonomic reflexes mediated by the two branches of the autonomic nervous system, namely the sympathetic and the parasympathetic nervous systems.

Anatomy

The sympathetic preganglionic nerves, originating from the intermedio- lateral columns of the upper eight thoracic segments of the spinal cord, synapse in a cervical sympathetic ganglion and then the postganglionic nerves travel down to the heart via the cardiac plexus. Whereas, the preganglionic vagal nerves originate from the dorsal motor nucleus and the nucleus ambiguus in the medulla oblongata, and then travel down the neck and thorax as the vagus nerves to reach the heart walls where they synapse with short postganglionic parasympathetic neurons (Levy & Martin 1979).

Sympathetic - Parasympathetic interaction

The postganglionic vagal and sympathetic fibres often lie in close apposition in the heart and they may be even surrounded by a common Schwann sheath (Levy & Martin 1979, Levy 1984). This anatomical proximity has a functional significance, as it has been shown that the acetylcholine liberated from vagal nerve endings acts on presynaptic muscuranic receptors located on the postganglionic sympathetic nerve terminals, to inhibit norepinephrine release (Levy & Martin 1979, Chassaing et al 1983, Mace & Levy 1983, Levy 1984).

The above mechanism (pre-junctional interaction) could not explain all the phenomena of sympathetic - parasympathetic interactions, hence an interaction at the receptor sites involving changes in the concentration of cAMP and possibly also cGMP (post-junctional interaction) was thought possible (Levy 1971, Levy & Martin 1979, Chassaing et al 1983, Mace & Levy 1983, Levy 1984).

In addition to the two peripheral mechanisms mentioned above, a third mechanism was thought to be involved where interaction takes place in the central nervous system (Kollai & Koizumi 1979, Zemaityte et al 1985, Levy 1984, Langhorst et al 1981, Koizumi & Kollai 1981, Reis & Cuenod 1965, Criscione at al 1983, Korner & Uther 1975).

Whatever the mechanism, interaction between sympathetic and parasympathetic innervation to the heart does occur. As a result of this interaction, the phenomenon of accentuated antagonism appears. Under normal conditions, both divisions of the autonomic nervous system are tonically active. The vagus with its negative

chronotropic effect is counteracted by the positive chronotropic effect of the sympathetic system. However, the net result is not the algebraic sum of the two opposing influences because of the dominance of vagal effect (Samaan 1935, Warner & Cox 1962, Levy 1971, Levy & Martin 1979, Levy 1984).

Sympathetic - Parasympathetic relation

The relationship between the sympathetic and the parasympathetic systems has been traditionally considered as a simple reciprocal relation, with increased activity in one system associated with a concurrent decrease in the activity of the other (Heymans & Neil 1958). This concept, however, has been questioned and an alternative relationship was proposed by Glick & Braunwald (1965). They suggested that the changes in heart rate in response to changes in blood pressure might be achieved by a predominant change in one branch of the autonomic nervous system without necessarily an appreciable concurrent change in the other branch. But, the background level of autonomic activity profoundly influences the final results (Robinson et al 1966).

Similar non-reciprocal relations between sympathetic and parasympathetic control in response to alteration of cerebral function was reported in cats (Reis & Cuenod 1965).

More recently, both reciprocal as well as non-reciprocal relations were shown to exist in dogs (Kollai & Koizumi 1979, Koizumi & Kollai 1981, Langhorst et al 1981). Which one is operating in a certain reflex, depends on the source of afferent impulses. The end result is an effective control of circulatory homeostasis, and

this could sometimes be achieved by only a change in quantitative balance of the antagonistic actions rather than a complete change in the relationship between them (Kollai & Koizumi 1979).

The relative contribution of the two divisions of the autonomic nervous system is not the same for transient as for sustained heart rate changes (Tyden 1977). This is due to the different speed of action of the two divisions. The parasympathetic is fast (less than a second), while the responses to sympathetic stimulation is much longer (1 - 8 seconds) (Samaan 1935, Warner & Cox 1962, Levy & Martin 1979, Koizumi et al 1985).

Low pressure versus high pressure receptors in the control of heart rate

Reflexes arising from aortic and cardiopulmonary baroreceptors are now thought to play a far more important role than carotid sinus reflexes in the regulation of heart rate in man (Zanchetti et al. 1976, Mancia et al 1977).

This quantitative difference between low pressure versus high pressure receptors in heart rate control, seems to be species specific as the extracarotid receptors are predominant in dogs (Vatner et al 1971) and man (Zanchetti et al 1976, Mancia et al 1977) , but not in cats (Bertinieri et al 1987).

Evidences are also accumulating that there is a significant interaction between the low pressure and high pressure receptors (Teo et al 1985), however contradictory results were reported (Takeshita et al 1979, Billman et al 1981), and again species differences in the role of cardiopulmonary receptors in controlling the circulation was blamed (Takeshita et al 1979).

Autonomic control of heart rate variability

The presence of two slower rhythms in heart rate in addition to the fast respiratory sinus arrhythmia in man was shown by Sayers in 1973. Later, it was shown that these three rhythms also exist in decerebrated cats and thought to be an intrinsic feature of the dynamic regulation of heart rate by the vagus system with no role for the sympathetic activity in their genesis (Chess et al 1975). Similar results were reported in fetal lambs (Dalton et al 1983).
In dogs, the heart rate spectrum was also claimed to show three distinctive peaks (Akselrod et al 1981). Parasympathetic blockade abolished the mid and high frequency peaks (i.e. "10 second" and "RSA"), whereas sympathetic blockade alone tended to reduce the amplitude of the low-frequency peak (i.e. Thermoregulatory rhythm) (Akselrod et al 1981).
A decrease in LTV by beta-adrenergic blockade was shown in neonatal lambs (Zugaib et al 1980a). However, beta-blockade also caused a decrease in STV as well, in spite of no significant change in STV by adrenergic stimulation with isoproterenol. Moreover, the amount of decrease in LTV varied in the different weeks of postnatal life.

The demonstration of a shift in the centre frequency of the "10 second" rhythm by spectral analysis, was suggested as a clinical test for sympathetic disorders in diabetic patients (Van den akker et al 1983). This suggestion was proposed at a time when most of the results available had shown that the sympathetic nervous system has no role to play in the mediation of this rhythm (Chess et al 1975, Akselrod et al 1981).

To clarify the autonomic mechanism(s) controlling the "10 second" rhythm, a study of heart rate variability was made. This was measured under single autonomic control by blocking the other with a drug, and then under no autonomic control by blocking both divisions of the autonomic nervous system in both the supine posture and during maintained standing.

METHODS

Subjects

Six subjects (3 male, 3 female) who showed prominent "10 second" oscillations during maintained standing were selected. Their ages ranged between 19 and 45 years with a mean of 27.2 $\pm$ 3.9. The physicial characteristic of the subjects are shown in Table (8 - 1).

A thorough physical examination of the subjects including ECG and FEV_1 was made. All subjects were informed of the possible side effects of the drugs before signing the consent form.

Recordings

As described in chapter II.

Experimental protocol

The sympathetic outflow to the heart was blocked by propranolol (a beta - blocker), while the parasympathetic was blocked by atropine sulphate. The effects of the two blocking drugs on the

	Sex	Age	Ht (cm)	Wt (kg)
1.	M	31	183	77
2.	F	21	155	51
3.	M	22	176	75
4.	M	19	180	70
5.	F	25	164	55
6.	F	45	160	59
Mean		27.2	169.7	64.5
± SEM		3.9	4.6	4.4

Table (8-1). Physical characteristics of the subjects.

heart rate pattern during the change of posture from supine to maintained standing was studied on two different days. On the first day, initially two supine-standing manoeuvres (chapter III) were recorded (control I), and then Propranolol 160mg. was given orally. One supine-standing manoeuvre was done half an hour and one hour after the oral ingestion. After one and a half hours, when the peak plasma level of Propranolol should have been reached, two supine-standing manoeuvres were done.

On the second day, two supine-standing manoeuvres (control II) were recorded before Atropine 0.03mg/kg. was given slowly subcutaneously. The supine-standing manoeuvre was repeated twice, half an hour after the injection of Atropine. Then, a booster dose of subcutaneous Atropine was given to bring the total Atropine given to 3.0mg. Recordings in the supine posture was continued until the heart rate became stable when Propranolol 0.25mg/kg. body weight was given slowly intravenously (the ECG was monitored continuously on an oscilloscope screen). Under the effect of both Atropine and Propranolol, the supine-standing manoeuvre was repeated twice.

The doses and the routes of administration were chosen to get maximum blocking effects, while at the same time, trying to inflict the least possible adverse reactions.

Analysis

As described in detail in chapter II.

Statistical analysis

For the results of MHR, the paired -t- test was used, while the Wilcoxon signed rank test was used for the MAD and CV% results.

RESULTS

MHR

Table (8 - 2) shows the MHR for the individual subjects, in both supine and maintained standing posture, under control conditions in the two days of the study, and also under the effects of "Propranolol alone", "Atropine alone" and "Atropine + Propranolol". The combined results for all the subjects are illustrated in Fig (8 - 1).

The MHR during maintained standing was significantly higher ($P<0.001$) than supine MHR during control I, control II and "Atropine alone". During "Propranolol alone" the MHR during maintained standing (66.1 ± 2.4) was also significantly higher than supine MHR (58.2 ± 1.9) but to a lesser degree ($P<0.01$). The MHR during "Atropine + Propranolol" was not significantly different between the two postures (Fig. 8 - 1).

The MHR during both supine and maintained standing during control II, were significantly ($P<0.05$) higher than the corresponding MHR during control I (Fig.8-1).This was probably due to the hightened anxiety of the subjects in anticipation of the drug injections. Accordingly, the results of the effects of the drugs were expressed as the changes from the control values of the same day. The results for the individual subjects are shown in Table (8 - 3).

During "Propranolol alone", the mean change from control in the standing posture (-21.5 ± 1.6) was significantly ($P<0.001$) bigger

	Control I		Propranolol		Control II		Atropine		Atropine + Propranolol	
	supine	standing	supine	standing	supine	standing	supine	standing	supine	standing
1.	59.0	89.0	61.0	68.0	65.5	103.0	105.0	127.0	89.5	92.0
2.	64.0	90.0	63.0	70.0	76.0	108.0	110.0	138.0	105.0	106.0
3.	60.0	84.0	56.0	66.0	66.0	88.0	100.0	115.5	88.0	87.0
4.	66.0	101.5	58.0	72.0	63.0	95.5	127.0	145.0	95.0	113.0
5.	50.0	74.0	50.0	55.5	56.0	83.0	89.0	113.0	81.0	86.0
6.	71.5	86.5	61.0	65.0	81.0	101.5	104.0	132.0	87.0	90.0
Mean	61.8	87.6	58.2	66.1	67.9	96.5	105.8	128.4	90.9	95.7
±SEM	3.0	3.6	1.9	2.4	3.7	3.9	5.1	5.1	3.4	4.6

Table (8-2). The individual MHR during both supine and maintained standing postures under control conditions on the two days (I & II) and also under the effect of propranolol and atropine separately and together.

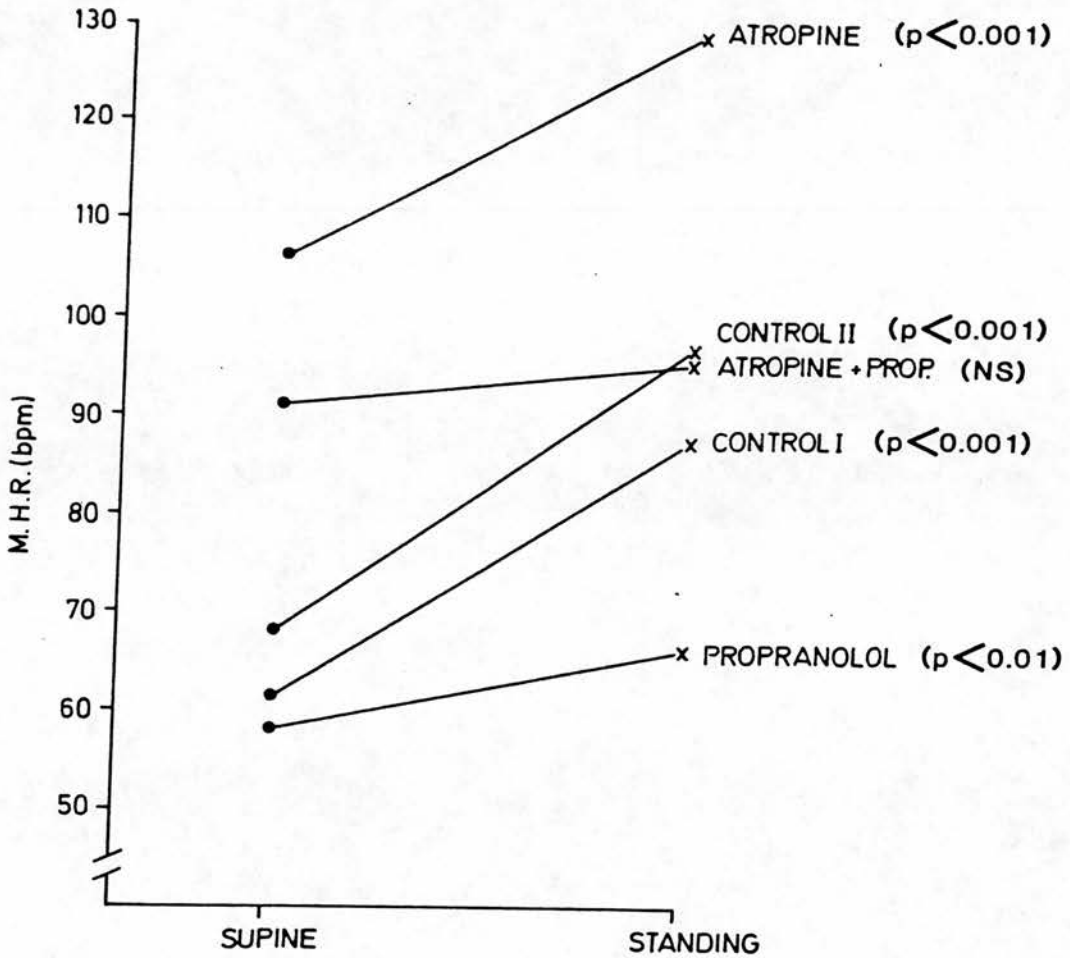


Fig.(8-1) shows the increase in MHR on changing posture from supine to maintained standing under control conditions on the two days (I & II) and also under the effect of propranolol and atropine separately and together. The statistical significance in this and the following figures refers to the difference between supine and maintained standing values.

	Propranolol – Control I		Atropine – Control II		((Atropine + Propranolol) – Control II)	
	Supine	Standing	Supine	Standing	Supine	Standing
1.	2	– 21	39.5	24	24	– 11
2.	– 1	– 20	34	30	29	– 2
3.	– 4	– 18.5	34	27.5	22	– 1
4.	– 8	– 29.5	64	49.5	32	17.5
5.	0	– 18.5	33	30	25	3
6.	– 10.5	– 21.5	23	30.5	6	– 11.5
Mean	– 3.6	– 21.5	37.9	31.9	23	– 0.8
± SEM	2.0	1.6	5.6	3.6	3.6	4.3

Table (8-3) shows the change in MHR from the corresponding control on the same day under propranolol and atropine separately and together, during supine and maintained standing postures.

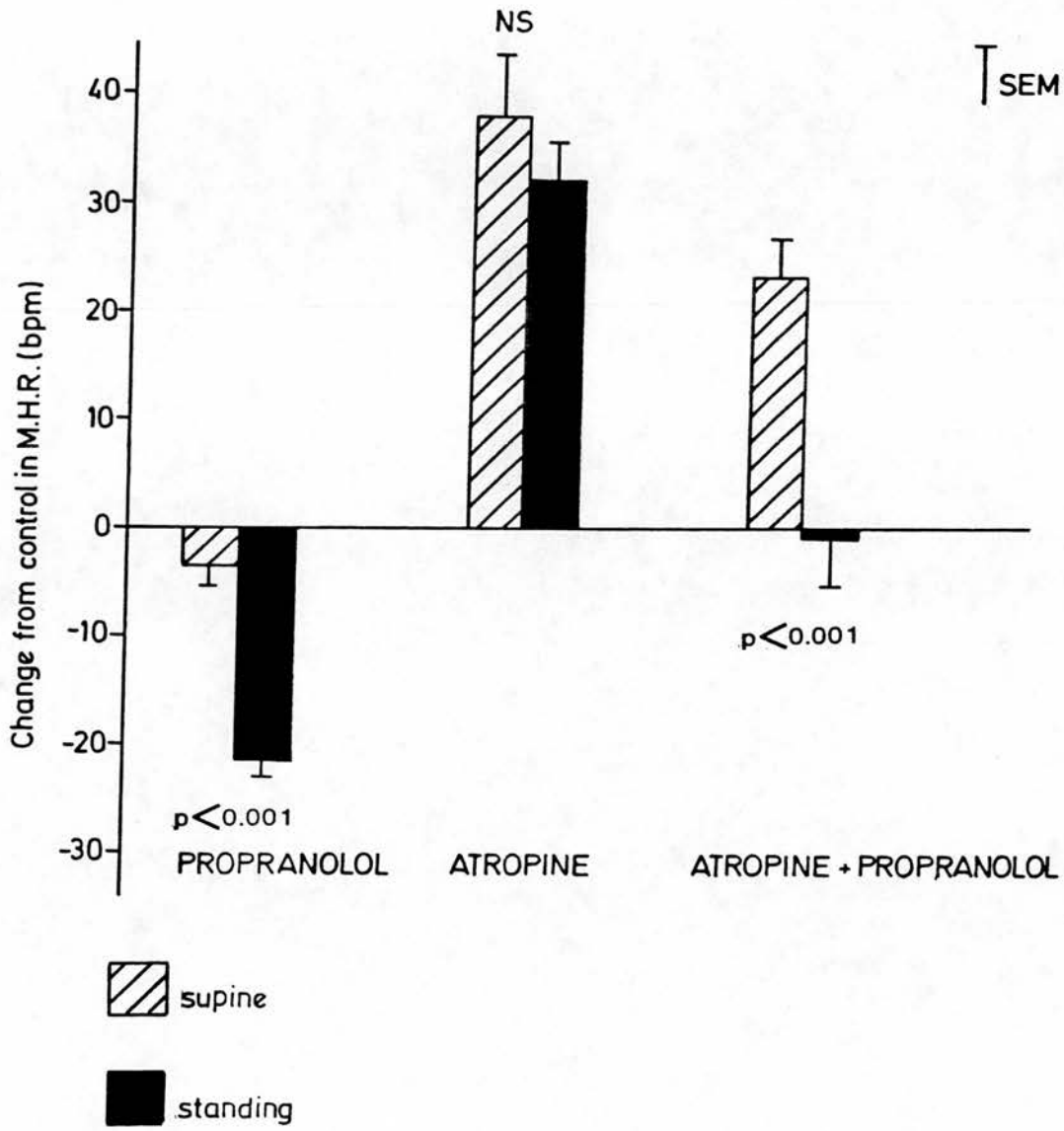


Fig.(8-2) shows the effect of propranolol and atropine separately and together on the change in MHR from control, during supine and maintained standing postures.

than the mean change in the supine posture (-3.6 ± 2.0)(Fig.8-2).

The decrease in MHR with Propranolol was significantly ($P<0.05$) related to the MHR during both supine ($r= 0.77$) and standing ($r = 0.86$) postures (Fig.8-3). So it seems that the higher the MHR the greater is the effect of Propranolol and consequently the decrease in MHR.

The increase in MHR during "Atropine alone" was not significantly different between the two postures (Fig.8-2). Adding Propranolol to Atropine had a differential effect on MHR. It lowered the MHR in both postures, but the decrease in MHR during standing (- 32.8 ± 2.2) was significantly ($P<0.001$) more than the reduction in MHR during supine posture (- 14.9 ± 3.8) (Fig.8-2).

In the supine posture, the increase in MHR with Atropine tended to be less with higher control MHR , but the correlation was poor ($r= -0.47$). In the standing posture there was no correlation whatsoever ($r= -0.08$) between control standing MHR and the increase in MHR with Atropine (Fig.8-4).

△ HR

The △ HR for the individual subjects during controls and under the effects of the drugs are shown in Table (8 - 4).

The △ HR during the two controls were not significantly different (Fig.8-5). However, △ HR during sympathetic blockade with oral Propranolol (7.9 ± 1.5) was significantly ($P<0.001$) lower than control △ HR (25.8 ± 2.8) (Fig.8-5).

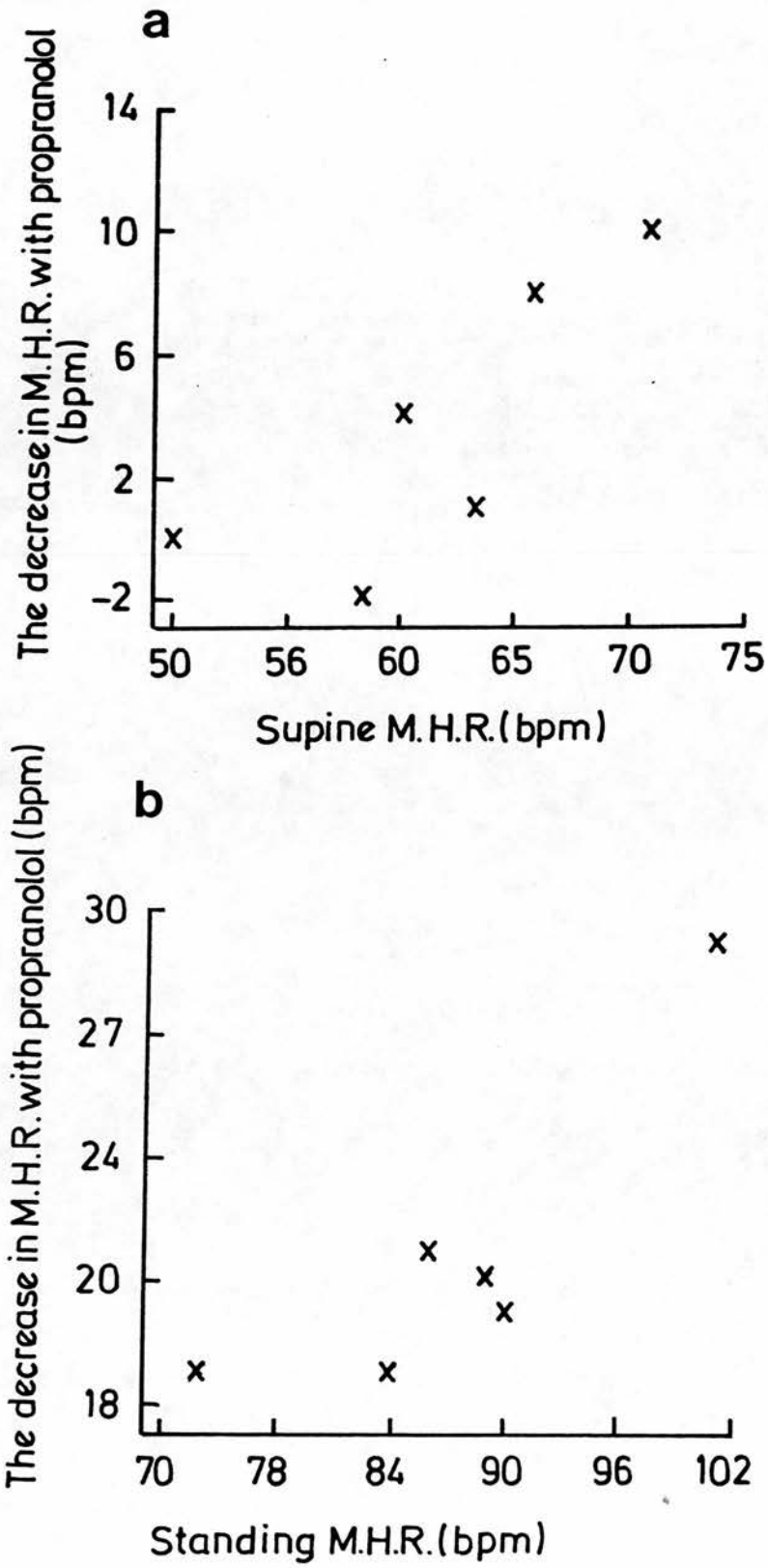


Fig.(8-3) shows significant ($p<0.05$) correlations between the decrease in MHR with propranolol and both supine MHR ($r=0.77$) in (a) and maintained standing MHR ($r=0.86$) in (b).

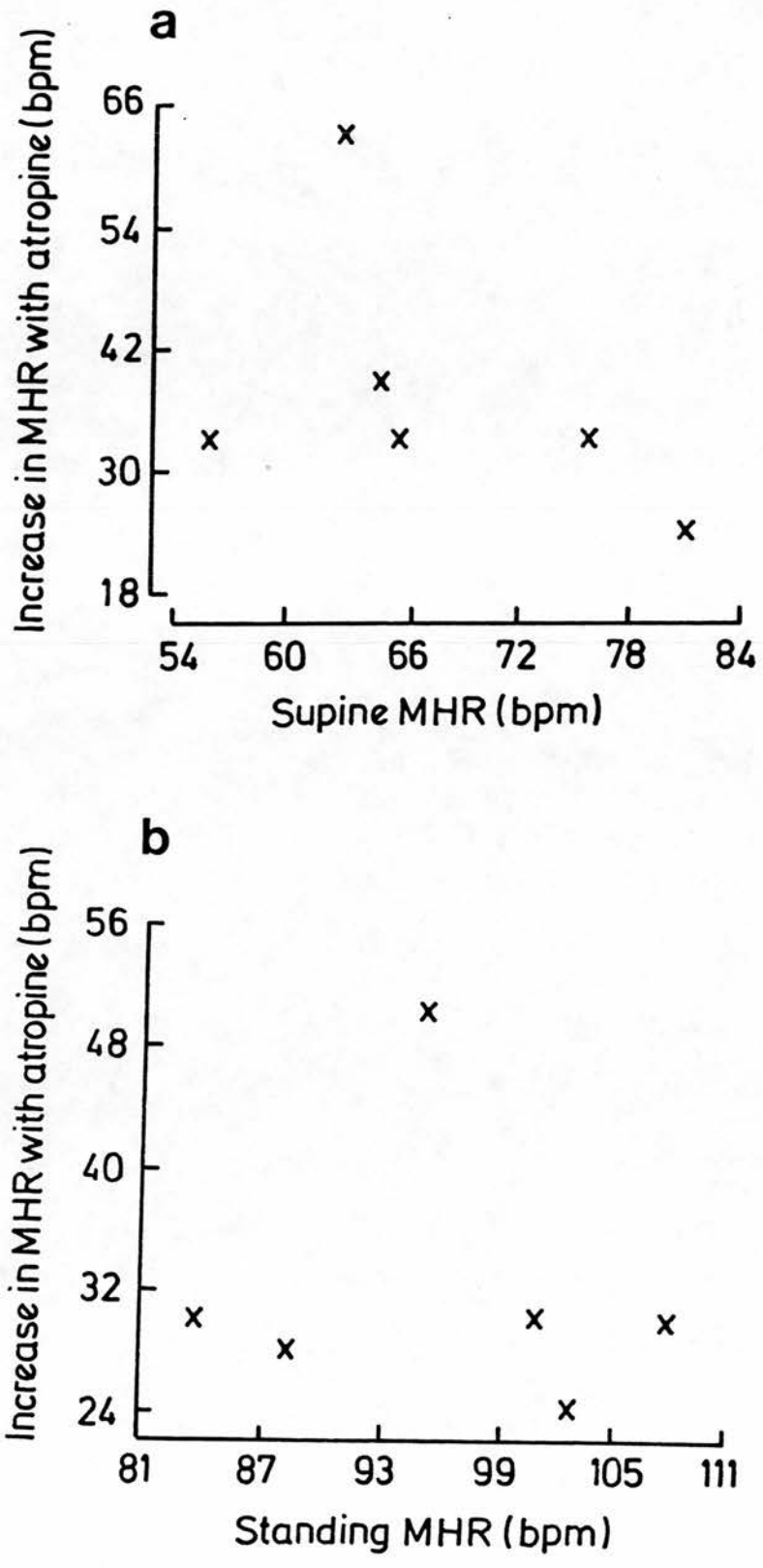


Fig.(8-4) shows the weak correlation (r=-0.47) between the increase in MHR with atropine and supine MHR in (a) and the lack of correlation with maintained standing MHR in (b).

	Control I	Propranolol	Control II	Atropine	Atrop. + Prop.
1.	30	7	37.5	22	2.5
2.	26	7	32	28	1
3.	24.5	10	22	15.5	−1
4.	35.5	14	32.5	18	18
5.	24	5.5	27	24	5
6.	15	4	20.5	28	3
Mean	25.8	7.9	28.6	22.6	4.8
± SEM	2.8	1.5	2.7	2.1	2.8

Table (8-4) shows ΔHR (the difference between maintained standing and supine MHR) under control conditions on the two days (I & II) and also under the effect of propranolol and atropine separately and together.

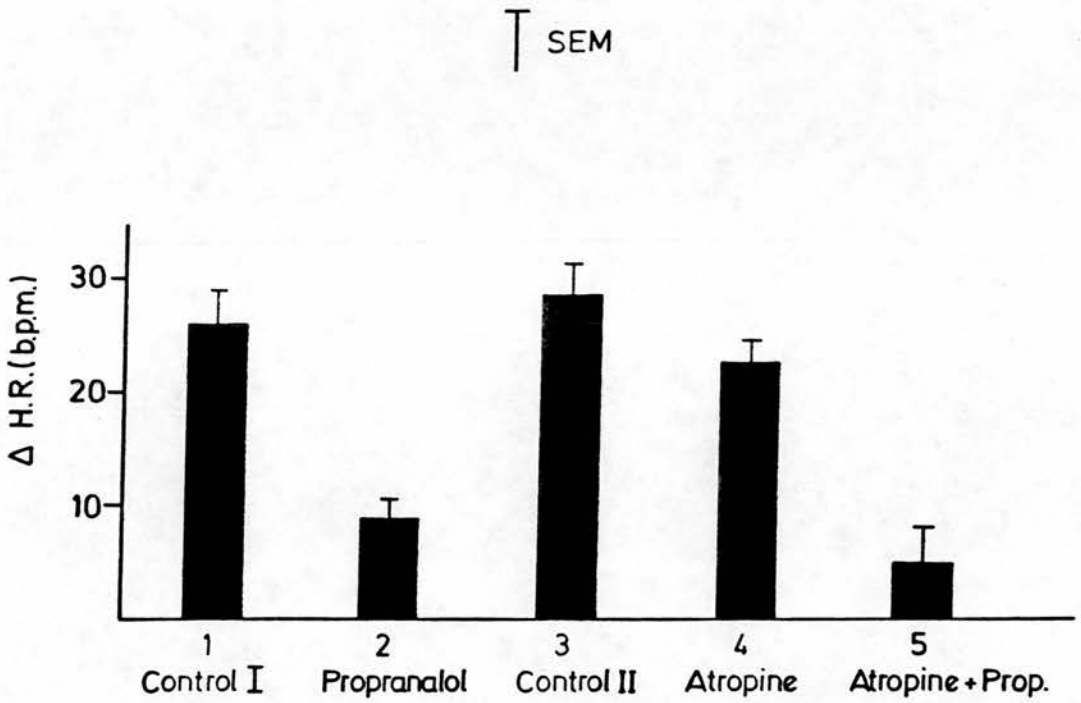


Fig.(8-5) shows the means of ΔHR (the difference between maintained standing and supine MHR) under control conditions on the two days (I & II) and also under the effect of propranolol and atropine separately and together.

Control I	V	Control II	NS
Control I	V	Propranolol	$p<0.001$
Control II	V	Atropine	NS
Atropine	V	Atropine + Propranolol	$p<0.01$
Control II	V	Atropine + Propranolol	$p<0.001$
Propranolol	V	Atropine + Propranolol	NS
Propranolol	V	Atropine	$p<0.001$

Atropine increased the MHR in both supine and standing postures to a similar extent and that made the $\triangle$ HR during "Atropine alone" (22.6 $\pm$ 2.1) not significantly different from control $\triangle$ HR (28.6 $\pm$ 2.7) (Fig.8-5).

The greater decrease in MHR during standing when Propranolol was added to Atropine caused the $\triangle$ HR during "Atropine + Propranolol" (4.8 $\pm$ 2.8) to be significantly ($P<0.01$) smaller than $\triangle$ HR during "Atropine alone" (22.6 $\pm$ 2.1) and also significantly ($P<0.001$) smaller than $\triangle$ HR during control (28.6 $\pm$ 2.7), but not significantly different from $\triangle$ HR during "Propranolol alone" (7.9 $\pm$ 1.5)(Fig 8 - 5).

MAD

Table (8 - 5) shows the change from control in MAD for the individual subjects during both supine and maintained standing postures, under different autonomic control.

"Propranolol alone" tended to increase the MAD. Although this increase was not significantly different between the two postures, it was more during maintained standing (11.3 $\pm$ 9.9) than during supine (1.4 $\pm$ 12.7) (Fig.8-6).

"Atropine alone" decreased the MAD significantly ($P<0.05$) in both postures, but the decrease during supine posture (-63.0 $\pm$ 23.8) was significantly ($P<0.05$) more than the decrease during standing (-9.7 $\pm$ 2.9) (Fig.8-6).

	(Propranolol – Control I)		(Atropine – Control II)		((Atrop. + Prop.) – Control II)	
	Supine	Standing	Supine	Standing	Supine	Standing
1.	– 11.2	4.4	– 31.9	– 3.7	– 31.4	– 2.8
2.	– 47.3	– 3.6	– 54.5	– 10.1	– 54.2	– 10.2
3.	23.5	6.3	– 34.4	– 8.2	– 32.7	– 7.8
4.	44.9	0.9	– 64.3	– 6.2	– 71.6	– 6.0
5.	– 8.3	61.4	– 178.8	– 23.8	– 176.6	– 23.4
6.	6.5	– 1.6	– 14.2	– 5.9	– 12.4	– 5.2
Mean	1.4	11.3	– 63.0	– 9.7	– 63.2	– 9.2
± SEM	12.7	9.9	23.8	2.9	23.7	3.0

Table (8-5) shows the change in MAD from the corresponding control on the same day under propranolol and atropine separately and together during supine and maintained standing postures.

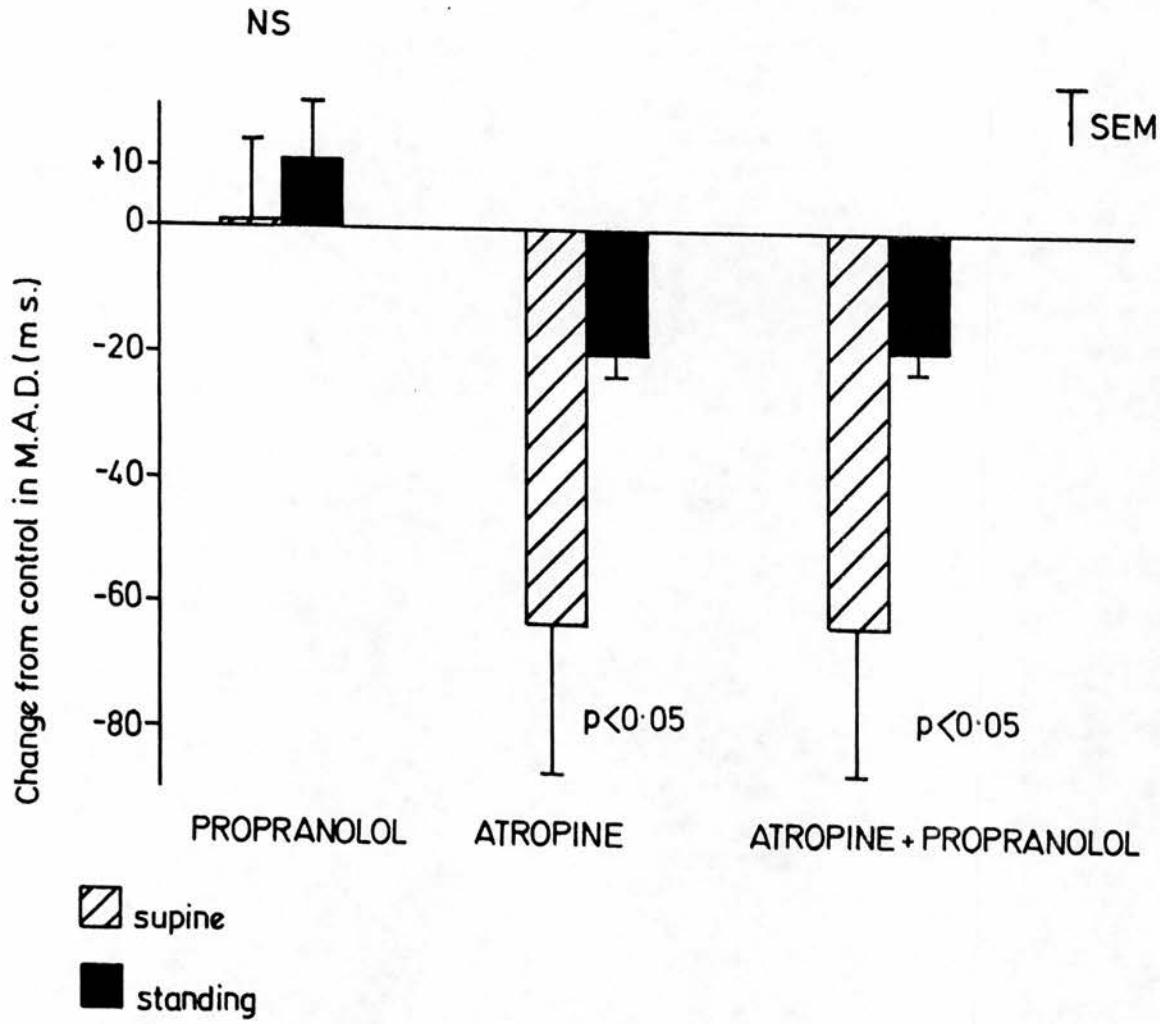


Fig.(8-6) shows the effect of propranolol and atropine separately and together on the change in MAD from control, during supine and maintained standing postures.

Adding Propranolol to Atropine did not make a significant change in the MAD during supine posture, but the reduction in MAD during standing (-9.2 ± 3.0) was smaller (P<0.1) than the reduction obtained with "Atropine alone" (-9.7 ± 2.9). So during "Atropine + Propranolol", the decrease in MAD during supine posture (-63.2 ± 23.7) was again significantly (P<0.05) bigger than the decrease during standing (-9.2 ± 3.0)(Fig.8-6).

In summary, "Atropine alone" was very powerful in reducing MAD, more significantly so in the supine posture. Propranolol tended to increase the MAD rather than decrease it. Although this tendency to increase MAD was not statistically significant, it did manage to counteract the effect of Atropine during standing, and that led to a decrease in the amount of reduction induced by both drugs compared with Atropine alone.

CV%

Table (8 - 6) shows the change from control in CV% for the individual subjects during both supine and maintained standing postures, under different autonomic control.

"Propranolol alone" tended to decrease the CV%. This decrease was more during maintained standing (-1.6 ± 1.3) than during supine posture (-0.8 ± 0.8) (Fig.8-7), but neither the decrease nor the difference between the two postures were statistically significant.

"Atropine alone" decreased CV% significantly (P<0.01) in both

	(Propranolol – Control I)		(Atropine – Control II)		((Atrop. + Prop.) – Control II)	
	Supine	Standing	Supine	Standing	Supine	Standing
1.	– 0.8	– 1.2	– 4.2	– 2.7	– 4.3	– 3.2
2.	– 4.0	– 5.6	– 10.5	– 7.1	– 9.2	– 7.8
3.	– 1.0	+ 0.3	– 1.6	– 2.8	– 2.1	– 4.6
4.	+ 2.3	– 2.6	– 4.3	– 3.1	– 5.4	– 3.6
5.	+ 0.5	+ 3.5	– 12.6	– 6.6	– 12.2	– 8.0
6.	– 1.6	– 4.2	– 3.6	– 2.9	– 4.0	– 3.8
Mean	– 0.8	– 1.6	– 6.1	– 4.2	– 6.2	– 5.2
± SEM	0.8	1.3	1.8	0.8	1.5	0.9

Table (8-6) shows the change in CV% from the corresponding control on the same day under propranolol and atropine separately and together, during supine and maintained standing postures.

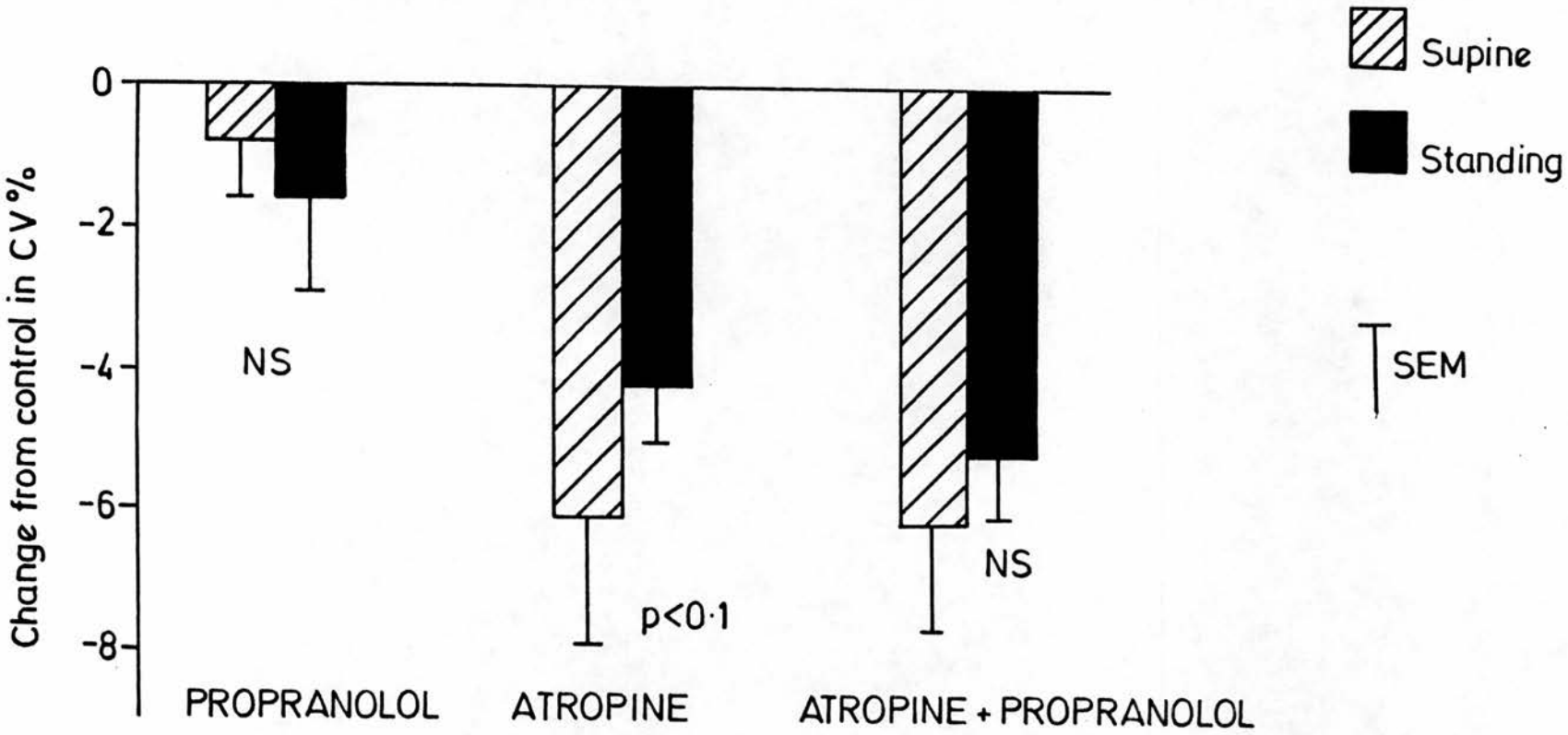


Fig.(8-7) shows the effect of propranolol and atropine separately and together on the change in CV% from control, during supine and maintained standing postures.

postures, but the decrease during supine posture (-6.1 ± 1.8) was significantly (P<0.1) more than the decrease during standing (-4.2 ± 0.8)(Fig.8-7).

Adding Propranolol to Atropine did not make a significant change in CV% during supine posture, but the reduction in CV% during standing (-5.2 ± 0.9) was significantly (P<0.05) bigger than the reduction obtained with "Atropine alone" (-4.2 ± 0.8) (Fig.8-7).

In summary, "Atropine alone" was effective in reducing CV%, more significantly so in the supine posture. Propranolol tended to decrease CV% as well, but more so in the standing posture.

During maintained standing, the change in CV% under "Propranolol alone" (-1.6 ± 1.3) was slightly (P<0.1) smaller than the change in CV% with "Atropine alone" (-4.2 ± 1.5) or "Atropine + Propranolol" (-5.2 ± 0.9). But, visual inspection of the records showed that Propranolol had already had a marked effect on the "10 second" rhythm during standing half an hour after the oral dose. Therefore, comparison of the results of MHR, MAD and CV% at half hour and one and a half hour after oral Propranolol was made (Table 8 - 7). Interestingly, the reduction in CV% at half hour (-2.8 ± 1.2) was found to be significantly (P<0.05) larger than the reduction caused at one and a half hour (-1.6 ± 1.3) (Fig.8-8).

In the light of this result, the effect of "Propranolol alone" during maintained standing at half hour was then compared with the effects of "Atropine alone" and "Atropine + Propranolol" and they were found not to be significantly different.

	MHR		MAD		CV%	
	½ hr.	1½ hr.	½ hr.	1½ hr.	½ hr.	1½ hr.
1.	– 18	– 21	– 0.8	4.4	– 1.8	– 1.2
2.	– 17	– 20	– 6.8	– 3.6	– 6.9	– 5.6
3.	– 16.5	– 18.5	10.5	6.3	– 0.9	0.3
4.	– 21.5	– 29.5	– 2.7	0.9	– 2.9	– 2.6
5.	– 16	– 18.5	38.9	61.4	1.5	3.5
6.	– 17	– 21.5	– 8.3	– 1.6	– 5.5	– 4.2
Mean	– 17.7	– 21.5	5.1	11.3	– 2.8	– 1.6
± SEM	0.8	1.6	7.1	9.9	1.2	1.3

Table (8-7). The MHR, MAD and CV% at half an hour and one and a half hour after oral propranolol (160 mg.).

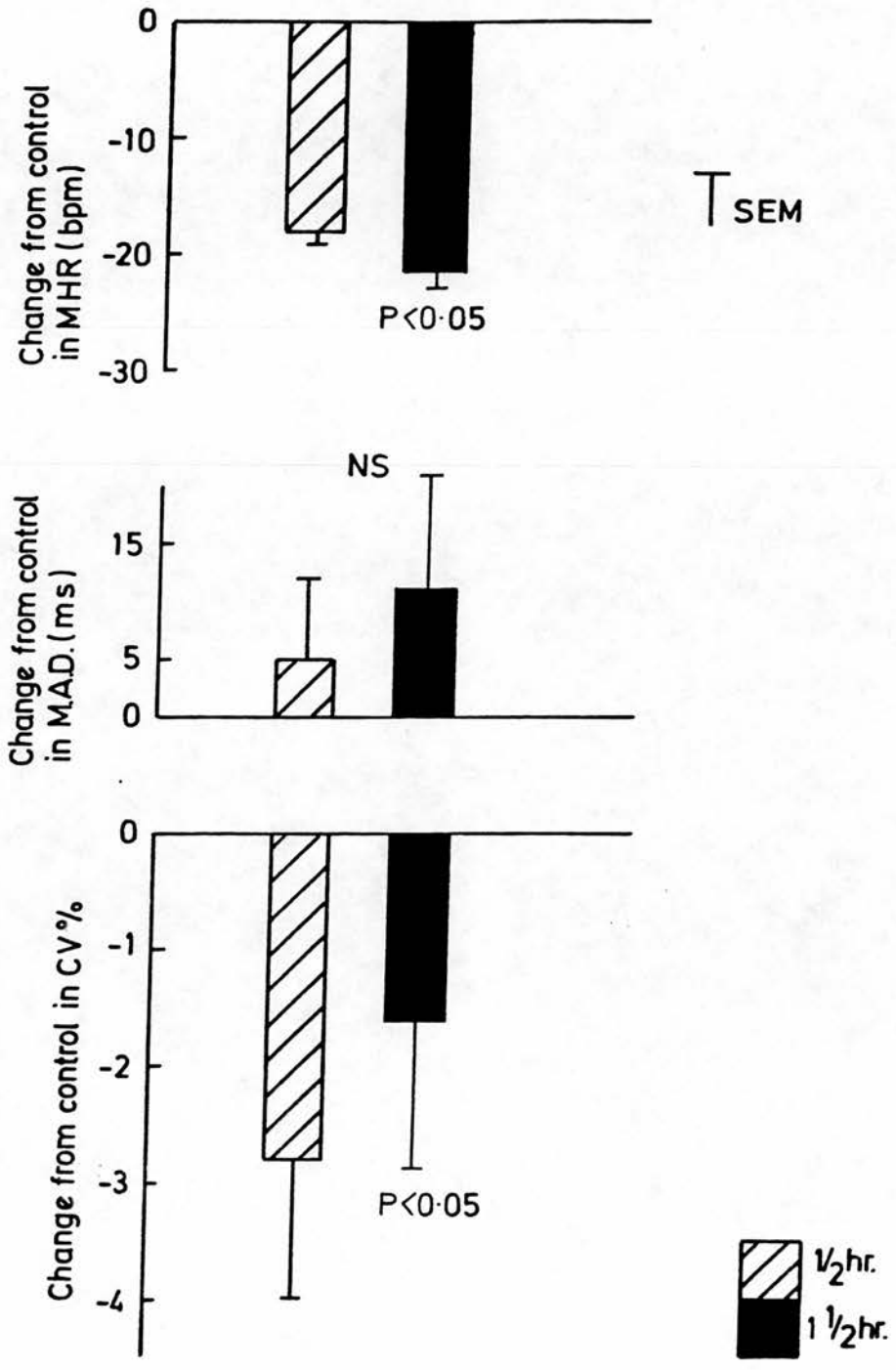


Fig.(8-8) compares the effect of oral propranolol (160 mg.) at half an hour and one and a half hour after ingestion, on the means of MHR, MAD and CV% for all the subjects.

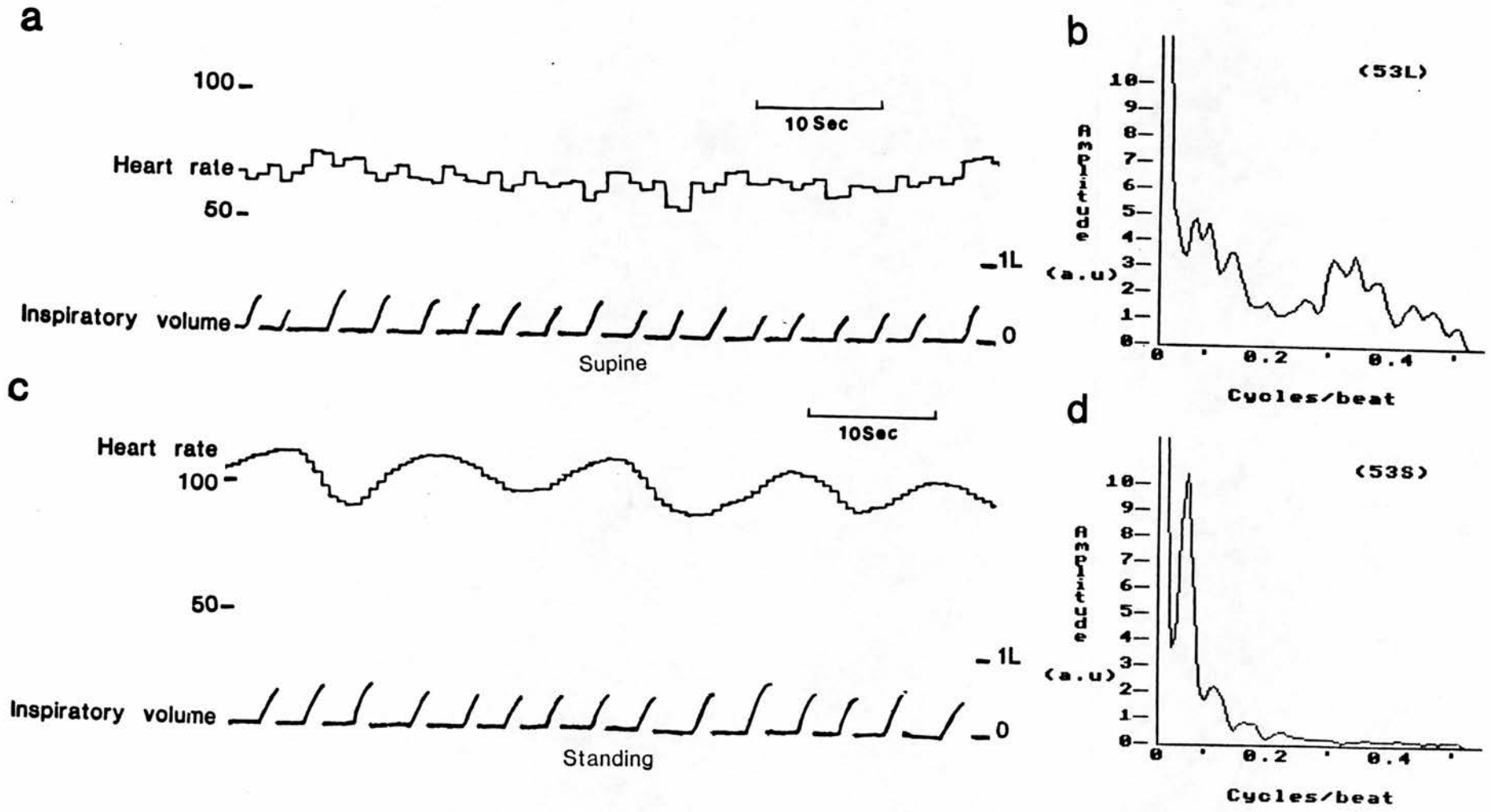
Due to selection, all subjects showed "10 second" rhythm during maintained standing.

In all the subjects, "Propranolol alone" caused a marked decrease in the amplitude of the "10 second" oscillations, while the "RSA" remained almost unchanged.

The effect of Propranolol in one subject is illustrated in Fig (8 - 9). During control, the "RSA" was predominant in the supine posture (a), while the "10 second" rhythm was predominant during maintained standing (c). The heart rate spectra reflected these differences. It showed two peaks, one at $\sim$0.1 cycles/beat and the other at the respiratory frequency ($\sim$0.31 cycles/beat) in the supine posture (b). During maintained standing, there was a large peak at $\sim$0.1 cycles/beat, while the peak at the respiratory frequency ($\sim$0.16 cycles/beat) was relatively very small.

One and a half hours after the oral Propranolol, the heart rate pattern during supine posture (e) was almost the same as it had been during control. However, during maintained standing (g) it was completely different. The "10 second" oscillations were markedly diminished, and the heart rate spectrum (h) showed no definite peak at $\sim$0.1 cycles/beat, in contrast to the one during control standing in (d).

In the same subject, the effect of Propranolol half an hour after the oral dose is shown in Fig (8 - 10) . During supine posture, the heart rate pattern (a) and spectrum (b) were very similar to


a
100
10 Sec
Heart rate
50
1L
Inspiratory volume
0
Supine
b
(53L)
Amplitude
(a.u)
10
9
8
7
6
5
4
3
2
1
0
0
0.2
0.4
Cycles/beat
c
10Sec
Heart rate
100
50
1L
Inspiratory volume
0
Standing
d
(53S)
Amplitude
(a.u)
10
9
8
7
6
5
4
3
2
1
0
0
0.2
0.4
Cycles/beat

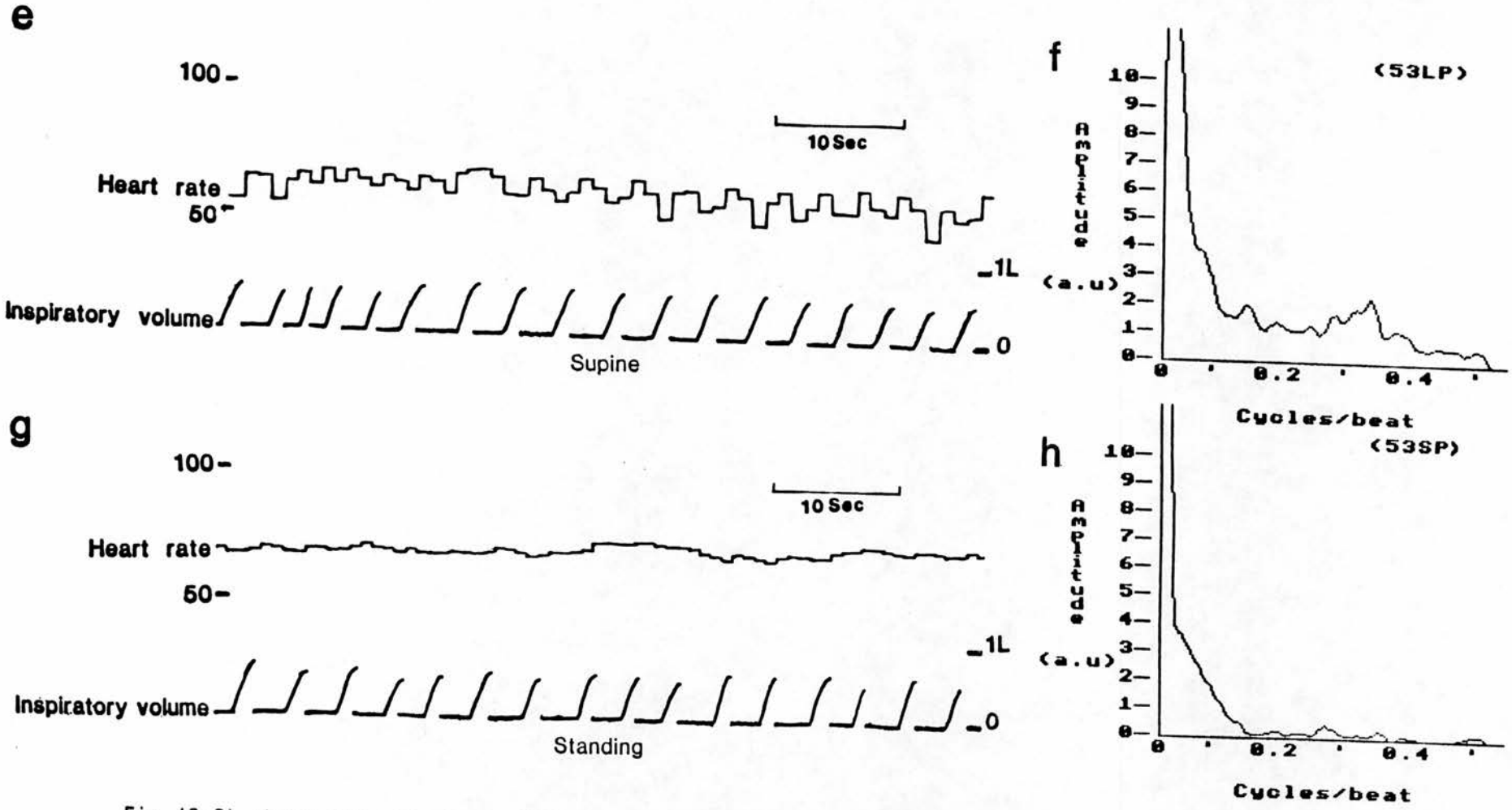


Fig.(8-9) shows the effect of 160 mg. of propranolol on the heart rate pattern, one and a half hour after oral ingestion. See text for details.

a & c ..... Control ; e & g ..... 1 1/2 hr. after propranolol.

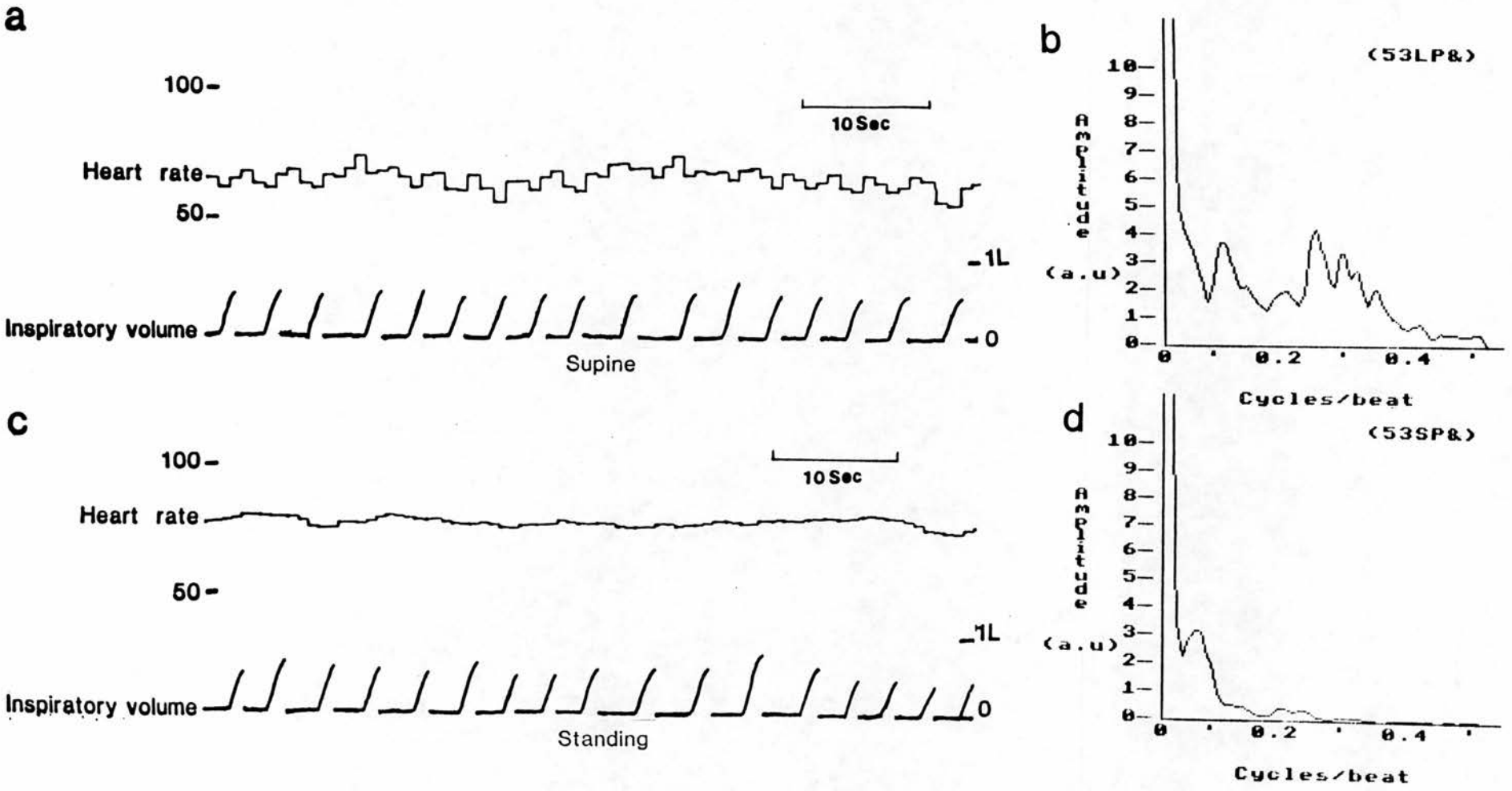


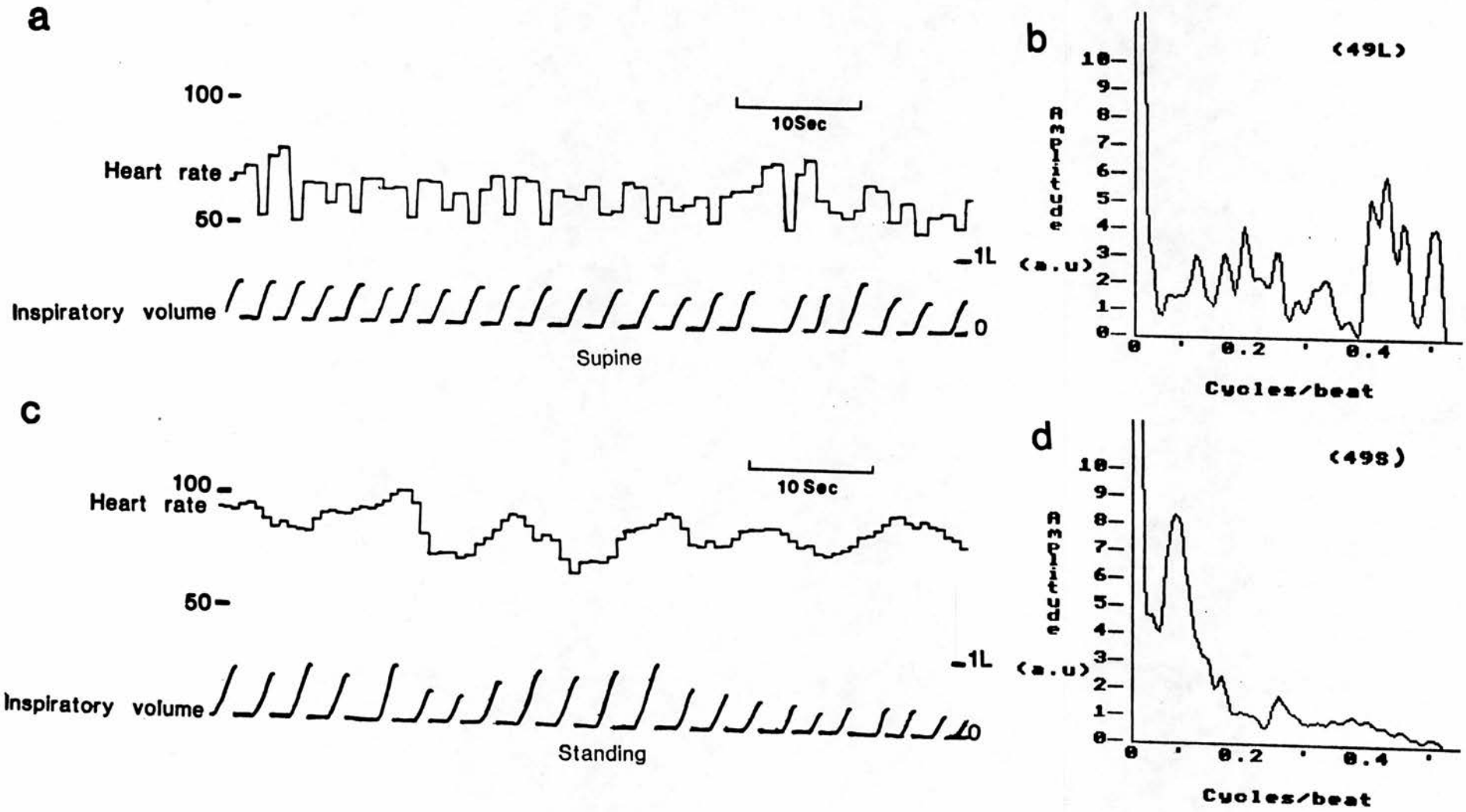
Fig.(8-10) shows the effect of 160 mg. of propranolol on heart rate pattern half an hour after oral ingestion. The heart rate patterns during supine and maintained standing postures prior to the drug intervension (control) are the same as in the previous figure.

the pattern and spectrum during control (Fig. 8-9 a & b). During maintained standing, it can be seen that even after half an hour there was a marked reduction in the "10 second" rhythm (Fig 8 - 10 c & d) compared with control (Fig. 8 - 9 c & d).

So, oral Propranolol had no significant effect on heart rate pattern during supine posture. However, during maintained standing, it markedly diminished the amplitude of the "10 second" rhythm, and this effect was clearly significant at half an hour after the ingestion of the dose, as it was at supposedly peak plasma level one and a half hours later.

"Atropine alone" has also reduced the amplitude of the "10 second" rhythm, but meanwhile it reduced the amplitude of the "RSA" significantly and this was universal in all the subjects. The effect of Atropine in one subject is illustrated in Fig (8 - 11). During control, the "RSA" was predominant in the supine posture (a), while during maintained standing (c), the "10 second" rhythm was predominant. The heart rate spectra reflected these differences. In the supine posture (b), the prominent peak (~0.45 cycles/beat) was at the respiratory frequency. During maintained standing (d), the peak at ~0.1 cycles/beat was the prominent one, while the peak at the respiraory frequency (~0.26 cycles/beat) was relatively very small.

When the effect of Atropine should have been maximum, i.e. half an hour after subcutaneous injection, the heart rate pattern was very different. During supine posture (e), the heart rate was almost flat. Atropine has markedly reduced the peak at the respiratory


a
100
Heart rate
50
10Sec
1L
Inspiratory volume
0
Supine
b
(49L)
(a.u)
0
0.2
0.4
Cycles/beat
c
100
Heart rate
50
10 Sec
1L
Inspiratory volume
0
Standing
d
(49S)
(a.u)
0
0.2
0.4
Cycles/beat

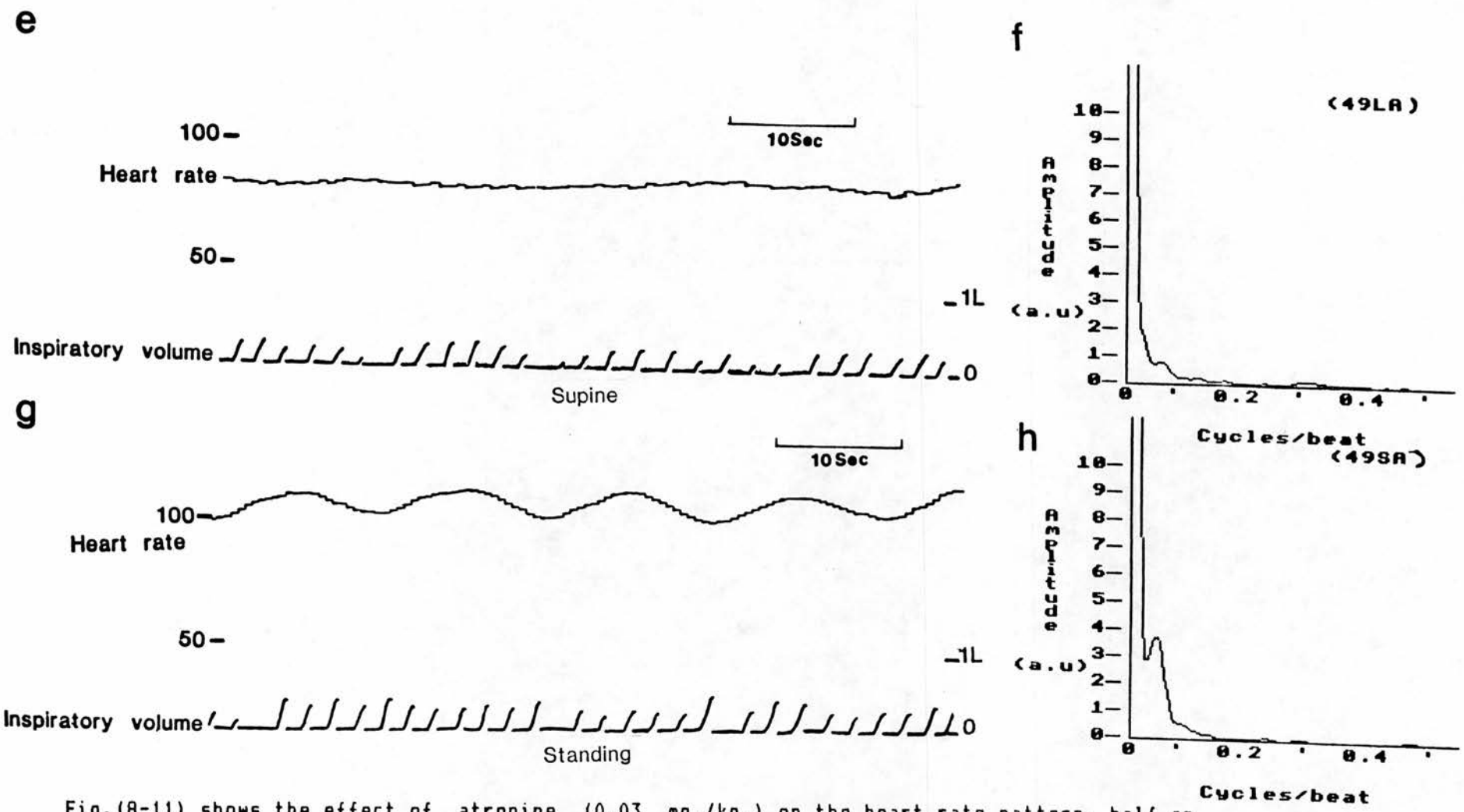


Fig.(8-11) shows the effect of atropine (0.03 mg./kg.) on the heart rate pattern, half an hour after subcutaneous injection. See text for details.

a & c ..... Control ; e & g ..... After atropine.

frequency (~0.29 cycles/beat) as well as other peaks (f).
During maintained standing (h), Atropine has also reduced both the respiratory peak at ~ 0.24 cycles/beat and the peak at ~ 0.1 cycles/beat markedly, but the "10 second" rhythm was still prominent in the heart rate pattern (g). This was probably due to a greater reduction in "RSA" than the "10 second" rhythm which made the ratio between the two ("10 second"/"RSA") greater than unity.

The effect of both Propranolol and Atropine, alone and combined, in a third subject is shown in Fig (8 - 12).
During supine posture (left of the figure), the predominant rhythm during control (a) and during sympathetic blockade with Propranolol (b), was the respiratory sinus arrhythmia. Parasympathetic blockade with Atropine abolished the "RSA" and the heart rate was almost flat (c). Adding Propranolol to the Atropine did not make a significant change in the heart rate pattern in spite of a significant reduction in mean heart rate (d).

During maintained standing, (Right of the figure), the predominant rhythm during control (a) was the "10 second" rhythm. During sympathetic blockade with Propranolol (b), the "10 second" oscillations were considerably diminished, and "RSA" rhythm was predominant. Atropine also diminished the "10 second" oscillations, however they were still visible after Atropine (c) but of much smaller amplitude. The addition of Propranolol to Atropine completely abolished the "10 second" rhythm and the heart rate pattern was flat, and not very different from the pattern under combined blockade in the supine posture (d).

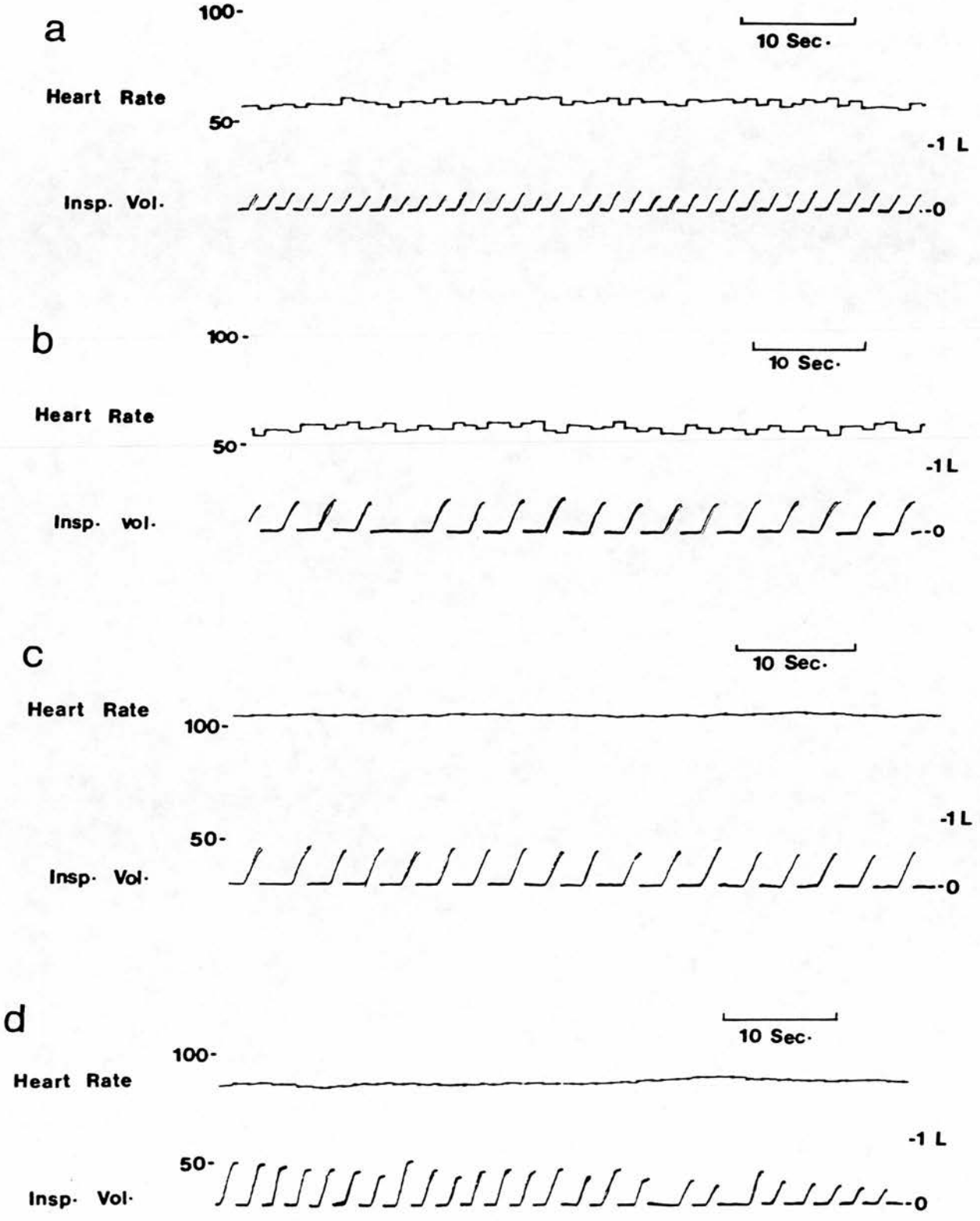
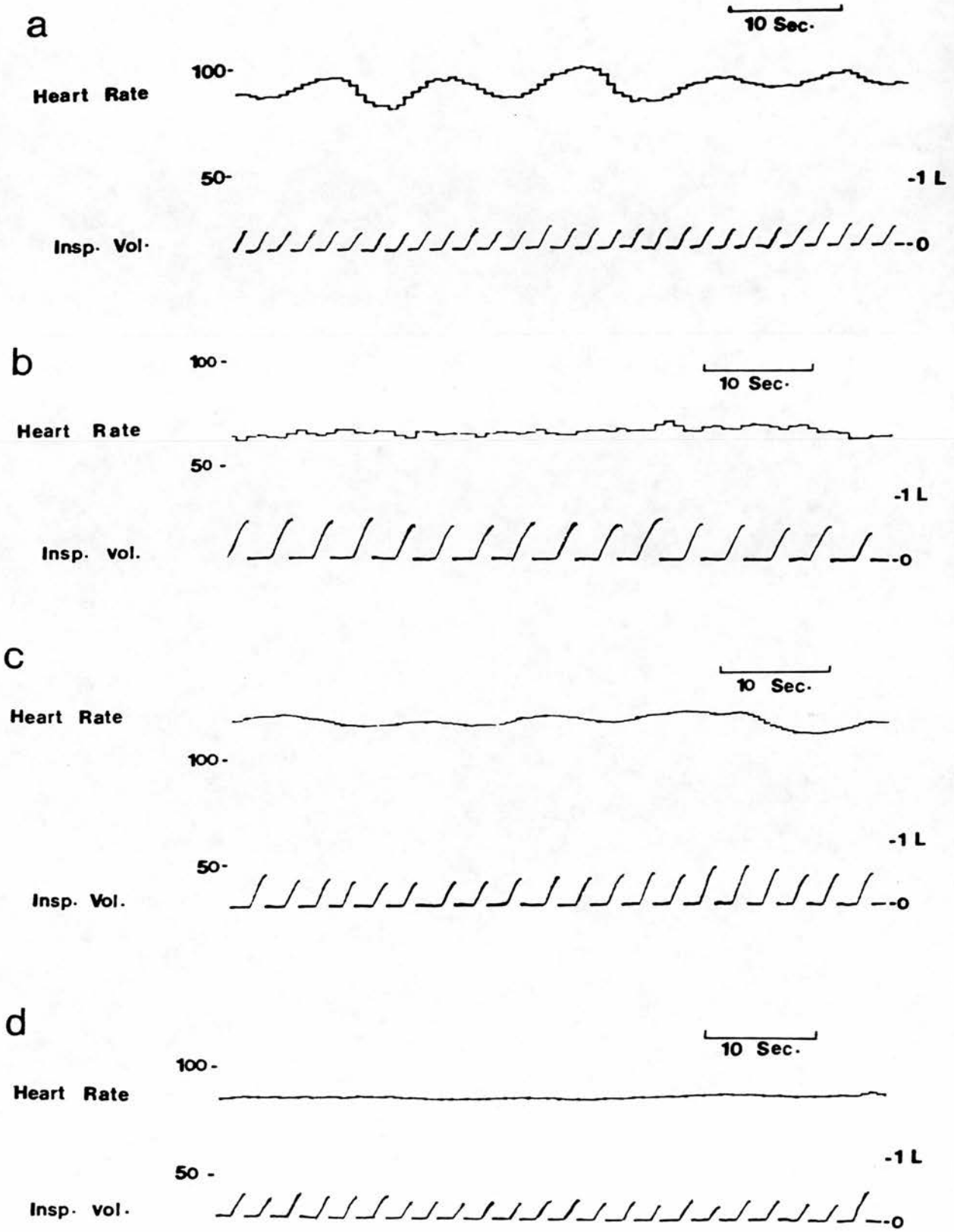


Fig.(8-12) shows the effect of atropine and propranolol separately and together on the heart rate pattern during supine and maintained standing postures. See text for details.

Standing



a = control, b = propranolol, c = atropine, d = atropine + propranolol

DISCUSSION

Effect of autonomic blockade on mean heart rate

The results show that the autonomic mechanism underlying the heart rate response to change of posture from supine to maintained standing is different from the initial heart rate response to standing.

In both the initial and the maintained response, the heart rate increases in comparison with the supine MHR. However, while the initial increase was shown to be predominantly under parasympathetic control (Ewing et al 1980), the increase in MHR during maintained standing seems to be predominantly under sympathetic control. Several of the findings in the present investigation support this contention: (a) $\triangle$ HR after propranolol was significantly lower than $\triangle$ HR during control. (b) $\triangle$ HR after atropine was not significantly different from $\triangle$ HR during control. (c) Adding propranolol to atropine made a significant difference to $\triangle$ HR, as it was then significantly smaller than $\triangle$ HR during control as well as during atropine alone. So, these results show that the increase in MHR during maintained standing was mediated predominantly by sympathetic stimulation with very little contribution, if any, by the parasympathetic system. Similar conclusion was reached for the increase in MHR after 5 minutes of 70° head up tilt (Marin-Neto et al 1980).

The different mechanisms involved in the increase in heart rate during the initial response to standing and in the later increase

during maintained standing (i.e. vagal withdrawal followed by vagal reactivation versus sympathetic stimulation), might be explained by the different response time of the two divisions of the autonomic nervous system. The parasympathetic responds quickly with a latency of less than one second whereas the sympathetic takes longer to respond to stimulation (1 - 8 seconds) (Samaan 1935, Warner & Cox 1962, Levy & Martin 1979, Koizumi et al 1985). Thus, transitory changes in heart rate like the initial response are mediated by the parasympathetic, while the more stable changes that appear later and persist, are mediated predominantly by the sympathetic.

The significant correlation between the reduction in MHR with propranolol and the resting MHR suggests that resting MHR could be used as a simple measure of sympathetic tone. This is thought to be justifiable in the light of the known use of resting MHR as a measure of vagal tone, in spite of the poor correlation, between the tachycardia induced by atropine and resting MHR, found in this study ($r = -0.47$) and others ($r = -0.43$, Fouad et al 1984).

Katona & Jih 1975 defined the degree of parasympathetic control (PC) as the change in mean RR interval during parasympathetic blockade with atropine while the sympathetic activity is kept unchanged. The change in mean heart rate correlated less closely with (PC) than the change in mean RR interval, however, it was still significant ($r = 0.71$, Fouad et al 1984). The change in MHR from control during sympathetic blockade with propranolol while keeping the parasympathetic activity unchanged is proposed here as a measure of the degree of sympathetic control (SC).

Robinson et al 1966 showed that there was a higher sympathetic activity during 80° head up tilt compared with mild supine exercise. In the present investigation, the results suggest that there is a higher sympathetic activity during active maintained standing when compared with resting supine. It was often found that MHR during maintained standing was significantly higher than supine MHR. This higher MHR could be achieved through either an increase in sympathetic stimulation or a release from vagal inhibition.

The two parameters (PC) and (SC) defined above, were used to determine the probable mechanism.The (PC) during standing was only slightly less than (PC) during supine, whereas the (SC) during standing was significantly larger than the (SC) during supine posture. Thus, the parasympathetic system has a large but similar control on MHR in both supine and standing postures, whereas the sympathetic system exerts a small effect in the supine posture and has a more powerful effect during maintained standing. Therefore, a higher MHR during standing is accomplished by predominantly an increase in the sympathetic activity rather than vagal withdrawal.

Effect of autonomic blockade on STV

The marked reduction in MAD by atropine shows that, in man, STV is predominantly under parasympathetic control, similar to the finding in fetal lambs (Dalton et al 1983). The significantly larger reduction in the supine posture is most probably due to the higher level of activity of the vagus nerve in this posture (Robinson et al 1966).

In addition to reducing MAD, atropine also reduced the "RSA" peak and this further substantiates the correlation between MAD and "RSA" (chapter III).

The tendency to increase MAD by propranolol was unexpected. It has been repeatedly stated that propranolol has no effect on beat-to-beat variation (Wheeler & Watkins 1973, Ewing et al 1980, Fouad et al 1984) and thus variability is mediated by the parasympathetic pathway (Wheeler & Watkins 1973, Katona & Jih 1975). However, Coker et al (1984) reported a significant increase in "RSA" under sympathetic blockade with atenolol in twelve young subjects in the supine position. Yet, they concluded that "RSA" was mediated through vagal efferents alone and the effect of atenolol was probably mediated through a central vagotonic effect. This is possible as low doses of atropine ($\sim$200 μg) caused augmentation of "RSA" (Selman et al 1983, Raczkowska et al 1983) and in these studies, this increase was atrributed to the central stimulant effect of atropine.

A more recent study by Pagani et al (1986) also reported a significant increase in RR interval variance with acute and chronic beta blockade by propranolol in man. In addition, there was a significant increase of high frequency component in heart rate spectral power i.e "RSA" with chronic blockade. However, no explanation was given for the possible mechanism (s) involved.

From animal experiments, there is evidence that sympathetic as well as vagal fibres discharge synchronously with respiratory activity (Adrian et al 1932, Joels & Samueloff 1956). More recently, Koizumi et al 1985 analysed spontaneously occurring beat-to-beat

changes in both vagal and sympathetic nerves to the heart in relation to respiratory activity and they concluded that sympathetic discharges can contribute to the shaping of sinus arrhythmia, but this depends on the background vagal activity. The higher the activity level in the vagus the less effective the sympathetic control, thus cutting or cooling the vagi causes almost total abolition of beat-to-beat changes in heart rate (Samaan 1935, Katona & Jih 1975). Whereas in other studies (Levy et al 1966, Koepchen et al 1961), slight respiratory cardiac arrhythmia persisted even after bilateral vagotomy, which must have been mediated via sympathetic pathways (Levy et al 1966, McGrady et al 1966).

Yongue et al (1982) reported an increase in heart rate variability, associated with respiration, by propranolol, in anaesthetised rabbits. Moreover, they recognised the conditions of neural cardiac control (i.e. low vagal tone and high sympathetic tone) that favour this effect.

The results of Koizumi et al (1985) leave no doubt that the sympathetic nerves to the heart do contribute to beat-to-beat changes in heart rate. The increase in MAD with propranolol, although not significant statistically, was indicative of this minor contribution. Furthermore, the slightly higher increment in MAD with propranolol during standing compared with supine posture, when sympathetic activity is relatively higher (as it was shown earlier), does support Koizumi et al (1985) conclusion that the degree of sympathetic contribution depends upon the background autonomic activity.

This interaction between the two divisions of the autonomic nervous system was clearly shown on the MAD results. The MAD under both sympathetic and parasympathetic blockade became significantly less than the MAD under parasympathetic blockade only. This seems to be in conflict with the conclusion of Pomeranz et al (1985) that the high frequency component in heart rate spectral power (i.e. RSA) was mediated entirely by the parasympathetic system. The difference in the results is possibly due to the difference in the background autonomic activity as their subjects were breathing in synchrony with a metronome, during which an enhanced vagal activity is known to prevail (Pagani et al 1986).

In those studies in which it was concluded that the sympathetic system has no effect on heart rate variability (Ewing et al 1980, Yongue et al 1982, Fouad et al 1984, Coker et al 1984, Pomeranz et al 1985), beta - blockers consistently caused an opposite effect to parasympathetic blockade (i.e. an increase in heart rate variability measure) and in one of these studies, this increase was statistically significant (Coker et al 1984).

Effect of autonomic blockade on LTV

Since CV% represents the overall variability and include STV expressed by MAD, and LTV, therefore inference about the changes in LTV might be deduced from relating the results of MAD and CV% (chapter III, Fig. 3 - 23).

Propranolol caused a decrease in total variability (CV%), more so

during standing, in spite of an increase in STV (MAD). So it seems that the LTV must have been reduced to bring the total sum (CV%) to a negative value.

The larger decrease in CV% at half an hour than at one and a half hours after the oral dose of propranolol during maintained standing can be explained with the help of Fig (8 - 13). As can be seen from the figure, the MAD was slightly higher at one and a half hours after propranolol than the MAD at half an hour. So, the increase in CV% at one and a half hours was most likely due to the increase in STV rather than an increase in LTV which probably stayed the same or might even slightly decreased. The marked reduction in LTV (reduced CV% in the face of increased STV) at half an hour after oral propranolol seemed unusual because the peak plasma level is supposed to occur 90 minutes after an oral dose of 80mg. of propranolol (Chamberlain 1967). However, a major increase in the beta-blocking effect was found to occur at plasma levels (0.5 - 20ng/ml) much lower than the maximum levels that can be attained (30 - 200ng/ml), with no further increase when plasma levels were higher than 80ng/ml (Mullane et al 1982). Thus, half an hour after 160mg. of oral propranolol (the dose used in this study), the plasma propranolol must have reached a level sufficient to cause appreciable beta-blockade and marked reduction in LTV.

The results from visual inspection of heart rate records and spectral analysis support the conclusion that propranolol caused a marked reduction in the "10 second" rhythm during maintained standing, whilst its effect on "RSA" was not appreciable. Consequently , the ratio "10 second"/"RSA" which reflects the

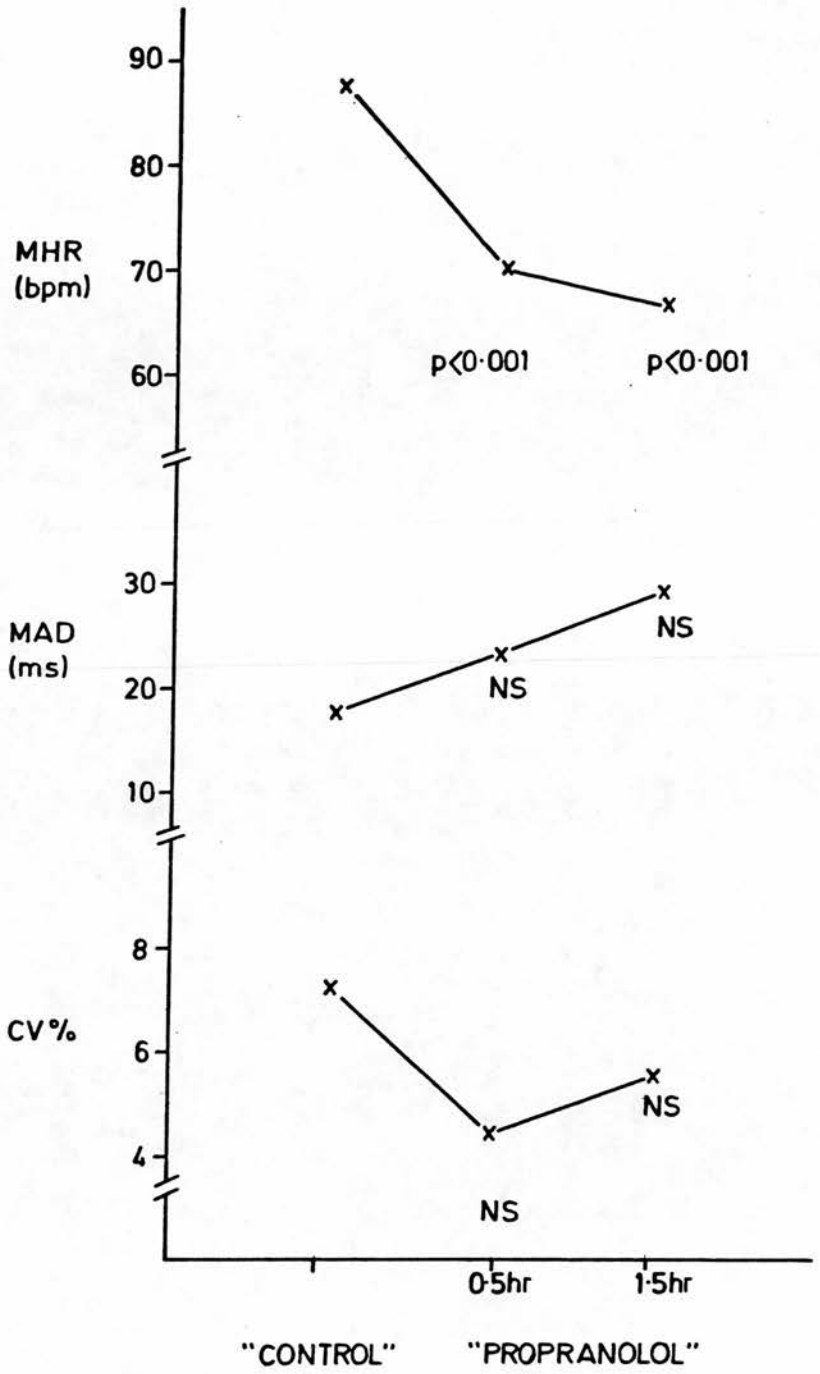


Fig.(8-13).The effect of propranolol on MHR, MAD and CV% during maintained standing, compared at half an hour and one and a half hour. The statsistical significance refers to the difference from control.

balance between the two rhythms, was markedly reduced.

Atropine on the other hand, markedly decreased both STV (MAD) and total variability (CV%). No conclusion about LTV can be drawn from these results only as it might have stayed the same, decreased as well, or even slightly increased. However, visual analysis of heart rate records and spectra showed that in the supine posture atropine markedly reduced all rhythms and the heart rate was almost flat. Whereas, during maintained standing, when there was higher sympathetic tone, atropine though it reduced the "10 second" rhythm, caused an even greater reduction in "RSA", and therefore the ratio between the two rhythms did not decrease to the same extent as it did with propranolol alone. Consequently, the slow "10 second" rhythm was still clearly seen but of much smaller amplitude.

The significantly larger reduction in total variability (CV%) during maintained standing when propranolol was added to atropine compared with "atropine alone", re-confirmed the marked effect of propranolol on LTV. The reduction in STV (MAD) under "Atropine + Propranolol" was smaller than under "Atropine alone". Therefore, a greater reduction in LTV must have been behind the larger reduction in CV% under combined blockade.

This marked effect of propranolol on LTV was also confirmed when the slow "10 second" oscillations disappeared completely after adding propranolol to atropine.

Autonomic control of the "10 second" oscillations

Even before the autonomic blockade study, several points from the earlier observations favoured a predominantly sympathetic mechanism for the mediation of these oscillations.

1) They appear more clearly and sometimes only during maintained standing when sympathetic tone is relatively high.

2) They appear in subjects with higher MHR during maintained standing, which indicates a higher sympathetic activity.

3) They appear also during maintained tilt, but not during mild supine exercise. Although in both, there is an increase in MHR, the mechanism is different. During tilt, the increase in MHR is achieved by sympathetic stimulation (Marin-Neto et al 1980), whereas during mild supine exercise, vagal withdrawal is the main mechanism (Robinson et al 1966, Maciel et al 1986).

4) They decrease with advancing age, when a decrease in sympathetic activity is known to occur (Ziegler et al 1976, Lakatta 1979, Vestal et al 1979, Sato et al 1981, Rodeheffer et al 1984, Shiraki et al 1987).

5) They decrease during immersion in water when sympathetic activity is thought to be decreased (Lollgen et al 1981, Corrall et al 1985).

So, all these observations tend to suggest that the sympathetic system should have a major role in the control of the "10 second" rhythm. However in animals, three out of four studies with autonomic blockers, concluded that the sympathetic system has no role to play in the genesis of this rhythm (Chess et al 1975, Akselrod et al 1981, Dalton et al 1983). Zugaib et al (1980a) study

did show a reduction in LTV with beta-blocker, but the degree of this reduction varied from week to week in the newborn lamb.

The results of the present study showed that the sympathetic nervous system has an important contribution to the change in heart rate pattern on changing posture from supine to maintained standing (Sattar & Young 1985 b). This involvement of the sympathetic nervous system in the control of the "10 second" rhythm in man was also reported concurrently by Pomeranz et al (1985) and Pagani et al (1986).

The conflicting results between human and animal studies may be due to species differences. Other possiblities are: the incomplete maturation of the nervous system in the fetus (Siimes et al 1984), or the different behavioral state as Zhu & Szeto 1987 found that beta-blocker abolished the cyclical variations in heart rate of fetal lambs but only when they coincided with high voltage slow electrocortical activity.

In addition to being decreased by propranolol the amplitude of the "10 second" rhythm was also decreased by atropine (Sattar & Young 1985 b, Pomeranz et al 1985). This decrease may have been due to atropine blocking the muscuranic receptors on the sinus node. Alternatively, it could have been mediated by partial blocking of the nicotinic receptors in the sympathetic ganglia, which was reported to occur with relatively high doses of atropine(Weiner 1985), or blocking of the nicotinic cholinergic receptors on the pace maker cells themselves. This latter mechanism has been implicated in the phenomenon of post vagal tachycardia (Copen et al 1968).

Thus, the effect of atropine suggests that the parasympathetic system may be involved in controlling the "10 second" rhythm. However, it is also possible that this effect was mediated by other actions of atropine apart from its muscurinic blocking effect.

To conclude, in the supine posture the vagal tone is high and the "RSA" is predominant. Atropine almost abolishes this rhythm and renders the heart rate flat, while propranolol has no appreciable effect and the heart rate pattern stays almost the same as during control.

During maintained standing, there is a higher sympathetic tone with the "10 second" rhythm predominant. Propranolol almost abolishes this rhythm, thus leaving the "RSA" predominant. Atropine also diminishes the "10 second" rhythm, however, at the same time it abolishes the "RSA" almost completely, so the ratio between the two stays large enough to leave the slow "10 second" rhythm clearly visible.

Chapter IX

GENERAL DISCUSSION

The presence of rhythms slower than respiratory sinus arrhythmia in the heart rate of normal individuals is now well established. These rhythms were thought to be important in the maintenance of precise homeostasis (Hyndman 1974). Moreover, one of these rhythms, the "10 second" oscillations was found to be affected by certain conditions that lead to changes in the activity of the central nervous system such as mental loading (Sayers 1971 & 1973, Hyndman 1978, Hitchen et al 1980) and sleep (DeBoer 1985, Pagani et al 1985).

Thus, it seems that the "10 second" oscillations are important in normal physiologial control of the circulation. However, the incidence of these oscillations in normal people, their origin, the factors that influence them and the mechanisms of control in humans are not well known.

In this study, a survey of 79 healthy subjects showed that maintained standing was a strong stimulus to potentiate the "10 second" rhythm in about half of them. In a few subjects, the rhythm was seen also during supine posture, but became more marked during maintained standing. However, the majority of subjects had respiratory sinus arrhythmia when supine (Sattar & Young 1983).

This contrast in the heart rate pattern in the two postures had not been described prior to the present investigation in spite of the large number of studies on the effect of standing on heart

rate. This could be due to:

1. The emphasis, in most of the previous studies, was on the initial response of heart rate to standing up rather than the changes in heart rate pattern during maintained standing.
2. The short periods of analysis that were probably sufficient enough to calculate the MHR and beat-to-beat changes, but they were too short to identify the slower changes in heart rate.
3. The use of statistical indices such as MSSD,MAD,MSD...etc., that were not sensitive to the low frequency changes in heart rate.
4. The recordings of the ECG directly on tapes and then further analysis by automated processing. The printout of these ECG's were usually made on short compressed strip charts so that identification of the slow oscillations were difficult if not impossible.
5. The variable responses of different subjects to the change of posture might have contributed to the difficulty in recognising these oscillations especially when small numbers of subjects were investigated.

These variable responses to change of posture were found to be associated with significantly different $\triangle$HR (the increase in MHR during maintained standing in relation to supine MHR) (Chapter III). Autonomic blockade results (Chapter VIII) showed that $\triangle$HR was largely mediated by the sympathetic system. Moreover, the results showed an important contribution of the sympathetic system in the mediation of the "10 second" rhythm during maintained standing. Therefore, it was concluded that those subjects who showed predominantly "10 second" rhythm during maintained standing

(i.e."oscillators") and had significantly higher $\triangle$HR, probably have higher sympathetic tone than the "non-oscillators".

The similarity of the heart rate pattern during maintained 70° tilt to that of maintained standing in the oscillators (chapter VI) is probably a reflection of the increased sympathetic activity in both conditions. An increase in muscle sympathetic nerve activity (MSA) was found in both passive (Delius et al 1972) and active (Burke et al 1977) head up postures. Furthermore, the increase in MSA was found to be linearly related to the sine of the tilting angle (Iwase et al 1987), so at the 70° tilt used, the MSA was only 6% less than during maintained standing.

The different heart rate pattern during supine exercise (chapter V) from that during maintained standing or 70° tilt in spite of similar increases in MHR in all the three conditions, suggests that the heart rate pattern is probably mediated separately from MHR and that the MHR may not be the only important factor in determining the heart rate pattern.
Moreover, the failure to induce the "10 second" rhythm during mild supine exercise was probably due to the fact that the increase in MHR during this manoeuvre was largely mediated by vagal withdrawal rather than an increase in sympathetic activity (Robinson et al 1966, Maciel et al 1986).

The smaller increase in the "10 second" rhythm during maintained standing in older subjects (Chapter IV) adds to the previous findings of decreased sympathetic heart rate responses to standing despite the greater and more sustained increase in plasma

norepinephrine level in old age (Rowe & Troen 1980). However, short term variability measured as the MAD tended to be smaller in both supine and maintained standing in the older group. The MAD was shown to be mediated largely by the parasympathetic system in humans (this study) and in fetal lambs (Dalton et al 1983). Therefore, it is possible that both sympathetic as well as parasympathetic activities are decreased in old age rather than a decrease limited to the sympathetic system only (Sever et al 1977, Rodeheffer et al 1984).

The marked reduction in the "10 second" rhythm with the prevention of venous pooling by immersion in water up to the level of the diaphragm (Chapter VII), showed the important contribution of the decrease in central venous pressure (CVP) and cardiac filling to the increased prominence of this rhythm during maintained standing. The significant effect of changes in CVP on heart rate pattern was indicated previously (Jennett et al 1982). However, it had the opposite effect on the fast oscillations that appeared during recovery from heavy exercise in the supine posture only.
It is known that manoeuvres that induce pooling of blood without significantly reducing the systemic arterial BP (e.g. lower body negative pressure), can cause stimulation of the receptors on the low pressure side of the circulation (Donald & Shepherd 1978). Recently it has been shown that this normotensive central hypovolemia can cause stimulation of the sympathetic nervous system (Sander-Jensen et al 1987) and this may explain the potentiation effect of maintained standing to the "10 second" rhythm. In contrast, immersion in water is probably associated with a reduction in sympathetic activity (Lollgen et al 1981,

Corrall et al 1985) and this led to the marked decrease in the "10 second" oscillations. Furthermore, the increased venous return to the heart during immersion to the level of the neck, caused almost complete abolition of these oscillations. It was also found that volume overloading by Dextran infusion caused a decrease in the amplitude of sympathetically mediated slow heart rate oscillations in anaesthetised dogs (unpublished observations).

The origin of these slow oscillations is not yet known. The controversy whether they are centrally or peripherally induced is reminiscent of the same controversy still surrounding the respiratory sinus arrhythmia (Chapter I).
Results from cardiovascular computer modelling (Hyndman et al 1971, DeBoer 1985) suggested that these oscillations were probably due to the time delay and the non-linear nature of the feed-back loop of the baroreceptor reflex. The advocates of a central origin of these oscillations postulate the presence of a pacemaker located at the brain stem or the spinal cord or several pacemakers at different levels of the CNS (Preiss & Polosa 1974, Taylor & Gebber 1975, Korner 1979, Gebber 1980, Gebber & Barman 1980, Koepchen et al 1981, Gootman & Cohen 1981, Polosa 1984). These oscillators are supposedly having an intrinsic rhythmicity of ~6/min. but they are entrained by peripheral input.
Although a central origin cannot be excluded, the results of this study showed an important modulating effect of peripheral input on these oscillations.

It was shown (Chapter VIII) that the sympathetic system had an important contribution to the mediation of the "10 second" rhythm.

Therefore, the changes in heart rate at slow breathing frequency ($\sim$ 6/min), are not entirely mediated by the parasympathetic system. Consequently, the practice of using the heart rate response to deep slow breathing, in testing for parasympathetic damage in patients with suspected involvement of the autonomic nervous system should be avoided.

Similarly, the use of resting MHR or the MHR response to atropine as a measure of the parasympathetic control of heart rate (i.e. vagal tone) is thought to be unjustifiable in the light of the new concept about the sympathetic - parasympathetic relation and the now known interactions between them.

The importance of recording the respiratory frequency in interpreting the results of heart rate variability was emphasized (Chapter II). Moreover, for the quantitative analysis of heart rate spectra, it is advisable to calculate the variability at the respiratory frequency on individual basis (unpublished results) rather than using a fixed range for all the spectra. The disadvantages of the latter method is the unavoidable use of wide ranges to include most of the variable respiratory frequencies among different individuals. Such a wide range (e.g. 0.2 - 0.35 Hz., DeBoer 1985) would include a lot of non-respiratory component, and moreover when the respiratory frequency is outside that range, the "HRV" measurement does not represent "RSA" at all.

Lastly, it was shown that the use of the available statistical indices alone could not express the changes in "HRV" at the different frequencies. Most of these indices (e.g. MAD) are more sensitive to the variability at high frequency i.e. "RSA" and the

others (e.g. CV%) measure the total variability. Spectral analysis shows the contribution of variabilities at different frequencies to the overall variation in heart rate. Moreover, to detect any possible significant differences using these indices, a probability value of 0.1 was used although this may not be physiologically significant.

The finding that during maintained standing, there is a differential contribution of the sympathetic and parasympathetic system to the low and high frequency rhythms respectively suggests that spectral analysis of "HRV" can give an indication of both sympathetic and parasympathetic activity simultaneously and non-invasively. In addition, all the complex analyses that were carried out in this study were performed on a BBC-microcomputer with a 64 K memory. So, in spite of the complex mathematics involved, it is quite feasible to use this type of analysis in the clinical field. However, the inter-individual variations should be recognised and normal ranges for different age groups should be established.

The variable responses of normal subjects to the postural stress seem to reflect differences in the autonomic control of the heart. This might be a factor influencing the predisposition to certain diseases, such as hypertension and sudden cardiac death. Therefore, "HRV" analysis during change of posture could be used as a screening test to identify those at risk in the hope of implementing preventive measures.

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Appendix:

"Computer programmes"

Programme A: is based on a BBC software provided with the Unilab computer interface that digitizes the RR intervals. The original programme was extended to exclude mistriggers, print out RR intervals, store files on disks and to calculate some statistics.

Programme B: calculates all the statistical indices listed in Table (2-3) on pages 50 - 51.

Programme C: uses procedure FFT from EMAS to compute the spectral estimates. The resulting amplitude spectrum is then plotted after being submitted to sequential spectral smoothing windows.

Programme D: prints RR intervals and plots intervals tachogram.

```
                " PROGRAMME  A "
               ******************
 30@%=10
 40VDU15:CLEAR:DIM POINTS 1280
 50REM Set up and get sample data.
 60REM ************************
 70REM Analog i/p (-5v to +5v)
 80 ?&FCC2=0:?&FCC3=255:?&FCC1=16
 90VDU12
100PRINT"               WINDOW SET"
110PRINT"               ====== ==="
120PRINT''''" Please input maximum signal and adjust the gain control."'''''''
130 PRINT"  Press any key when you are ready to start sampling ..."
140K$=GET$:IF K$="" THEN GOTO 140
150 PRINT'"Please wait"
160FOR P = POINTS TO (POINTS+1279)
170?P=?&FCC0
180NEXT P
190REM Set up ready for plot.
200REM *)*******************
210MODE4
220GCOL0,1:GCOL0,128
230CLG
240REM   Plot.
250REM   ****
260PLOT 4,0,(?(POINTS)*4.0118)
270 FORX=1TO 1279
280Y=(?(POINTS+X))*4.0118
290PLOT5,X,Y
300NEXT X
310REM WINDOW SET
320REM **********
330PRINTTAB(0,1)"Set the lower window - 'U' up, 'D' down"
340PRINTTAB(0,2)"When satisfied, enter 'S'."
350REM Lower window set
360REM ****************
370GCOL0,3
380X=0:Y=512
390MOVEX,Y
400X=X+1200:PLOT6,X,Y
410A$=GET$
420IFA$="U" THEN PLOT4,0,Y:PLOT6,X,Y:Y=Y+5
430IFA$="D" THEN PLOT4,0,Y:PLOT6,X,Y:Y=Y-5
440IFA$="S" THEN ?&70=INT(Y/4.0118):GOTO460
450X=0:GOTO390
460REM Upper window set
470REM ****************
480PRINTTAB(0,1)"Set the UPPER window - 'U' up, 'D' down"
490PRINTTAB(0,2)"When satisfied, enter 'S'."
500GCOL0,3
510X=0:Y=512
520MOVEX,Y
530X=X+1200:PLOT6,X,Y
540A$=GET$
550IFA$="U" THEN PLOT4,0,Y:PLOT6,X,Y:Y=Y+5
560IFA$="D" THEN PLOT4,0,Y:PLOT6,X,Y:Y=Y-5
570 IFA$="S" THEN ?&71=INT(Y/4.0118):GOTO590
580X=0:GOTO520
```

```
585VDU12:PRINT'''''"Lower window"?&70
590PRINT'''"Upper window"?&71
600FORK=0 TO 5000:NEXTK
610REM Set up ready for real sample
620REM ****************************
630CLEAR:MODE7
640?&FCCB=0
650B=256*((?5)-(?3))+(?4-?2):S=300
660DIM H(S)
670DIM L(S)
680DIM RRI(255)
690DIM TRRI(255)
700 DIM HBIN(40)
710 DIM LBIN(40)
720DIM FRITZ (8*S)
730FORX=0 TO 2 STEP 2
740P%=&0900
750[OPT X
760.UNILAB CLC:CLD:CLV:SEI
770LDY £0
780LDA£255:STA&FE69
790.LL1 LDA&FCC0:CMP&70:BCS LL1
800.LL2 LDA&FCC0:CMP&71:BCC LL2
810LDA £255:STA&FCC5
820.LL3 LDA&FCC0:CMP&70:BCS LL4
830LDA&FCC5:LDX&FCC4
840STA(&74),Y
850LDA£255:STA&FCC5
860INX:INX:INX:INX:INX:INX
870INY
880TXA
890STA(&74),Y
900INY
910LDA&FE69
920STA(&74),Y
930INY
940LDA&FE68
950STA(&74),Y
960LDA£255:STA&FE68:STA&FE69
970INY
980.LL5 LDA &FCC0:CMP&71:BCC LL6
990LDA&FCC5:LDX&FCC4
1000STA(&74),Y
1010LDA£255:STA&FCC5
1020INX:INX:INX:INX:INX:INX
1030INY
1040TXA
1050STA(&74),Y
1060INY
1070LDA&FE69
1080STA(&74),Y
1090INY
1100LDA&FE68
1110STA(&74),Y
1120LDA£255:STA&FE68:STA&FE69:CLC
1130INY
```

```
1140CPY£0:BEQ LL7:CLC
1150.LL8 CLC:CPY&7A:BCS LL9
1160.LL11 LDA&D7:CMP£226:BEQ LL10
1170JMP LL3
1180.LL4 LDA&FCCD:AND£64:EOR£64:STA&FE60:CMP£0:BEQ LL12:JMP LL3
1190.LL6 LDA&FCCD:AND£64:EOR£64:STA&FE60:CMP£0:BEQ LL13:JMP LL5
1200.LL7 INC&75:JMP LL8
1210.LL9 CLC:LDA&75:CMP&81:BCS LL10:JMP LL11
1220.LL10 STY&74:CLI:RTS
1230.LL12 LDA£255:STA&FCC5:JMP LL3
1240.LL13 LDA£255:STA&FCC5:JMP LL5
1250]
1260NEXTX
1270 ?&75=(FRITZ DIV 256)+1:?&74=0:Z%=?&75*256:REM Z% IS FIRST LOCATION USED
1280?&FCC8=255:?&FCC6=255:?&FE62=255:?&FE60=255:?&FE6B=32:?&FE68=255
1290PRINT'''"HOW MANY COMPLETE CYCLES DO YOU WANT TO RECORD"
1300 PRINT''"I HAVE SPACE FOR "S" CYCLES."
1310PRINT''"ENTER '0' IF YOU REQUIRE MAXIMUM NUMBER"
1320INPUT NR
1330IF NR =0 THEN NR=S
1340IF NR>S THEN GOTO1290
1350?&81=(((?&75)*256)+(NR*8)) DIV 256:?&7A=(?(&75)*256)+(NR*8)-(?(&81)*256)
1360REM ?&81 AND ?&7A HOLD THE HIGHEST MEMORY LOCATION
1370REM THAT WILL BE NEEDED FOR THE NUMBER OF SAMPLES REQUESTED.
1380CALL UNILAB
1390PRINT"FINISHED SAMPLING"
1400 FINAL=((?&75)*256)+(?&74)-1
1410PRINT'''"PRESS ANY KEY TO START PRINT OFF"
1420K$=GET$:IFK$=""THEN GOTO1420
1430 PRINT'"Please wait"
1440C=0
1450    FOR Q=Z% TO FINAL STEP 8
1460A=255-?Q:B=255-?(Q+1):I=255-?(Q+2):D=255-?(Q+3)
1470E=255-?(Q+4):F=255-?(Q+5):G=255-?(Q+6):H=255-?(Q+7)
1480H(C)=15+B+(256*A)+(65615*D)+(65615*256*I)
1490L(C)=16+F+(256*E)+(65616*H)+(65616*256*G)
1500   C=C+1:NEXTQ:C=C-1
1510PRINT " DO YOU REQUIRE RESULTS OUT TO THE PRINTER ( Y/N ) ? "
1520K$ =GET$: IF K$= "Y" THEN VDU2,15 ELSE VDU3,14
1530PRINT'''"PRINT OUT OF TIMES -"'
1540 FOR Q=0 TO C
1550PRINT ;Q"    RR  =    ";INT((H(Q)+L(Q))/1000);"ms"
1560NEXT Q
1570INPUT"  Disk file name (7 chars max):"F$:W=OPENOUT(F$)
1580PRINT£W,"Sequence of 256 RR-intervals",INT(255)
1590J=0
1600 FOR Q=0 TO C
1610IF ((H(Q)+L(Q))/1000)>400 AND ((H(Q)+L(Q))/1000)<1500THEN GOTO 1630
1620GOTO 1660
1630 RRI(J)=INT((H(Q)+L(Q))/1000):PRINT£W,RRI(J)
1640PRINT ;J" RRI = ";RRI(J);"ms"
1650J=J+1 :IF J>255 THEN GOTO 1670
1660NEXT Q
1670 CLOSE£W:VDU3
1680 IF K$= "Y" THEN VDU2,15 ELSE VDU3,14
1690PRINT "THE PREECEDING RR-INTERVALS WERE STORED IN THE FILE NAMED " ;F$
1700VDU3
```

```
1710REM Obtain the mean
1720REM ***************
1730TRRI=0:FOR J=0 TO 255
1740TRRI=TRRI+RRI(J):NEXT
1750PRINT''''"PRESS ANY KEY AND (return) TO CONTINUE"
1760VDU15
1770INPUTK$:VDU12
1780PRINT"DO YOU REQUIER RESULTS OUT TO THE PRINTER(Y/N)?"
1790K$=GET$:IF K$="Y"THEN VDU2,14 ELSE VDU3,14
1800FOR I=1TO7:PRINT:NEXT
1810PRINT"STATISTICS FOR THE FILE NAMED:";F$:PRINT:PRINT
1820@%=131850
1830PRINT"TOTAL TIME OF ANALYSIS=";(TRRI)/60000;"minutes":PRINT:PRINT
1840PRINT"TOTAL TIME OF RR-INTERVALS=";TRRI;"ms":PRINT:PRINT
1850RRAV=TRRI/256
1860PRINT"MEAN RR-INTERVALS=";RRAV;"ms":PRINT:PRINT
1870PRINT"MEAN HEART RATE=";(60000/(RRAV));"bpm":PRINT
1880PRINT'"AVERAGE FREQUENCY = ";(1000/(RRAV));" Hz"
1890VDU15
1900VDU3
1910PRINT''''"Press 'S' if you wish to take a new set of samples"
1920PRINT''''"Press 'E' if you wish to exit ";"from program"
1930K$=GET$:IFK$=""THEN GOTO 1930
1940IFK$="R"THEN GOTO1840
1950IFK$="S"THEN GOTO30
1960IFK$="E"THEN @%=10:MODE7:END
1970GOTO1930
```

```
                    " PROGRAMME  B "
                   ******************
 30 MODE4
 40DIM TM%(255)
 50INPUT'' " File name: "F$:W=OPENIN(F$):INPUT£W,A$,NS
 60CLS:FOR Q=0 TO 255:INPUT£W,TM%(Q):SUM = SUM+ TM%(Q)
 70SIG = TM%(Q)*TM%(Q): SUMSIG=SUMSIG+SIG
 80SUMHR=SUMHR+(60000/TM%(Q)):SQSUM=SUMHR*SUMHR
 90HRSQ=(60000/TM%(Q))*(60000/TM%(Q))
100THRSQ=THRSQ+HRSQ:NEXT:CLOSE£W
110W=OPENIN(F$):INPUT£W,A$,NS:FOR Q=0 TO 254
120INPUT£W,TM%(Q):RRD=ABS(TM%(Q+1)-TM%(Q))
130TRRD=TRRD+RRD:TDS=TRRD*TRRD:RRDS=RRD*RRD
140SUMSSD=SUMSSD+RRDS:D=TM%(Q+1)-TM%(Q)
150TD=TD+D:NEXT:CLOSE£W
160 MSD=TD/255
170 MEAN =INT( SUM/256): SUMSQ =SUM*SUM
180MEAND=TRRD/255
190 S= (SUMSIG -SUMSQ/256)/255:SD=SQR(ABS (S))
200 RMSM=SQR((SUMSIG -SUMSQ/256)/256)
210SDHR=SQR(ABS((THRSQ-SQSUM/256)/255))
220SDD=SQR(ABS((SUMSSD-TDS/255)/254))
230 SEM= SD/SQR(256)
240SEMD=SDD/SQR(255)
250 SUMSEC = SUM/1000
260CVD=SDD/MEAND
270MSSD=SUMSSD/255
280RMSSD=SQR(MSSD)
290SDM=TRRD/255
300SDMS=SDM*SDM
310PRINT"DO YOU WANT A PRINT OUT OF STATISTICS(Y/N)"
320X$=INKEY$(200):IF X$=""VDU2,15 ELSE VDU3,14
330FOR I=1 TO 5:PRINT:NEXT
340PRINT" File name:";; F$:FOR I=1TO2:PRINT:NEXT
350@%=131850
360PRINT"TOTAL=";SUMSEC/60;"min.";
370PRINT TAB(40);"MEANRR= "; MEAN " ms":PRINT
380 PRINT "Var.RR=  " S " ms";
390PRINT TAB(40);"SDRR=  " SD " ms":PRINT
400 PRINT "SEMRR= "SEM " ms";
410PRINT TAB(40);"CVRR= "SD/MEAN:PRINT
420PRINT"***I.I.***="100*(SD/MEAN);
430PRINT TAB(40);"***M.H.R.***=";60000/MEAN"bpm":PRINT
440 PRINT"SDHR=";SDHR;"bpm";
450 PRINT TAB(40);"SEMHR=";SDHR/SQR(256);"bpm":PRINT
460 PRINT"CVHR=";SDHR/(60000/MEAN);
470PRINT TAB(40);"***M.A.D***= " MEAND "ms ":PRINT
480PRINT "SDAD= " SDD " ms";
490PRINT TAB(40);"SEMAD=";SEMD"ms":PRINT
500PRINT"CVAD= "CVD;
510PRINT ;TAB(40);"***RMSSD***=";RMSSD;"ms":PRINT
520 PRINT"***TD***=";TD;"ms";
530PRINT TAB(40);"***RMSM***=";RMSM;"ms":PRINT
540PRINT ;"MSD=";MSD;"ms":PRINT
550VDU3,14
```

```
560STOP
570PRINT"DO YOU WANT TO PRINT RR-INTERVALS (Y/N)"
580X$=GET$
590IFX$="Y"VDU2,15 ELSE VDU3,14
600FOR Q%=0 TO 255
610PRINT;Q%;TAB(20);"RR=";INT(TM%(Q%));"ms"
620NEXT:VDU3
630PRINT"DO YOU WANT TO PRINT RR-DIFFERENCIES(Y/N)"
640X$=GET$:IF X$="Y"VDU2,15 ELSE VDU3,14
650FOR Q%=0 TO 254
660PRINT;Q%;TAB(20);"RRD=";INT(TM%(Q%+1)-TM%(Q%));"ms"
670NEXT:VDU3
```

" PROGRAMME C "

```
 30 MODE4
 40DIM V%(255),ZZ%(255),XX%(255),SS%(255),SF%(255),SUMFR%(255);
 50DIM CS(255),SN(255),TM%(255),FR%(255),RL%(255),IM%(255)
 60C=2*PI/256
 70PRINT:PRINT:PRINT''"Calculating sine & cosine tables for FFT"'
 80PRINT"please wait "
 90FOR X%=0 TO 255:SN(X%)=SIN(C*X%):CS(X%)=COS(C*X%):NEXT
100 CLS:FORI=1TO5:PRINT:NEXT
110INPUT" File name: "F$
120W=OPENIN(F$):INPUT£W,A$,NS:FOR Q%=0 TO 255
130INPUT£W,TM%(Q%):NEXT:CLOSE£W
140CLS:PRINT TAB(22,2);"("F$")"
150PROCFFT
160SUMFR%(N%)=0
170FOR N%=1 TO 127
180SUMFR%(N%)=SUMFR%(N%)+((0.5*FR%(N%))+(0.25*FR%(N%-1))+(0.25*FR%(N%+1)))
190NEXT
200SF%(N%)=0
210FOR N%=1 TO 127
220SF%(N%)=SF%(N%)+((0.5*SUMFR%(N%))+(0.25*SUMFR%(N%-1))+(0.25*SUMFR%(N%+1)))
230NEXT
240SS%(N%)=0
250FOR N%=1 TO 127
260SS%(N%)=SS%(N%)+((0.5*SF%(N%))+(0.25*SF%(N%-1))+(0.25*SF%(N%+1)))
270NEXT
280XX%(N%)=0:FOR N%=1 TO 127
290XX%(N%)=XX%(N%)+((0.5*SS%(N%))+(0.25*SS%(N%-1))+(0.25*SS%(N%+1)))
300NEXT
310ZZ%(N%)=0:FOR N%=1 TO 127
320ZZ%(N%)=ZZ%(N%)+((0.5*XX%(N%))+(0.25*XX%(N%-1))+(0.25*XX%(N%+1)))
330NEXT
340V%(N%)=0:FOR N%=1 TO 127
350V%(N%)=V%(N%)+((0.5*ZZ%(N%))+(0.25*ZZ%(N%-1))+(0.25*ZZ%(N%+1)))
360NEXT
370 GCOL 0,1:PROCaxes
380 PROCmax:PROCmin:range=fmax-fmin:PROCplot
390 FORI=1TO12:PRINT:NEXT
400*E4
410 END
420 REM ** The DEFinition of PROCedure FFT follows.
430 DEFPROCFFT:LOCAL X%,Y%,V%,A%,B%,S%,T%,D%,Z%,L%,I%
440FOR X%=0 TO 255:Y%=0
450FOR V%=0 TO 7:A%=2^V%:B%=128/A%:Y%=Y%+B%*(A% AND X%)/A%:NEXT
460IM%(X%)=0:RL%(Y%)=TM%(X%):NEXT
470FOR S%=0 TO 7:T%=2^S%:D%=128/T%
480FOR Z%=0 TO T%-1:L%=D%*Z%
490FOR I%=0 TO D%-1:A%=2*T%*I%+Z%:B%=A%+T%
500F1=RL%(A%):F2=IM%(A%):P1=CS(L%)*RL%(B%):P2=SN(L%)*IM%(B%)
510P3=SN(L%)*RL%(B%):P4=CS(L%)*IM%(B%)
520RL%(A%)=F1+P1-P2:RL%(B%)=F1-P1+P2
530IM%(A%)=F2+P3+P4:IM%(B%)=F2-P3-P4
540NEXT:NEXT:NEXT
550FOR X%=0 TO 255
```

```
560FR%(X%)=SQR(RL%(X%)*RL%(X%)+IM%(X%)*IM%(X%))
570NEXT
580 ENDPROC
590DEFPROCaxes
600MOVE 304,904
610DRAW 304,264
620DRAW 972,264
630VDU 23,250,0,0,0,0,255,0,0,0:VDU 23,251,24,24,24,0,0,0,0,0
640PRINT TAB(6,3)"10"CHR$(250)
650FOR J =0 TO 9
660PRINT TAB(7,(J+1)*2+3);9-J;CHR$(250)
670NEXT J
680PRINT TAB(9,24)"0  "CHR$(251)"  0.2  "CHR$(251)"  0.4  "CHR$(251)
690PRINT TAB(14,27)"Cycles/beat"
700x$="Amplitude":PRINT TAB(4,7)LEFT$(x$,1)
710FOR J =8 TO 15
720x$=RIGHT$(x$,LEN(x$)-1)
730PRINT TAB(4,J)LEFT$(x$,1)
740NEXT J
750PRINT TAB(2,18)"(a.u)"
760ENDPROC
770DEFPROCmax
780fmax=V%(1)
790 FOR N% = 1 TO 127
800  IF V%(N%)>fmax THEN fmax=V%(N%)
810NEXT N%
820ENDPROC
830DEFPROCmin
840fmin=V%(1)
850FOR N%=1 TO 127
860  IF V%(N%)<fmin THEN fmin=V%(N%)
870NEXT N%
880ENDPROC
890DEFPROCplot
900GCOL 0,1:MOVE 305,264
910FOR N%=1 TO 127
920  xplot=305+(N%*5)
930  yplot=264+INT((V%(N%)-fmin)*2000/range)
940DRAW xplot,yplot
950NEXT N%
960ENDPROC
```

```
                    " PROGRAMME  D "
                   ******************
 30 MODE4
 40 DIM TM%(255)
 50INPUT''"To list RR intervals from disk file"'' File name: "F$
 60W=OPENIN(F$):INPUT£W,A$,NS
 70PRINTA$:FOR Q=0 TO 255:INPUT£W,TM%(Q):NEXT:CLOSE£W
 80PRINT"DO YOU WANT TO PRINT RR-INTERVALS(Y/N)"
 90X$=GET$
100IFX$="Y" THEN VDU2,15 ELSE VDU3,14
110CLS:PRINT"     File name="  ;F$   ;
120FOR I=1 TO 3:PRINT:NEXT
130FOR Q%=0 TO 255
140Q2%=Q%MOD4
150Q3%=Q2%*20
160PRINT;Q%;TAB(Q3%+5);"RR=";TM%(Q%);
170IF Q2%=3 THEN PRINT"ms"ELSE PRINT"ms";TAB(Q3%+20);
180NEXT Q%:VDU3
190PRINT"DO YOU WANT A PRINT OUT OF THE GRAPH(Y/N)?"
200K$=GET$:IF K$="Y" THEN GOTO210
210W=OPENIN(F$):INPUT£W,A$,NS:CLS:PRINT"File name:";F$
220MOVE 0,400:FOR Q=0 TO 255:INPUT£W,TM%(Q)
230DRAW 4*Q,TM%(Q)-400:NEXT:CLOSE£W:VDU2,15:*E4
240GOTO50
```