Hemodynamic Responses to Graded Treadmill Exercise in Young Untreated Labile Hypertensive Patients

By Arthur M. Levy, M.D., Burton S. Tabakin, M.D., and John S. Hanson, M.D.

SUMMARY
Twenty labile hypertensive patients and their age-matched controls were studied at rest and during five levels of treadmill exercise. Intra-arterial blood pressure, cardiac output, and various aspects of the pressure pulse wave were analyzed under these conditions. Exercise provoked diastolic hypertension in 30% of the patient group. Mean group pressure responses demonstrated an almost constant differential through all phases of the study. The validity of a previously suggested classification of labile hypertensive subjects based on resting cardiac output estimations is questioned. A differentiation of modes of adjustment to an increased pressure load was suggested from exercise measurements of arterial ejection time. Despite numerous factors affecting the measurement, first derivative of the peripheral arterial pulse correlated well with indices of ejection time and mean rate of left ventricular ejection.

Additional Indexing Words:
Intra-arterial blood pressure Cardiac output Ejection time index

In Accord with the final recommendations of the Second National Conference on Cardiovascular Disease hypertensive research group, we have thought that one of the most important pathways for future study in this field should be the examination of blood pressure and other hemodynamic responses of hypertensive patients under varied conditions. With few exceptions, investigations of this nature have been primarily oriented toward those individuals with fixed and usually severe levels of hypertension. The paucity of data that exists relating to labile hypertension has largely been collected from resting studies, and has left many questions with prognostic and therapeutic implications essentially unanswered. Among the more interesting of these are the following: 1. Is an office blood pressure reading taken at rest in any way indicative of the blood pressure levels that a labile hypertensive will experience during his daily activities? 2. Is it valid to classify labile hypertensive patients on the basis of their resting cardiac output? 3. What is the pattern of hemodynamic response to exercise in labile hypertensive subjects—is there a homogeneity of response or marked individual variation? 4. What, if any, are the hemodynamic compensations for increased blood pressure under the demands of physical activity?

The present study was undertaken in an attempt to answer some of these questions. A group of 20 young, untreated labile hypertensive subjects and their age-matched normal controls were studied at rest and during graded upright exercise with measurement and calculation of several hemodynamic parameters. Results are presented as well as

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conclusions concerning possible pathways for further fruitful study in this entire area.

**Methods**

The hypertensive patients were 20 white men aged 10 to 41 years who had been enrolled in the Outpatient Hypertension Clinic of the Mary Fletcher Hospital or referred to the Cardiopulmonary Laboratory from practicing physicians in the area. They were selected because clinical measurements of diastolic blood pressure had varied in each individual from less than 90 mm Hg to greater than 100 mm Hg. Fourteen of these men evidenced repeated elevation of diastolic blood pressure above 90 mm Hg but became normotensive during hospitalization or, infrequently, during office visits. Antihypertensive therapy had been employed at one time in 13 of the group, but at the time of study all subjects had been without medication for a period of at least 3 months, with the exception of two who had interrupted therapy 4 weeks prior to investigation. Electrocardiographic and vectorcardiographic findings consistent with left ventricular hypertrophy and strain were present in only one of the group, and clinical signs of cardiac decompensation had never been detected in any of the subjects.

Age-matched controls for the hypertensive group were recruited from undergraduate and graduate students at the University, student radiology technicians, and faculty volunteers. The control subjects were offered a monetary inducement for their participation, but payment was not dependent on successful completion of a predetermined amount of work, which conceivably could have exceeded an individual’s exercise capabilities.

The anthropometric data for the hypertensive (H) and control (C) groups can be summarized as follows, with ranges and means (in parentheses) for age, height, weight, and body surface areas in that order: H: 19 to 41 years (31), C: 10 to 41 years (31); H: 162 to 188 cm (174), C: 162 to 186 cm (176); H: 66 to 101 kg (80), C: 65 to 99 kg (80); H: 1.72 to 2.18 m² (1.95), C: 1.70 to 2.23 m² (1.96).

Method of study has in large part been described in detail elsewhere. In brief, determinations of cardiac output, systolic, diastolic, and mean intra-arterial blood pressures, minute volume of ventilation, oxygen utilization, and carbon dioxide elimination were made for each subject recumbent at rest, standing at rest, and during treadmill walking on the level and at inclinations of 4°, 8°, 12°, and 14° at a speed of 3 mph. Cardiac output was estimated by dye-dilution technique with a Waters 300A cuvette densitometer* and Cardio-Green†, injection of the latter occurring 2% to 4 minutes after initiation of exercise, depending on treadmill inclination. Expired gas was collected in 150-liter Douglas bags, and gas volume was measured in a Tissot spirometer at BTPS. Oxygen and carbon dioxide content of expired gas was determined with the Beckman E-2 and LB-1 analyzers, respectively, with oxygen utilization and carbon dioxide elimination calculated at STPD. Oxygen ventilatory equivalent (O₂V) was calculated as liters of total ventilation per liter of oxygen utilization.

Direct arterial pressure was recorded at rest and for each exercise level with a Statham P23Db transducer, output of the latter as well as that of the densitometer being suitably amplified and recorded in the Electronics for Medicine DR-8 photographic recorder. Mean pressure was obtained through electrical damping of the strain-gauge signal, whereas mean systolic pressure was determined from planimetry of the pressure pulse curve. Left ventricular work index (LVWI) and stroke work index (LVSWI) were calculated as the products of cardiac and stroke indices, respectively, mean arterial pressure, and the constant 13.6/1,000.

In addition to the above, the following variables were measured or calculated. The first derivative of the arterial pressure pulse (dp/dt) was measured from a resistance-capacitance circuit (time constant: 1.1 msec) in the recorder’s SGM-2 pressure amplifier and was in turn recorded via a DC amplifier with a frequency response range of 0.1 to 2,000 c/s. Calibration of the derivative was accomplished by means of an instrument devised in this laboratory for generation of truly linear ramps and thus accurate derivative measurements. Blood pressures and derivatives were recorded at paper speeds of 200 and 100 mm/sec with superimposed 0.02 second time lines. From the photographic records measurements were made of peak systolic dp/dt and ejection time (ET). Although it has been considered impractical to attempt measurement of ET during exercise because of difficulty in delineating onset of both systolic upstroke and dicrotic notch, this problem was circumvented through use of the dp/dt tracing for timing at the points of initial and secondary positivity (fig. 1). Tension-time index (TTI), ejection-time index (ETI), diastolic-filling period (DFP), ejection-time: diastolic-filling-period ratio (ET/DFP), tension-time index per minute (TTI/min), and mean rate of left ventricular ejection (MRLVE) were also computed.

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*Waters Company, Rochester, Minnesota.
†Hyynson, Wescott and Dunning, Baltimore, Maryland.
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Simultaneous recording of radial arterial pressure pulse wave and its first derivative at peak exercise. Arrows mark points of initial and secondary positivity defining onset of systole and dicrotic notch, respectively. Time lines 0.02 second.

Vectorcardiograms (VCG) were recorded in all subjects by the Frank lead system. Maximal spatial vector (MSV) was measured from 13.4 X magnifications of the vector loops, which had been photographed on 35-mm film. Standard 12-lead electrocardiograms and 6-foot chest x-rays were also obtained.

Appropriate statistical analysis of data was accomplished with the IBM 1620 Data Processor employing standard programs. For the purposes of this study adherence to the following P-value interpretations was made: <0.05 = probably significant; <0.01 = significant; <0.001 = highly significant.

Results

It is of consequence to note that the physical characteristics of the two groups studied are closely matched as regards both mean data and range of intragroup variation. Since group mean difference in body surface area amounts to only 0.01 m² the results presented for variables such as cardiac output and stroke volume, are readily comparable. In addition, calculated work loads for each level of exercise are practically identical, thus facilitating direct comparison of the various responses to physical stress.

Vectorcardiograms, electrocardiograms, and chest radiographs were interpreted as normal in 19 of the 20 hypertensive patients. The exception to this pattern was a 30-year-old man whose ECG showed ST-segment and T-wave changes of left ventricular hypertrophy and strain. Chest films were consistent with left ventricular enlargement, but his VCG maximal spatial vector was within normal limits.

Of the 20 hypertensive subjects 10 exhibited diastolic blood pressure greater than 90 mm Hg while resting recumbent at the start of the study. During exercise an additional six subjects evidenced diastolic hypertension. The remaining four men in this group, despite frequent previous recordings of diastolic hypertension clinically, maintained normal diastolic blood pressure throughout the present study. Only one control subject's diastolic pressure exceeded 90 mm Hg on a single occasion during strenuous exercise.

Mean values for systolic, diastolic, and mean direct arterial blood pressure in the hypertensive group while resting recumbent were 159/89 (114) mm Hg, and the figures for the corresponding control group were 130/70 (89) mm Hg. During peak exercise the pressures for the hypertensive group were 198/93 (127) mm Hg and for the controls 165/74 (107) mm Hg. As seen in figure 2, the two groups demonstrated practically parallel pressure alterations during the study. The statistically highly significant pressure differences seen between the two groups at rest remained constant through all exercise levels.

Heart rate, cardiac output, and stroke volume did not differ significantly in the two groups either at rest or during exercise. Employing the normotensive subjects' mean value plus two standard deviations of cardiac index as the criterion for a high resting index (5.32 L/min/m²), only three of the group with high pressure may be categorized as "high output, low resistance" labile hypertensive patients. One control subject also demonstrated this phenomenon. At the three highest exercise levels corresponding to oxygen uptakes of 2,182 to 2,965 ml/min, the hypertensive group maintained higher levels of cardiac output and stroke volume than the control group, although the differences were not statistically significant. Whereas the former
subjects maintained an essentially stable output at both 12° and 14° treadmill elevations, the hypertensive men manifested a 2.0 L/min decrement of output on transition to the maximal work load. This has also been observed in large groups of age-categorized normal males without significant intergroup variance.

By virtue of the similarity of cardiac output and the disparity in mean arterial blood pressure, calculated peripheral vascular resistance was significantly higher at rest and during the first three work loads in the hypertensive group. At the 12° and 14° treadmill elevations, however, the cardiac output response discrepancies previously noted were associated with more comparable mean resistances without significant intergroup variance.

Estimations of LVWI and LVSWI also reflected the elevated mean arterial pressure observed at rest and during exercise in the hypertensive subjects, significantly elevated ventricular minute and stroke work loads being performed in this group. The variation between groups is accentuated at the two highest work loads on the basis of augmented flow per minute and per beat exhibited by the hypertensive group. Obviously, however, the majority of this added myocardial energy expenditure is dissipated in performance of pressure rather than flow work.

There were no significant differences between the group mean values for minute ventilatory volume, oxygen utilization, or carbon dioxide production. However, the hypertensive subjects consistently produced less CO₂ during performance of the four highest work loads, the maximum divergence amounting to 10.5% of the control group mean at the 14° level. Hemodynamic and ventilatory results are summarized in table 1.

Ejection times, measured from the pressure pulse recordings, and ejection-time index, representing a correction for heart rate, were not significantly different in the two groups, nor was diastolic filling period. Fourteen hypertensive subjects exhibited ETI’s nearly identical to the normal group’s mean for all seven measurements. Contrary to this majority trend, three men had prolonged ETI and three short ETI. In view of the marked uniformity of ETI about mean within the normal
### Table 1

**Circulatory and Ventilatory Variables**

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*Hypertensive group.
†Control group.

HR = heart rate; CO = cardiac output; CI = cardiac index; SV = stroke volume; MV = minute volume ventilation; O₂ = oxygen utilization; CO₂ = carbon dioxide elimination; PVR = peripheral vascular resistance; LVWI = left ventricular work index; LVSWI = left ventricular stroke work index; WL = work load.
group, these hypertensive intra-group differences are quite striking. Because of the often considerable variations in individual acceleration of heart rate during exercise, ETI would appear to represent a more convenient means of comparing systolic duration under test conditions such as those of the present study. 6

Representing a calculated value derived from measurements of ET and mean systolic pressure, TTI was predictably found to be significantly elevated under resting and exercise conditions in the high-pressure individuals as a group. The six patients described above with unusually short or long temporal ejection phases, however, are of particular interest. Of the three with short ET, two were able to “compensate” for their rather marked hypertension and thus produce a normal TTI. The magnitude of the remaining subject’s pressure elevation was such that despite a significantly abbreviated ET, the net result remained an abnormally high TTI. The three instances of protracted ejection periods recorded naturally produced a striking summation effect in terms of TTI, compounding the increases in arterial pressure.

In both groups mean values for TTI were inversely related to the exercise load. Despite the progressive rise in blood pressure with each work increment, a relatively greater simultaneous shortening of ET occurred. Tension-time index per minute, however, exhibited augmentation with increasing exertion, since the resulting tachycardia counterbalanced decrements in TTI. Group mean values for TTI and TTI/min differed throughout to a highly significant degree.

Mean rates of left ventricular ejection were identical for the two groups at rest and, with only one exception, very similar during exercise. During the 12°-inclination walk, the hypertensive subjects had a higher stroke volume response and demonstrated their ability to expel this volume at a more rapid rate despite a comparatively prolonged ET. Seven of the hypertensive group evidenced consistently high MRLVE. Of these, three were the men with short ET and four were producing relatively high stroke volumes.

No significant difference in maximal upstroke velocity of the pressure pulse existed between the groups either at rest or during any exercise period. It was apparent that maximal dp/dt increased in linear fashion with respect to work load up to oxygen utilization levels of 2,600 to 2,700 ml/min. Beyond this point no further rise of pressure derivative was recorded in either group. Both categories of subjects effected the major single increase in maximal dp/dt immediately on initiation of exercise with comparatively small subsequent enhancement of peak values.

Eight hypertensive men achieved maximal dp/dt values of greater than 2,500 mm Hg/sec at a minimum of one exercise level. Of these, six had simultaneously increased MRLVE (600 ml/sec). Furthermore, of seven men with high MRLVE, only one did not have an elevated maximal dp/dt. Thus, out of a group of nine subjects with either alteration, six had both (fig. 3). Referring again to the six men with abnormally shortened or prolonged ETI, a constant inverse relationship between dp/dt and ETI is observed. These abnormalities in duration of ejection represent, therefore, the major factor effecting the close correlation of

![Figure 3](image-url)

**Figure 3**

Relationship of each hypertensive subject’s maximal peak dp/dt to simultaneous calculated mean rate of left ventricular ejection.
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Table 2

Pressure Pulse Analysis

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*Hypertensive group.  
†Control group.

ET = ejection time; ET/DFP = ejection time/diastolic filling period; ETI = ejection-time index; TTI = tension-time index; TTI/min = tension-time index per minute; MRLVE = mean rate of left ventricular ejection; Max. dp/dt = maximal first derivative of arterial pressure pulse.

MRLVE and maximal dp/dt, since unusual alterations in stroke volume were not noted in conjunction with these measurements.

Results of the pressure pulse analyses are presented in table 2.

Discussion

Clinical examination of each of the hypertensive subjects in the present study had on numerous occasions revealed diastolic blood pressure greater than 100 mm Hg as well as levels less than 90 mm Hg. Prior to performance of exercise, direct arterial diastolic pressure recordings in the resting recumbent state were greater than 90 mm Hg in only half the group. During exercise these 10 men maintained diastolic hypertension, and an additional six exceeded the 90 mm Hg level. According to our past experience gained from study with the same test protocol of 62 normal men age 19 to 40 years, the development of such diastolic blood pressure during exercise is distinctly abnormal.

Since each individual in the present hypertensive group was selected because of his having demonstrated periods of normal and elevated diastolic blood pressure, it is not surprising that four of this group were normotensive throughout this exercise study. It must therefore be kept in mind that a normotensive exercise response does not of necessity exclude a diagnosis of labile hypertension. The finding of definite hemodynamic abnormalities during exercise in six subjects who were normotensive at rest does not lend credence to the statement that normal blood pressure at rest is synonymous with hemodynamic normalcy.

The constant group differences in blood pressure seen in all phases of the study (fig. 2) are striking. In view of previous concepts regarding the role of vascular hyperreactivity as a contributing factor in labile hypertension, it might have been expected that there would have been either a divergence of these responses during exercise, with the usual increase in circulating humoral agents secondary to physical stress, or a convergence of
these responses with a dissipation of any resting anxiety effect while absorbed in the exercise procedure. It is important to emphasize that not a single hypertensive subject evidenced a significant tendency toward exercise pressure normalization once hypertensive levels had been achieved.

On the basis of resting cardiac output determinations from several studies a categorization of labile hypertensive patients has been established according to the presence of either high output with low vascular resistance or normal output with high resistance. The reported incidence of the former phenomenon varies from 33 to 82%. It has even been postulated that such a high-output labile state may represent a more benign form of hypertension with a better prognosis, although subsequent data from the same patients seem to contradict this hypothesis. In view of the frequent occurrence of often marked fluctuations in serial resting cardiac output values for any given individual, the validity of subclassifying labile hypertension from such data should be questioned. Certainly, conclusions asserting that a hypertensive patient had changed his classification and prognosis by a change in resting cardiac output are unwarranted. The three “high output” hypertensive subjects in the present study displayed an exercise cardiac output response well within the range of variability observed in the remainder of the group. This finding suggests in a more positive manner that resting cardiac output estimations should not be employed for classification and/or gradation of the severity of labile hypertension.

Although neither a clear delineation of the two groups nor a subclassification within the hypertensive group could be made on the basis of the present cardiac output data, interesting differences were noted in results from pressure pulse wave analysis. It has been reported that changes in ejection time may give valuable information about myocardial status, being sufficiently sensitive to detect an effect of digitalis administration, even in normal subjects. Precise measurements have been difficult to make from exercise pulse wave recordings because of the relatively slow slope changes at the onset of systole and dicrotic notch under these conditions. However, the points of initial and secondary positivity of a simultaneously recorded first derivative of the pressure pulse clearly define the ejection interval (fig. 1).

Six of the hypertensive subjects demonstrated distinctive changes in ejection time during the exercise studies (fig. 4 and 5), as compared to the control group’s mean values plus or minus two standard deviations. Of these, three had abnormally short ejection times (fig. 4), and, excluding the four men who were normotensive throughout the study, they were the only members of the hypertensive group with near-normal TTI. If it is true that TTI is a major determinant of left ventricular oxygen consumption, these men

![Figure 4](image)

*Abnormally short ejection-time index related to simultaneously measured peak dp/dt in three hypertensive subjects. Lower line represents normal group’s mean data.*

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are consequently producing comparable myocardial work more economically than other members of the group. Weissler and associates\textsuperscript{14} have suggested that a shortened ET correlates well with reduced stroke volume in patients with congestive heart failure, but this relationship is obviously not applicable to the present subject material or results.

Freis\textsuperscript{17} has summarized the possible mechanisms of left ventricular adjustment to systemic hypertension as (1) augmentation of myocardial contractility independent of fiber length, (2) myocardial hypertrophy, and (3) an increase in ventricular residual volume and a related fiber lengthening. As judged from measurements of ET, the patients discussed above appear to have adapted to their pressure load by the first mechanism. The only patient in the present series with ECG and radiographic findings of left ventricular hypertrophy is one of the three subjects with short ET (L.C., fig. 4). It is possible that this man, whose blood pressure was the highest recorded in the group, has maintained a protracted period of inotropic compensation, and, in addition, has evoked the second mode of compensation.

Abnormally prolonged ET during exercise was observed in three hypertensive subjects (fig. 5). Although these men do not obviously differ from other members of the group, because they expel a normal stroke volume relatively slowly against increased resistance, they are operating inefficiently from the myocardial standpoint. This is, of course, reflected in their markedly elevated TTI's. Assessed according to the methods of study employed, these men are not presently adjusting to their increased pressure by any of the means proposed. The significance of this response is as yet obscure, but because it may represent a transitional stage, longitudinal follow-up of such findings is certainly indicated.

Maximal first derivatives of the ascending limb of peripheral arterial pulse waves have not been subjected to the scrutiny that has been afforded central pulse derivatives.\textsuperscript{18, 19} As a result, the validity and application of this measurement have not been well evaluated. Certainly, the number of factors affecting this variable in peripheral arterial sites might be expected to limit its value seriously. Nevertheless, although not necessarily reflecting left ventricular function per se, the rate of rise of the radial arterial pressure pulse correlated to a highly significant degree with systolic blood pressure, mean blood pressure, ET, and MRLVE. As seen in figures 4 and 5, the six hypertensive subjects with abnormal ET's demonstrated a close inverse relationship between this variable and maximal dp/dt. In addition, it is of interest that rate of arterial pulse rise and rate of volume ejection

\begin{figure}[ht]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Prolonged ejection-time index relative to simultaneously measured peak dp/dt in three hypertensive subjects. Subject B.W.'s response deviates from the normal group's mean starting at the 4th exercise level.}
\end{figure}
(MRLVE) correlate so well. This is particularly well emphasized in figure 3 where each hypertensive subject’s highest peripheral dp/dt is related to the simultaneously derived value for MRLVE. The correlation of these two parameters for all measurements is similar in these two groups of young men (r = 0.60 and 0.54) despite probable significant differences in the functional state of their respective peripheral arterial beds.

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