# Kinetocardiogram, Phonocardiogram, and Arterial Pulse Waves During Acute Hemodynamic Changes

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THERE is currently a need for simple, atraumatic methods of assessing cardiovascular status. The kinetocardiogram (KCG) and external recordings of arterial pulse waves represent possible approaches which have not yet been adequately explored. Both techniques have been applied in various cardiovascular disorders, but little information has been obtained on the effects of acute alterations in hemodynamics. Since it is possible to force the circulation in known directions by the administration of vasoactive drugs with specific hemodynamic actions, it seemed worthwhile to assess the effects of such acute changes on the KCG, carotid pulse contour, and the speed of transmission of the central arterial pulse wave. Such observations on the effects of known changes in hemodynamics should help clarify the interpretation of KCG and arterial pulse-wave tracings.

## Part I: The Kinetocardiogram

### Methods

The subjects consisted of 28 males who were either normal volunteers or patients without cardiovascular disease, selected from the wards of the Veterans Administration Hospital. No patients were acutely ill and none were suffering from chronic debilitating diseases. The subjects ranged in age from 25 to 48 years with a mean age of 37.4 years. Each received one to three drugs during the recording session. When more than one drug was used in the same subject, the short acting agents, such as amyl nitrite and angiotensin II, were given first and then sufficient

time was allowed for return of the KCG, pulse wave recordings, and blood pressure to control values before the next agent was administered.

The kinetocardiograms were recorded according to the method of Eddleman[1] using two pickups, one in the $K_1$ and the other in the $K_4$ position. These are similar in location to the electrode placements $V_1$ and $V_4$ of the standard 12-lead electrocardiogram. Lead I of the electrocardiogram was used as a time reference. Recordings were made simultaneously through Sanborn amplifiers and a direct writing multichannel oscillograph at a paper speed of 100 mm/sec. Blood pressure was measured in the upper extremity by the auscultatory method.

Following the control tracings, various vasoactive drugs were administered. Synthetic angiotensin II or methoxamine were used to increase total peripheral vascular resistance. Amyl nitrite or isoproterenol was administered to decrease total peripheral resistance and increase cardiac output and also myocardial contractility. Hexamethonium was given to decrease myocardial contractility, cardiac output, and arterial pressure. All drugs except amyl nitrite (which was given by inhalation) were administered by slow intravenous infusion after dilution in 5% dextrose solution. The infusion rates were regulated to obtain a significant change in arterial pressure as determined by frequent monitoring.

Both the amplitude and the duration of the various components of the KCG were measured and expressed respectively as percentages of total cycle amplitude and cycle length. Changes were determined as differences in these percentages between the control and post-drug periods. Statistical analysis of the changes following administration of the various drugs was carried out by the signed ranks method.[2]

### Results

*Increased Left Ventricular Pressure Load*

Angiotensin II and methoxamine increase total peripheral resistance without an increase in cardiac output.[3] They were used to impose an acute pressure load on the left ventricle. Despite considerable elevations of both systolic and diastolic blood pressures, averaging

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Table 1

*Changes in Precordial Movements Following Vasoactive Drugs Expressed as Per Cent of Cycle Amplitude*

| Drugs | No. of Subjs. | Mean | | | $K_1$ | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | B.P. change | | H.R. change | Right ventricular movement* | | | | Systolic-retraction | | | | |
| | | Sys. | Dias. | % | Mean (%) | No. incr. | No. decr. | P | Mean (%) | No. incr. | No. decr. | No. unch. | P |
| Angiotensin II | 9 | +47 | +42 | −18.9 | +10.3 | 6 | 1 | < 0.05 | −11.5 | 3 | 6 | 0 | ns |
| Methoxamine | 9 | +34 | +27 | −26.1 | − 8.8 | 3 | 6 | ns | + 3.0 | 6 | 3 | 0 | ns |
| Amyl nitrite | 13† | −27 | −29 | +44.5 | + 1.0 | 4 | 6 | ns | + 4.0 | 6 | 3 | 1 | ns |
| Isoproterenol | 14 | +14 | −35 | +61.2 | + 8.0 | 7 | 4 | ns | + 5.1 | 9 | 5 | 0 | ns |
| Hexamethonium | 7 | −17 | −22 | +17.9 | − 1.8 | 4 | 3 | ns | +17.0 | 5 | 2 | 0 | ns |

*Not present in all subjects.

†$K_1$ not obtained in three subjects after amyl nitrite.

47/42 mm Hg in nine subjects receiving angiotensin II, and 34/27 mm Hg in a similar number given methoxamine, there were no significant changes in the amplitudes of either the pre-ejection movement or the left ventricular thrust as recorded in the $K_4$ position (table 1). The duration of the thrust was also essentially unchanged when expressed as a percentage of the cycle length. The systolic retraction which occurs during left ventricular ejection fell significantly after both drugs (table 1, figs. 1 and 2). The mean change was a reduction in systolic retraction of 13.9% ($P < 0.05$) of the total cycle amplitude following angiotensin II, and 18.3% ($P = 0.01$) after methoxamine.

The right ventricular outward movement which preceded ventricular ejection as recorded in the $K_1$ position increased slightly during angiotensin II infusion (mean + 10.3, $P < 0.05$) but showed no definite trend during methoxamine infusion. Systolic retraction decreased in the $K_1$ position after angiotensin II, but the change was not significant. It remained essentially unchanged after methoxamine. Atrial waves were recorded in the $K_1$ position in five subjects receiving angiotensin II. The atrial wave increased in three subjects and decreased in two, the average change being + 8.3% of the total cycle amplitude. Atrial waves were present in three subjects who were given methoxamine. Two subjects had increased atrial waves and one had decreased

atrial waves, the average change being + 4.3%. The changes in the atrial wave after either agent were not significant. The durations of
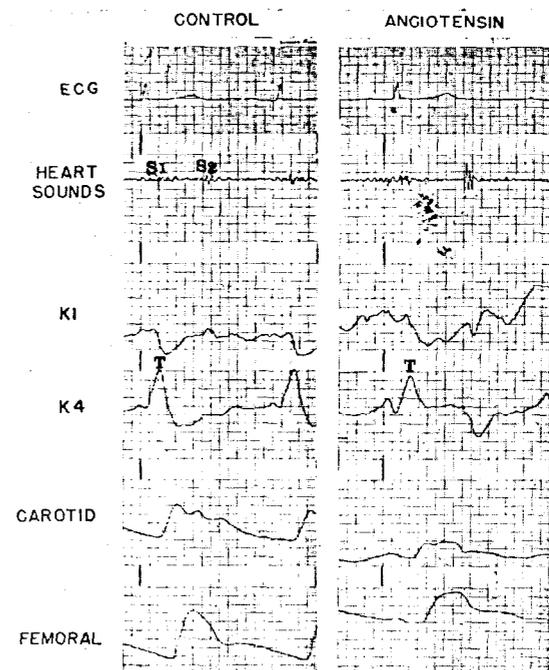


Figure 1

Simultaneous records of lead 1 of the electrocardiogram, heart sounds, $K_1$ and $K_4$ positions of the kinetocardiogram, and carotid and femoral pulse waves before and after raising the arterial pressure with intravenous infusion of angiotensin II. Paper speed was 100 mm/sec. Left ventricular thrust is indicated by the letter T. The systolic retraction wave following the thrust has disappeared after angiotensin II. The duration of the thrust is not increased as a percentage of cycle length, and the amplitude is unchanged.

| | $K_4$ | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pre-ejection movement* | | | | | Left ventricular thrust | | | | Systolic retraction | | | | |
| Mean (%) | No. incr. | No. decr. | No. unch. | P | Mean (%) | No. incr. | No. decr. | P | Mean (%) | No. incr. | No. decr. | No. unch. | P |
| + 5.5 | 5 | 4 | 0 | ns | + 2.0 | 5 | 4 | ns | −13.9 | 1 | 7 | 1 | < 0.05 |
| − 2.3 | 4 | 2 | 0 | ns | + 0.6 | 4 | 5 | ns | −18.3 | 0 | 8 | 1 | = 0.01 |
| + 9.5 | 5 | 4 | 2 | ns | −29.3 | 1 | 12 | < 0.01 | +25.2 | 11 | 2 | 0 | < 0.01 |
| +14.0 | 7 | 2 | 0 | ns | −28.2 | 3 | 11 | = 0.01 | +30.9 | 12 | 1 | 1 | < 0.01 |
| −14.8 | 0 | 3 | 1 | ns | −11.4 | 3 | 4 | ns | +29.2 | 6 | 1 | 0 | < 0.05 |

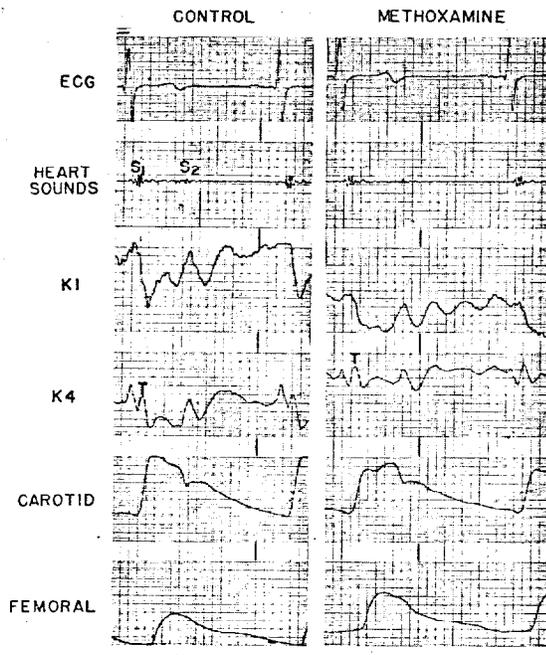either the atrial wave or the right ventricular movement were essentially unchanged.

*Increased Cardiac Output with Decreased Pressure Load*

Both amyl nitrite[4] and isoproterenol[5] increase cardiac output and diminish total peripheral resistance. The increase in output is due primarily to increased heart rate rather than



**Figure 2**

*Records showing increase in P/F and I/F ratios of the carotid pulse (see text) during elevation of arterial pressure with methoxamine. Carotid-femoral transmission time difference decreased form 82 to 66 msec. Other notations as in figure 1.*

to stroke volume. The ventricular stimulation produced by amyl nitrite is probably reflex in origin secondary to the diminished arterial pressure whereas isoproterenol has a direct inotropic effect on the heart. The mean decrease in arterial pressure following amyl nitrite inhalation was 27/29 mm Hg. After isoproterenol, systolic pressure increased by an average of 14 mm Hg while diastolic pressure decreased by 35 mm Hg.

Eleven of 13 subjects receiving amyl nitrite and nine of 14 subjects who were given isoproterenol exhibited pre-ejection movements in the records taken in the $K_4$ position. In the amyl nitrite group there was no significant change in amplitude of this deflection, five increased, four decreased, and two exhibited no change (table 1). In the nine subjects receiving isoproterenol, seven increased and two decreased, the mean change being + 14.0% ($P < 0.1$) of the total cycle amplitude.

The amplitude of the left ventricular thrust decreased significantly following both drugs. The mean reduction after amyl nitrite was 29.3% ($P < 0.01$), and after isoproterenol it was 28.2% ($P = 0.01$). The duration of the thrust expressed as a percentage of the cycle length shortened slightly after both drugs, but these changes were not significant. Following amyl nitrite, the mean decrease was 2.0% of the total cycle length with 11 of the 13 subjects showing this response. In the 14 patients receiving isoproterenol, seven showed a decrease in duration, four an increase, and

three remained unchanged, the mean change being — 1.2% of the total cycle amplitude.

The degree of systolic retraction during the left ventricular ejection phase of the cardiac cycle, as recorded in the $K_4$ position, increased (table 1, figs. 3 and 4). The increase in negative deflection averaged 25.2% ($P < 0.01$) after amyl nitrite inhalation, and 30.9% ($P < 0.01$) in the subjects receiving isoproterenol. There were no significant changes in the recordings taken from the $K_1$ position following either amyl nitrite or isoproterenol.

*Decreased Left Ventricular Pressure Load and Output*

Hexamethonium lowers arterial pressure primarily by reducing cardiac output, the total peripheral resistance remaining essentially un-
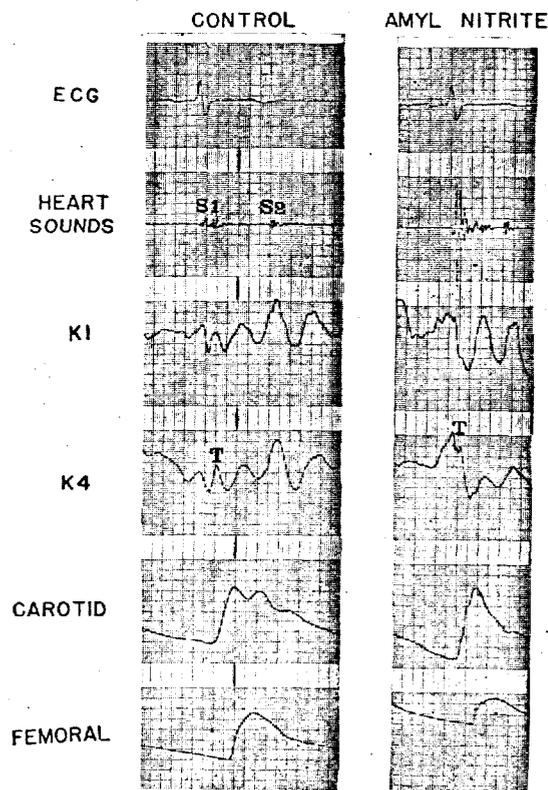


**Figure 3**

*Recordings before and after reduction of blood pressure with amyl nitrite showing increase in systolic retraction and decrease in magnitude of left ventricular thrust in the $K_4$ position recording of the KCG. Other notations as in figure 1.*
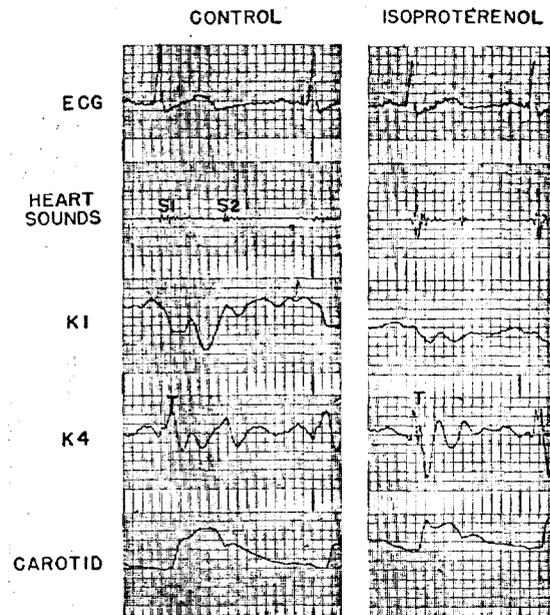


**Figure 4**

*Records showing disappearance of P maximum and reduction in I/F ratio of the carotid pulse wave following infusion of isoproterenol. Other notations as in figure 1.*

altered.[6] The only significant change in the KCG following hexamethonium was an increased systolic retraction in the $K_4$ position (table 1, fig. 5). The mean value for the amplitude of the left ventricular thrust decreased 11.4%, but the response was too variable in the different subjects to be regarded as significant.

**Discussion**

The KCG abnormalities characteristically associated with chronic left ventricular overload, as seen in patients with aortic valvular disease or hypertension, have been described by Davie and associates.[7] These changes consisted of an increase in the magnitude and duration of the left ventricular thrust recorded in the $K_4$ position. Davie and associates were unable to differentiate between the possible effects of hypertrophy, dilatation, or increase in work of the left ventricle as a cause of these abnormalities.

In the present study acute left ventricular overloads were imposed by elevating total
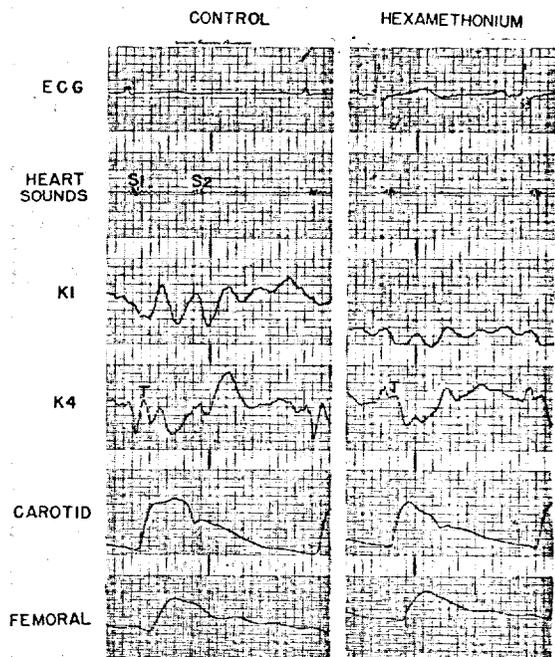
**Figure 5**

*Records showing reduction in P/F and I/F ratios of the carotid pulse wave during reduction of arterial pressure after infusion of hexamethonium. Carotid-femoral transmission time increased from 68 to 76 msec. Other notations as in figure 1.*

peripheral resistance with angiotensin II or methoxamine. No significant changes were noted in either the magnitude or duration of the left ventricular thrust. The pre-ejection movement was similarly unaffected. These results are in contrast to the changes found by Davie and associates[7] in patients with chronic overloads. This suggests that in patients with long-standing hypertension and aortic valvular disease the increase in both amplitude and duration of the thrust is related not so much to the magnitude of the load but more specifically to its chronicity. The principal difference in the adjustment of the ventricle to a chronically imposed load as contrasted to an acutely imposed load is myocardial hypertrophy. Davie and associates[7] did not find a significant correlation between the degree of thrust abnormality and cardiomegaly as determined by x-ray. However, it is well known that ventricular hypertrophy

in the absence of dilatation often cannot be detected in the x-ray.

On the other hand, reduction in arterial pressure with amyl nitrite and isoproterenol resulted in a significant decrease in the magnitude of the left ventricular thrust and a slight but insignificant shortening of its thrust, each expressed as a percentage of the total cycle amplitude and duration, respectively. Hexamethonium resulted in a reduction in the magnitude of the ventricular thrust in some patients, but the responses were too variable to be regarded as significant. These results indicate that the magnitude of the thrust is relatively independent of increases in left ventricular load although reduction in pressure load may reduce the percentage magnitude but not the percentage duration of the thrust.

In contrast, the changes in systolic retraction as a percentage of total cycle amplitude were consistent and significant with all of the acutely imposed alterations in left ventricular load. Systolic retraction decreased after angiotensin II and methoxamine and increased after amyl nitrite, isoproterenol, and hexamethonium. Thus, the changes in systolic retraction were inversely related to the pressure loads imposed on the left ventricle.

Since systolic retraction is an inward movement of the chest wall occurring during the period of ventricular ejection, it is probably a reflection of the decrease in ventricular volume occurring during the phase of rapid ventricular ejection. An acute increase in the pressure load with angiotensin II reduces left ventricular emptying thereby increasing the end-diastolic volume of the ventricle.[8] When ventricular volume is expanded, less shortening of ventricular diameter will be required to expel a given stroke volume than when ventricular volume is reduced. If this interpretation is correct, the magnitude of the downstroke beginning at the peak of the thrust and ending at the completion of the systolic retraction wave should provide an indication of the approximate percentage change in left ventricular volume during the period of rapid left ventricular ejection. This suggestion obviously needs to be investigated under a

wide variety of clinical and experimental conditions before it can be accepted.

## Summary

A variety of vasoactive drugs were employed to produce acute hemodynamic alterations and their effects were determined on the kineto-cardiogram. The most consistent alteration was a change in the systolic retraction wave recorded at the $K_4$ or apex region. Imposition of a left ventricular overload using angiotensin II or methoxamine decreased the amplitude of the wave expressed as a percentage of the total cycle amplitude. Reduction of left ventricular pressure load, by using amyl nitrite, isoproterenol, or hexamethonium increased the degree of systolic retraction. These alterations in the magnitude of the downstroke from the peak of left ventricular thrust to the end of the systolic retraction wave may reflect percentage changes in left ventricular volume during this period.

In contrast to patients with chronic hypertension or aortic valvular disease, the imposition of an acute left ventricular overload in normal subjects produced no significant change in the magnitude or duration of the left ventricular thrust expressed as percentages of the total cycle amplitude and duration, respectively. These results supply additional evidence that the duration of the thrust is a useful index of left ventricular hypertrophy.

## Part II: Changes in Arterial Pulse Waves

Aside from the recording of changes in contour in aortic valvular and peripheral vascular occlusive disease, little use has been made of externally recorded arterial pulses in clinical medicine. Nevertheless, characteristic alterations in the shape of the carotid pulse occur with aging and hypertension.[9, 10] These appear to be related to the loss of arterial distensibility associated with these conditions.[11] In addition, Katz and Feil[12] and Weissler and associates[13] have shown that the carotid pulse can be used as an indicator of alterations in left ventricular dynamics.

In the present study, the effects of acutely induced changes in cardiac output or total peripheral vascular resistance were evalu-

ated on various indices provided by simultaneous recordings of the carotid and femoral pulse waves, heart sounds, and electrocardiogram (ECG). Such studies might prove useful in the interpretation of alterations in these functions observed in different age groups and in the presence of cardiovascular disorders.

## Methods

The subjects were the same as those described in Part I, the KCG and pulse waves being recorded simultaneously. The arterial pulse-wave transducer has been described previously.[14] It consists essentially of a water-filled chamber sealed at one end with a compliant plastic membrane, and at the other by a metal diaphragm, on which two strain gauges are mounted. One of these transducers was used to record the carotid pulse. It was attached to the subject's neck with an adjustable clamp previously described.[15] Another similar transducer used to record the femoral pulse was attached to a rigid support overlying the femoral triangle. The transducer then was lowered over the artery and clamped in place at the overhead support.

The measurements taken on the carotid pulse were based on the relative heights of three inflections, two positive inflections or maxima occurring during systole followed by a negative inflection, the incisura. A line was drawn connecting the foot points at the beginning and end of a pulse cycle and perpendiculars were dropped from the three inflections. The ratio of the height of the second to that of the first maximum (P/F ratio) and of the height of the incisura to the first maximum (I/F ratio) were calculated.

The difference in pulse-wave transmission time between the carotid and femoral arteries was determined by using a magnifying lens as follows: The steep ascending upslope of the wave was extrapolated downward until it intersected a horizontal line drawn between the foot points at the beginning and end of the cycle. The point of intersection was taken as the onset of the wave. The time difference between the onset of the carotid and femoral pulses during the same cardiac cycle was taken as the carotid-femoral transmission time difference.

The ejection time was measured from the time of onset of the carotid wave, as defined above, to the minimum point of the incisura. The ejection time index (ETI) was calculated by the method of Weissler and associates[16] which normalizes the ejection time with respect to heart rate. The isovolumic contraction time (ICT) was determined by measuring the time between the beginning of the first and second heart

sounds and subtracting from this the ejection time. Low-frequency and low-amplitude vibrations preceding the first and second heart sounds were disregarded,[17] the onset of each sound being taken as the first high frequency vibration of amplitude at least twice that of the background noise level. With respect to the first heart sound this point in time coincides with the onset of the steep rise in left ventricular pressure and does not take into account the slow initial phase of left ventricular contraction which lasts 10 to 20 msec. Thus ICT may be underestimated by this method but is probably satisfactory for comparative purposes. In some cases, following isoproterenol, the second heart sound was not clearly delineated. In the cases where it was recognizable after isoproterenol, the time interval between the beginning of the second heart sound and the carotid incisura remained unchanged from the control. Therefore, in cases of doubt, the onset of the second heart sound following isoproterenol was determined by subtracting the control time interval from the carotid incisura.

The heart sounds were recorded with a Sanborn dynamic microphone and amplifier using a high-pass filter of 12 db per octave, and a nominal frequency cut-off of 100 cycles per second. The amplitude of the first heart sound was measured from peak to peak in millimeters, and the postdrug results were expressed as a percentage of the control.[18] Tension period[19] was measured from the time of onset of the QRS complex to the onset of the second heart sound, and from this interval the ejection time was subtracted. The Q-$S_1$ interval was taken as the time between the beginning of QRS and the onset of the first heart sound. The average of three consecutive pulse cycles was used in all of the above measurements.

**Results**

The externally recorded carotid pulse characteristically displayed two positive inflections or maxima during systole. The first (F maximum) was temporally related to the anacrotic bend of the aortic pressure pulse and to peak blood velocity, while the second (P maximum) was related to peak aortic pressure.[20] The ratio of the heights of P to F was previously found to increase with age and hypertension.[9, 10, 20] The ratio of I, the height of the incisura, to F, also increased.

Angiotensin II and methoxamine elevate peripheral vascular resistance thereby raising both systolic and diastolic pressure.[3] The ratios of P/F and I/F were significantly increased

## Table 2

*Changes in Carotid Pulse Contour and Carotid to Femoral Transmission Time Following Vasoactive Drugs*

| Drug | No. of subjs. | Blood pressure (mm Hg) Systolic Control | Systolic Change | Diastolic Control | Diastolic Change | Heart rate change (%) | P/F Control | P/F % change | P | I/F Control | I/F % change | P | Carotid-femoral Transmission time differences Control (msec) | % change | P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Angiotensin II | 9 | 118.0 | +46.5 | 68.7 | +42.4 | −18.9 | 0.919 | +57.7 | <0.01 | 0.574 | +45.3 | <0.01 | 64.5 | −20.2 | <0.01 |
| Methoxamine | 9 | 126.6 | +33.8 | 73.5 | +26.6 | −26.1 | 0.966 | +38.3 | <0.05 | 0.588 | +34.0 | <0.05 | 67.7 | −11.8 | =0.01 |
| Amyl nitrite | 13 | 126.7 | −27.0 | 74.4 | −29.4 | +44.5 | 0.966 | * | <0.01 | 0.601 | −46.2 | <0.01 | 66.1 | +18.1 | <0.01 |
| Isoproterenol | 14 | 120.5 | +14.2 | 73.1 | −35.0 | +61.2 | 0.934 | * | <0.01 | 0.562 | −51.5 | <0.01 | 66.6 | − 5.4 | ns |
| Hexamethonium | 7 | 122.6 | −17.1 | 79.2 | −21.6 | +17.9 | 0.844 | * | <0.05 | 0.465 | −21.5 | <0.05 | 69.1 | + 8.7 | <0.05 |

*P maximum disappeared in 8 subjects following infusion of amyl nitrite, in 10 following isoproterenol, and in one after hexamethonium.

by both agents (table 2, figs. 1 and 2). By contrast, amyl nitrite and isoproterenol decrease total peripheral resistance,[4, 5] and these agents produced a significant decline in P/F and I/F ratios (table 2, figs. 3 and 4). Hexamethonium lowers blood pressure primarily by reducing cardiac output rather than by lowering peripheral resistance. This drug also produced a decrease in P/F and I/F ratios (fig. 5).

The interval between the foot points of the carotid and the femoral pulses was designated as the carotid-to-femoral transmission time difference and was used to serve as an index of pulse-wave velocity changes occurring in the aorta in response to the various vasoactive agents. The transmission time difference increased significantly following amyl nitrite and hexamethonium but not after isoproterenol (table 2). Both angiotensin II and methoxamine decreased the transmission time significantly.

The ejection time measured as the interval from the foot of the pulse wave to the incisura increased after angiotensin II and methoxamine and decreased following amyl nitrite, hexamethonium, and isoproterenol (table 3). These changes in ejection time were approximately inversely related to the alterations in heart rate produced by these agents.

The ejection-time index which normalizes the ejection time with respect to heart rate[16] remained essentially unchanged following methoxamine, angiotensin II, and isoprotenerol (table 3). It increased after amyl nitrite ($P < 0.01$) and decreased slightly following hexamethonium ($P < 0.10$).

The isovolumic contraction time (ICT), measured by subtracting the ejection time from the interval between the two heart sounds increased after angiotensin II and decreased after amyl nitrite and isoproterenol (table 3). There was no significant change after methoxamine or hexamethonium. The quotient of diastolic pressure divided by ICT (DP/ICT) provides an index of the mean rate of the left ventricular pressure rise during the isovolumic contraction period.[21] As calculated by this method, the rate of left ventricular pressure

**Table 3**

Summary of Data Derived from Simultaneously Recorded Electrocardiogram, Phonocardiogram, and Carotid Pulse

| Drug | No. of subjs. | Change mean B.P. (mm Hg) Syst. | Change mean B.P. (mm Hg) Diast. | Heart rate Control (min) | Heart rate % change | Heart rate P | Ejection time Control (msec) | Ejection time % change | Ejection time P | ETI Control (msec) | ETI % change | ETI P | ICT Control (msec) | ICT % change | ICT P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Angiotensin II | 9 | +47 | +42 | 77.8 | −18.9 | ns | 269.6 | + 8.4 | <0.05 | 392.6 | 0.0 | ns | 34.3 | +70.8 | <0.01 |
| Methoxamine | 9 | +34 | +27 | 77.4 | −26.1 | ns | 270.0 | +14.6 | <0.01 | 383.7 | +2.2 | ns | 35.8 | +22.3 | <0.05 |
| Amyl nitrite | 13 | −27 | −29 | 72.9 | +44.5 | ns | 277.5 | −11.5 | <0.01 | 394.2 | +4.8 | <0.01 | 42.6 | −59.2 | <0.01 |
| Isoproterenol | 14 | +14 | −35 | 77.1 | +61.2 | <0.10 | 271.0 | −30.1 | <0.01 | 386.1 | −0.3 | ns | 34.8 | −57.7 | <0.01 |
| Hexamethonium | 7 | −17 | −22 | 72.7 | +17.9 | <0.05 | 287.7 | − 4.6 | <0.10 | 403.6 | −2.3 | <0.10 | 41.4 | − 6.5 | ns |

| Drug | No. of subjs. | DP/ICT Control (mm Hg/sec) | DP/ICT % change | DP/ICT P | Tension period Control (msec) | Tension period % change | Tension period P | Q-S1 Interval Control (msec) | Q-S1 Interval % change | Q-S1 Interval P | Amplitude of S1 % change | Amplitude of S1 P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Angiotensin II | 9 | 1999 | − 3.7 | ns | 99.7 | +17.8 | <0.05 | 62.2 | − 1.0 | ns | +15.6 | ns |
| Methoxamine | 9 | 2126 | +10.6 | ns | 88.0 | +10.9 | <0.10 | 51.5 | + 0.9 | ns | −15.2 | ns |
| Amyl nitrite | 13 | 1906 | +10.9 | ns | 92.6 | −27.3 | <0.01 | 56.0 | −14.2 | <0.10 | +124.3 | <0.05 |
| Isoproterenol | 14 | 2155 | +19.5 | <0.10 | 89.2 | −35.5 | <0.01 | 54.7 | −34.7 | <0.01 | +284.4 | <0.01 |
| Hexamethonium | 7 | 2060 | −20.3 | <0.05 | 98.6 | + 4.8 | ns | 58.0 | +17.6 | <0.05 | −24.6 | <0.05 |

rise for the 28 subjects during the control period averaged 2,043 ± 1,280 mm Hg/sec. This index increased 19.5% ($P < 0.10$) after isoproterenol and decreased 20.3% ($P < 0.05$) in the subjects given hexamethonium. There were no significant changes in this index following amyl nitrite, angiotensin II, or methoxamine. The measurements of diastolic pressure by the auscultatory method during the peak action of isoproterenol probably were falsely low since the hemodynamic changes associated with this agent led to a persistence of the Korotkoff sounds. If the diastolic pressure had been recorded directly, the ratio of the latter to ICT probably would have been greater.

Tension period is similar to ICT except that it also includes the period beginning at the time of onset of the QRS complex of the electrocardiogram. Tension period increased slightly after angiotensin II and methoxamine and decreased considerably after both amyl nitrite and isoproterenol (table 3). Tension period did not change significantly following hexamethonium.

The $Q-S_1$ interval, which is the period between the beginning of QRS and the first heart sound, remained unchanged after angiotensin II and methoxamine. It decreased after both amyl nitrite and isoprotorenol, the change being more marked with the latter drug (table 3, fig. 6). Following hexamethonium, $Q-S_1$ increased.

The amplitude of the first heart sound increased after amyl nitrite and isoproterenol with the greater change (mean +284%) occurring after isoprotorenol (table 3 and fig. 6). The amplitude decreased after hexamethonium and was insignificantly changed following angiotensin II and methoxamine.

### Discussion

*Aortic Wall Stiffness*

The changes in relative amplitudes of the two systolic maxima observed in the carotid pulse produced by vasoactive drugs, have been described in a previous report.[20] The height of the first positive inflection, or F maximum, is related to the acceleration of the blood in the central arterial system during

early ventricular ejection. The height of the second or P maximum is related to the input impedance of the arterial system.[20] The present study confirms and extends the former observations. Elevation of input impedance by angiotensin II and methoxamine increased the second maximum probably by restricting systolic runoff with resulting distention of the large arteries.[22] The incisura, which was inscribed soon after the second maximum, rose in association with the latter. These changes resulted in elevation of P/F and I/F ratios. Reduction of input impedance and wall tension with the vasodilator drugs used in this study had an opposite effect on the P/F and I/F ratios.

The velocity of the arterial pulse wave has long been used as an indicator of the changes in arterial elasticity occurring with age and cardiovascular disease.[23, 24] Past attempts to
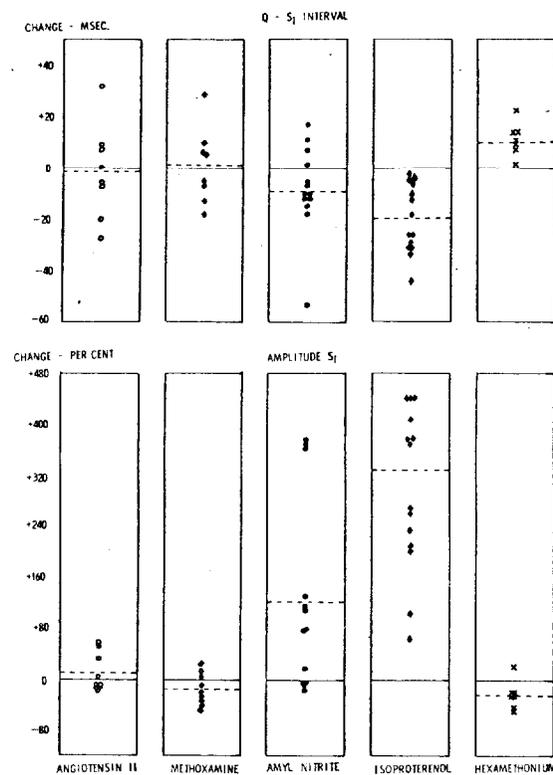


**Figure 6**

*Changes in the $Q-S_1$ interval and in the amplitude of the first heart sound following various drug-induced hemodynamic alterations.*

characterize the elasticity of the aorta in precise quantitative terms from pulse-wave velocity data have not been accepted because of many indeterminable factors such as variations in wall structure in different portions of the aorta, difficulties in accurately measuring the vessel length between the pickups, viscoelastic properties of the arterial walls, and other variables. Nevertheless, the available evidence suggests that pulse-wave velocity may serve as an approximate index of arterial elasticity of sufficient accuracy to be useful clinically.[23, 24]

In the present studies the carotid-femoral transmission time difference was used to determine whether the speed of propagation of the pulse wave through the aorta would change in the expected direction with alterations in aortic wall stiffness. Both angiotensin II and methoxamine increase aortic wall tension as indicated by the rise in systolic and diastolic pressures. As would be expected under such circumstances, the transmission time difference was consistently shortened. On the other hand, lowering of both systolic and diastolic pressures with amyl nitrite or hexamethonium decreased aortic wall tension and lengthened carotid-femoral transmission time, again demonstrating that changes in the stiffness of the aortic wall were reflected in the speed of propagation of the pulse wave.

The inconsistent changes which occurred in the pulse-wave transmission time during isoproterenol may reflect opposing influences on the pulse-wave velocity. This drug decreased diastolic pressure which would reduce the speed of transmission. However, aortic blood velocity rises considerably after isoproterenol which, as pointed out by Bramwell and Hill,[25] will cause an equal increase in the velocity of the pulse wave.

The present study employed the method of external pulse-wave recording using drugs as hemodynamic forcing functions. One purpose was to determine whether certain characteristics of these waves could be used as indices of the extent of changes in central arterial wall structure which are known to occur with advancing age.[11, 26] The results indicate

that both contour changes in the carotid pulse wave and transmission time through the aorta can be used as indices of alterations in central arterial wall stiffness. Furthermore, both indices have been shown to change characteristically with advancing age although the correlation shows considerable spread.[10, 23, 24] The use of several criteria of central arterial wall stiffness recorded simultaneously, such as carotid pulse contour and carotid-femoral transmission time differences, should increase the reliability of the method.

### Cardiac Function

Another purpose of this study was to determine whether externally applied transducers can be used as a measure of cardiac performance. Weissler and associates[13] found a reduction in left ventricular ejection time index (ETI) in normal subjects given digitalis which they attributed to the inotropic effects of the drug. In the present study, ETI remained unchanged except for a slight increase following amyl nitrite, and decrease after hexamethonium. These small variations may be due to alterations in stroke volume following use of these agents. Stroke volume falls after hexamethonium[6] and may rise after amyl nitrite, although the increase in cardiac output produced by amyl nitrite and isoproterenol is due primarily to an elevation in heart rate rather than in stroke volume.[4, 5] The ejection-time index did not seem to provide an accurate reflection of ventricular contractility in the present study since the index was insignificantly altered after isoproterenol, a drug which considerably augments ventricular power. Following digitalis, the contraction is not only more powerful but also is more sustained whereas after administration of isoproterenol contractile force is increased but the contraction period is shortened. Thus, ETI by itself does not appear to express changes in myocardial contractility under all circumstances.

The isovolumic contraction time (ICT) refers to the interval between the closure of the mitral valve and the opening of the aortic valve. Frank and Kinlaw,[27] using the same indirect method employed in the present study,

found an average ICT of 49 msec in normal subjects with a standard deviation of consecutive cycle variation of 4.0 msec. In the present series ICT averaged 38.3 msec. The difference may be due at least in part to the somewhat lower diastolic pressure of 72.1 mm Hg in the present series as contrasted to an average value of 80.7 mm Hg in Frank and Kinlaw's subjects.[27] Katz and Feil,[12] who also employed the same method, concluded that ICT was an index of the velocity of ventricular contraction. Reeves and associates,[28] using the left ventricular and aortic pressure pulses, also related ICT to myocardial contractility.

If ventricular power remains unchanged, ICT should rise or fall with corresponding changes in aortic diastolic pressure since ejection begins at the moment that left ventricular pressure exceeds aortic pressure. ICT increased with angiotensin II and methoxamine and decreased following amyl nitrite and isoproterenol. ICT did not shorten significantly after hexamethonium despite a reduction in diastolic pressure suggesting that ventricular power had decreased under the influence of ganglionic blockade. An attempt was made to find a regression equation that would normalize ICT with respect to diastolic pressure because of the apparent relationship between diastolic pressure and ICT. However, the correlation coefficient between diastolic pressure and ICT in the 26 subjects during the control period was only 0.47. This degree of scatter was considered too great to make such normalization useful.

The ratio of diastolic pressure to ICT (DP/ICT) should provide an index of the mean rate of rise of left ventricular pressure during the initial phase of ventricular contraction. Both Reeves and associates[28] and Rushmer[29] have indicated that the maximum rate of pressure rise in the left ventricle (maximum dp/dt) is closely correlated with other indicators of myocardial contractility. Landry and Goodyer[21] have shown recently in dogs that DP/ICT correlated closely with maximum dp/dt measured directly in the left ventricle. Their average control value was approximately 2,300 mm Hg/sec by both methods.

They also observed changes in the rate of rise of ventricular pressure after beta-adrenergic stimulation, and use of a ganglion blocking drug and methoxamine that were similar to those observed in the present studies in man. Gleason and Braunwald[30] measured the maximum rate of left ventricular pressure rise directly in man. These investigators also found that it increased significantly following isoproterenol but remained unchanged after methoxamine. In the control state, they found that maximum left ventricular dp/dt varied between 841 and 1,696 mm Hg/sec. This range is considerably lower than is indicated by the mean value of $2,043 \pm 1,280$ mm HG/sec found in the present study, obtained by the indirect method. Their patients had valvular lesions or septal defects and, therefore, probably did not have entirely normal ventricular dynamics. Another factor producing the higher values in the present series is that the end-diastolic pressure in the left ventricle was assumed to be zero.

The onset of the first heart sound also is sometimes indistinct due to low frequency vibrations which precede the closure of the mitral valve. This difficulty can be avoided by measuring total systole including electrical systole from the onset of the QRS complex to the beginning of the second heart sound. The difference between this interval and the ejection period as determined from the carotid pulse has been called the tension period.[19] The latter changed in the same direction as ICT in all instances except that the magnitude of the change was not as great. Thus, although easier to determine, tension period is a less sensitive index of changes in the pre-ejection phase of systole than is ICT.

In the absence of mitral stenosis, the Q-S$_1$ interval may provide a useful index of contractility. It shortened considerably after administration of isoproterenol, moderately following amyl nitrite, increased with hexamethonium, and remained unchanged following angiotensin II and methoxamine. The latter two agents are believed to have little or no inotropic effects on the heart. Isoproterenol and amyl

nitrite stimulate adrenergic activity, the former directly, and the latter through reflex action, while hexamethonium blocks sympathetic nerve transmission.

Sakamoto and associates,[18] who used the directly measured maximum dp/dt as an index of left ventricular contractility in closed chest dogs, found that percentage changes in the peak-to-peak amplitude of the first sound varied directly with changes in ventricular contractility induced by a variety of procedures and pharmacological agents. The results of the present study in man are consistent with their conclusion and suggest that changes in ventricular contractility can be estimated by this simple method. Unfortunately, due to chest configurations, degrees of adiposity and other factors, variations occur in the transmission of the heart sounds among different subjects making comparisons between subjects invalid by this method. However, in studies of drug effects or other acute procedures on ventricular contractility in the same individual, the amplitude changes in the first heart sound may provide an attractively simple method for assessing this important cardiodynamic variable.

## Summary

The effects of drugs that produce known hemodynamic alterations were assessed on externally recorded pulse waves, heart sounds, and the relationship of these to each other and to the electrocardiogram.

The shape of the carotid pulse and the carotid-femoral pulse-wave transmission time difference showed changes that could be related to alterations in central arterial distensibility. The ratio of the second to the first positive inflection, and of the incisura to the first positive inflection of the carotid pulse wave, increased following use of drugs which raised mean arterial pressure and decreased after those which lowered blood pressure. The carotid-femoral transmission time difference decreased with vasopressor agents, increased with amyl nitrite and hexamethonium, and showed no consistent change after isoproterenol.

Left ventricular ejection time, measured from the carotid pulse, changed in relation to heart rate, increasing with cardiac slowing and decreasing when the rate accelerated. The ejection time index remained unchanged except for a slight increase following amyl nitrite and a decrease after hexamethonium.

Alterations in isovolumic contraction time approximately paralleled changes in diastolic pressure. The ratio of diastolic pressure to isovolumic contraction time provides an index of the rate of rise of left ventricular pressure. The quotient of diastolic pressure divided by isovolumic contraction time increased with adrenergic stimulation (isoproterenol) and decreased after ganglion blockade. It was not significantly changed by angiotensin II, methoxamine, or amyl nitrite.

The interval between the onset of QRS and the beginning of the first heart sound ($Q$-$S_1$), shortened considerably after isoproterenol and moderately following amyl nitrite. It increased after hexamethonium and remained essentially unchanged following angiotensin II or methoxamine. These results suggest that the $Q$-$S_1$ interval may reflect ventricular contractility in the absence of mitral valvular disease.

The amplitude of the first heart sound appeared to be a sensitive indicator of ventricular contractility increasing with isoproterenol and amyl nitrite, decreasing with hexamethonium and remaining unchanged following use of angiotensin II or methoxamine.

### Conclusions: Parts I and II

The present studies indicate that external transducers may provide important information on structural and functional alterations in the cardiovascular system. The following indices appear to merit further study:

1. Percentage change in left ventricular volume during the interval from the onset to the peak rate of left ventricular ejection. This is estimated in the $K_4$ position of the kinetocardiogram from the magnitude of the downstroke beginning at the peak of the left ventricular thrust to the end of the systolic retraction wave expressed as a percentage of the total cycle amplitude.

2. Left ventricular hypertrophy from the magnitude and duration of the left ventricular thrust.

3. Left ventricular contractility either from the Q-S$_1$ interval or the estimated mean rate of rise of left ventricular pressure as derived from the ratio of diastolic pressure to the isovolumic contraction time (DP/ICT). Changes in contractility in the same individual due to drugs or other factors may be estimated simply from percentage changes in the amplitude of the first heart sound.

4. Central arterial distensibility from the contour of the carotid pulse as well as the carotid-femoral transmission time difference.

### Acknowledgment

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