Responses of the Ballistocardiogram in Hypertensive Patients to the Acute Administration of Apresoline, Hexamethonium, Veratrine, Regitine and Sodium Amytal

By Dan C. Roehm, M.D., Ross C. Kory, M.D., and George R. Meneely, M.D.

Acute ballistocardiographic responses to five hypotensive drugs have been evaluated in 15 patients with essential hypertension in conjunction with depressor effects. In the majority of experiments qualitative and quantitative ballistocardiographic improvement paralleled the pressure reductions. On occasion the reverse was true. Inferences were drawn from these reactions based on the pharmacodynamics of the drugs. Because of the fundamental nature of the ballistic record, it is concluded that the capacity of the hypertensive heart to respond ballistocardiographically to a depressor agent permits a useful evaluation of its functional reserve and aids in a more physiologic selection of a hypotensive agent.

Clinical use of the ballistocardiograph has gained considerable impetus in recent years from the demonstration of a high incidence of abnormal tracings in persons with cardiovascular disease. Particularly striking has been the poor prognosis established for persons demonstrating either abnormal contours or amplitudes thought to be associated with low cardiac output. An even higher proportion of persons with heart disease reveal abnormal ballistocardiographic responses when stimuli known to increase cardiac output, such as anoxemia, exercise and eating of meals, are applied.

Nevertheless, the value of the ballistocardiograph is somewhat impaired by the lack of specificity of abnormal records for certain pathologic states. With the possible exception of the pattern associated with coarctation of the aorta, no abnormal pattern may be considered to have unique implications. In particular, abnormal ballistocardiographic tracings in hypertensive cardiovascular disease and arteriosclerotic heart disease may be indistinguishable.

Administration of depressor drugs makes it possible to alter the conditions under which the hypertensive heart labors. Ballistocardiographic tracings taken at these times might yield information leading to a better understanding of the etiology of the abnormal record and indicate the efficacy of a given agent in improving the mechanical action of the heart. Although no extended reports of such studies have appeared in the literature, brief mention has been made of ballistocardiographic responses in hypertensive patients who received depressor drugs.

Method and Material

The subjects consisted of 15 male patients all with benign hypertension of several years' known duration and all with initially abnormal ballistocardiograms. The following five drugs were administered parenterally in acute experiments with serial ballistocardiograms and blood pressure determinations: Apresoline, Hexamethonium bromide (C-6), Veratrine, Sodium Amytal, and Regitine.

Apresoline (1-hydrazinophthalazine, C-5968), is a recently introduced hypotensive agent which has been shown to increase renal blood flow, heart rate, and cardiac output while lowering arterial blood pressure. A relatively greater reduction in diastolic pressure has been reported both in dogs and in man. The drug has been found to antagonize certain humoral pressor substances and to block vasopressor reflexes from breath holding and immersion of the hand in ice water.

Hexamethonium compounds are anticholinergic.
agents capable of blocking equally sympathetic and parasympathetic ganglia. The sympathetic blockade is manifested by hypotension particularly of the postural variety and relaxation of the peripheral arterioles with increased skin temperature and diminished sweating. Parasympathetic blockade is manifested by decreased salivation and gastric secretion, constipation, and reduced visual accommodation. Cardiac output is either unchanged or slightly decreased following Hexamethonium.

Veratrum, a mixture of alkaloids derived from veratrum viride, is a hypotensive agent whose depressor effect has been ascribed to inhibition of the pressoreceptors of the carotid sinus, of the aortic arch, and of a similar vasodepressor reflex pathway arising in the heart itself. Veratrum in addition produces marked vagal slowing of the heart which can effectively be blocked by atropine without affecting the depressor effect.

Sodium Amytal is known to cause a reduction of blood pressure in some hypertensive patients. This depressor effect has been thought to be of central origin with depression of the vasoconstrictor center and relaxation of peripheral arterioles. On this basis it has been advocated as a testing agent to aid in selection of patients for sympathectomy, but this concept has recently been challenged.

Regitine, 2-[N-p-toly-N-(m'-hydroxy-phenyl)-aminomethyl] imidazole hydrochloride, C-7337, is a potent adrenergic blocking substance but is less active as a sympatholytic drug. Although some degree of hypotension is obtained in many subjects, this depressor effect is not maintained in most instances. In addition the drug has been shown to decrease coronary flow in the isolated perfused rabbit heart. Regitine at present is used chiefly in the detection and surgical removal of epinephrine-producing tumors.

The ballistocardiograph used in this investigation was of the undamped, high-frequency type with physical properties essentially the same as those of the apparatus originally described by Starr. The patient was permitted to rest 30 minutes on the ballistic table before the control record was taken. All records were made two to four hours after meals. Serial ballistocardiographic tracings were taken and blood pressure variations were recorded at frequent intervals during the course of the experiments. The amount of drug administered and time elapsed were simultaneously noted.

Regitine was administered in a single 5 mg. dose intravenously. The other drugs, diluted in 5 per cent glucose in water, were introduced by slow intravenous drip. The total amount of fluid injected never exceeded 300 ml.; the period of observation ranged from 15 minutes (Regitine) to two hours. No drug was administered within 24 hours of a preceding test. In the case of the four drugs where the dosage was varied (table 1), administration was continued until a significant blood pressure fall, a

### Table 1: Effects of Acute Intravenous Administration of Each of Five Drugs to 15 Hypertensive Patients Maximal Blood Pressure Decrease, Increase in Maximum Cardiac Force (Starr), Index of Qualitative Ballistocardiographic Improvement (the Algebraic Sum of Individual Graded Responses) and Dosages of the Drugs Employed

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maximum Blood Pressure Fall</th>
<th>Percentage of Change in Maximum Cardiac Force</th>
<th>Index of Qualitative Ballistocardiographic Improvement</th>
<th>Dose of Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Range</td>
<td>Mean Range</td>
<td>Mean</td>
</tr>
<tr>
<td>Apresoline</td>
<td>17/18</td>
<td>0/0 to 50/40</td>
<td>+25</td>
<td>0 to +76</td>
</tr>
<tr>
<td>Hexamethonium</td>
<td>45/20</td>
<td>20/5 to 95/30</td>
<td>+13</td>
<td>-50 to +50</td>
</tr>
<tr>
<td>Veratrine</td>
<td>11/25</td>
<td>5/5 to 100/40</td>
<td>+15</td>
<td>0 to +58</td>
</tr>
<tr>
<td>Na Amytal</td>
<td>51/22</td>
<td>20/5 to 100/20</td>
<td>+16</td>
<td>-41 to +46</td>
</tr>
<tr>
<td>Regitine</td>
<td>11/12</td>
<td>10/5 to 40/20</td>
<td>+3</td>
<td>-30 to +57</td>
</tr>
</tbody>
</table>

heart which can effectively be blocked by atropine without affecting the depressor effect.

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The ballistocardiograph used in this investigation was of the undamped, high-frequency type with physical properties essentially the same as those of the apparatus originally described by Starr. The patient was permitted to rest 30 minutes on the ballistocardiographic change, or a disagreeable side-reaction was encountered or until the maximum accepted initial dose was reached.

The ballistic records were analyzed and classified as to degree of abnormality by the method of Brown and associates and the alterations produced were coded 1 to 4 plus according to the degree of improvement achieved; in instances of worsening a corresponding 1 to 4 minus was recorded. The net results were totaled for each drug to obtain an "index of qualitative ballistocardiographic improvement." Maximum cardiac force per beat was calculated before and after the drug administration. The difference obtained was expressed as percentage of normal based on body surface area. The maximum depressor response occurring at any point during the study was also recorded (table 1).

### RESULTS

The mean initial maximum cardiac force per beat for the group was 67 per cent of the predicted. All drugs tested were found capable of improving the ballistic contours in certain patients; none was maximally effective in all. Each patient showed some degree of improve-
ment in the ballistocardiogram with one or more of the drugs. Improvement in the ballistocardiogram occurred in 49 of the 75 experiments or 65 per cent. In only 10 instances did the ballistocardiogram become more abnormal after drug administration, and in an additional 16 the ballistic tracings did not change.

Table 1 summarizes dosage, systolic and diastolic pressure responses, "index of qualitative ballistocardiographic improvement," and percentage of change in maximum cardiac force for each drug. In the dosages employed, the relative ability of these drugs to produce a fall in blood pressure irrespective of the duration of the effect is as follows (listed in decreasing order): Sodium Amytal, Veratrine, Hexametho-

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**Fig. 1.** Ballistocardiographic and blood pressure responses to Apresoline. Note striking increase in amplitude of all waves and more normal contours.

**Fig. 2.** Ballistocardiographic and blood pressure responses to 6 mg. of Hexamethonium (C6) administered intravenously. The record illustrates improved contours of individual complexes and increased maximum cardiac force. The 40-minute tracing shows regression to a pattern slightly worse than the control, despite some persistent hypotensive effect.

**Fig. 3.** Ballistocardiographic and blood pressure responses to Veratrine. Note qualitative improvement in ballistic contours.

**Fig. 4.** Ballistocardiographic and blood pressure responses to Regitine. The conspicuous ballistic improvement here is associated with a definite lowering of diastolic pressure, no change in systolic pressure. By 45 minutes the ballistocardiogram has returned to the control pattern.
nium, Apresoline, and Regitine. With respect to qualitative improvement in the ballistocardiogram the order is: Apresoline and Veratrone, Hexamethonium, Sodium Amytal, and Regitine; with regard to improvement of the maximum cardiac force, the following is the order: Apresoline, Sodium Amytal, Veratrone, Hexamethonium, and Regitine. Although ballistocardiographic improvement tended to parallel the hypotensive response, this was not invariably; in certain instances a fall in blood pressure provoked further ballistic abnormality. The diastolic pressure fall was more generally correlated with ballistic improvement, but this was by no means constant. In some instances large falls in diastolic pressure were associated with deterioration of the ballistocardiogram. Conversely striking ballistic improvement sometimes occurred with no change or a slight rise in diastolic pressure.

Figures 1 to 6 illustrate ballistocardiographic responses to each drug employed.

**Discussion**

In 1943, Taylor and Page observed hypertensive patients as a group to have low-output type ballistocardiograms and found that administration of an angiotonin-inhibitor preparation caused a striking improvement in ballistocardiographic contour and output. Conversely, administration of angiotonin in acute experiments to normal subjects produced records similar to those of hypertensive patients. Because tyramine and methyl guanidine, known vasoconstrictors, did not produce ballistocardiograms similar to those of hypertension or those following angiotonin administration, they concluded that these agents were not instrumental in the genesis of renal hypertension. Of the drugs studied in the present series, only Apresoline is known to antagonize angiotonin and this drug although fourth-ranking as a hypotensive agent at the dosages employed, was the most effective in improving the ballistocardiogram. Thus, it appears that Apresoline may exert its beneficial effect partly in ways other than by lowering systemic blood pressure. In no instance did it produce adverse effects on the ballistocardiogram in contrast to all other agents tested. Experience in therapy of several months duration with this drug indicates that this effect is persistent.

Hexamethonium, a potent vasodepressor, although capable, on occasion, of causing remarkable reversions toward normal in the ballistic record (fig. 2), caused increased abnormality in 4 of 15 records. When it is considered that Hexamethonium, through its action of ganglionic blockade, causes peripheral pooling of blood, it is possible that decreased venous return to the heart may have diminished diastolic filling. Such diminished filling as seen in the expiratory phase of respiration has been
considered responsible for complexes of poor amplitude and quality in a heart otherwise capable of producing normal complexes.\textsuperscript{43}

With the possible exception of the veratrum alkaloids which have some structural resemblance to digitalis\textsuperscript{32} none of the agents used has a direct myocardial action. Sodium Amytal, the most effectively hypotensive drug in the present study, has been considered to produce hypotension as the result of a decrease in peripheral resistance. Winchell and co-workers,\textsuperscript{35} however, have recently ascribed this to reduced cardiac output from ballistocardiographic experiments. In patient H. M. (fig. 4), a reduced cardiac output is not suggested ballistocardiographically following administration of Sodium Amytal. Accordingly, administration of the drug was repeated and accompanied by cardiac catheterization. The resting cardiac output was determined by the direct Fick principle to be 6.07 L per minute initially and 6.02 L per minute 45 minutes after intravenous administration of the drug, at which time the blood pressure had decreased from 194/120 to 165/100.

Regitine, primarily an antagonist of epinephrine-like compounds,\textsuperscript{34, 35} was on occasion quite active ballistically in several patients who had no depressor response suggestive of the presence of an epinephrine secreting tumor (figs. 4 and 6).

The increased maximum cardiac force (IJ amplitude) seen after administration of these drugs stands in contrast to a lack of similar response to exercise in hypertensives as a group.\textsuperscript{9} This would seem to indicate that the drugs have enabled the heart to eject blood in a more normal manner rather than imposing an increased demand upon the heart. From the demonstration of Starr\textsuperscript{40} the IJK waves of the ballistocardiogram agree in form with the rate of change of acceleration of cardiac ejection, greater amplitudes of IJ, for a given stroke volume, indicate a more nearly normal early acceleration of the blood. In the present study of initially abnormal records where the Starr formula for calculation of stroke volume cannot be applied, no statement can be made with certainty as to cardiac output.

The significance of the achievement of a more normal cardiac ejection form is on a much firmer basis. In those instances in which marked ballistic improvement accompanies a hypotensive response, it is reasonable to ascribe the original abnormality to the handicap arising from the large work requirement.

Failure of the ballistocardiogram to improve despite a hypotensive response is less easily understood. Several possibilities might be considered: (A) Reduced coronary flow secondary to lowered perfusion pressure. In animals, Apresoline, Sodium Amytal, Hexamethonium, and veratrum alkaloids lower blood pressure without decreasing coronary blood flow.\textsuperscript{20, 44-46} It is apparent that in abnormal human hearts, factors favoring diminution of coronary flow (notably reduced perfusion pressure) might well outrun other actions of the drugs tending to maintain coronary flow. (B) Pooling of blood and impaired venous return as a result of peripheral vasodilatation. Correlation of the unimproved ballistocardiograms with the rate and magnitude of blood pressure fall indicates that 6 of the 26 unimproved ballistocardiograms could conceivably be explained by peripheral pooling or lowered coronary artery perfusion pressure. Three of these were responses to Hexamethonium, two to Sodium Amytal and one to Veratrine. (C) Direct deleterious effect of the drug upon the myocardium. There is no evidence in the literature of these drugs to support this in the dosages employed.

(D) Lack of sufficient cardiac reserve to take immediate advantage of a decrease in work load. The condition of the myocardium in a given patient with hypertension is the resultant of a multiplicity of factors both mechanical and metabolic. This seems to be the most attractive hypothesis: that some hearts do not have sufficient reserve to improve the character of systolic ejection, at least during the period of observation in these acute experiments. If this latter mechanism is operative, the ballistocardiographic responses to depressor drugs should prove of increasing value in assessing myocardial reserve in patients with hypertensive cardiovascular disease.

**Summary and Conclusions**

1. The ballistocardiographic effects of five hypotensive drugs have been studied in 75
acute experiments in patients with essential hypertension.

2. Initially, as has been found characteristic of hypertensive patients, the records revealed low cardiac output with decreased maximum cardiac force and complexes of abnormal form.

3. Upon administration of depressor drugs, improvement of the ballistic tracings was frequently obtained (65 per cent of experiments) which often, but not invariably, paralleled the hypotensive response. In certain instances, hypotensive responses were associated with increasing abnormality in the tracings for reasons discussed.

4. From the ballistic response of the individual to a given agent and the known pharmacodynamics of the drug administered, insight may be obtained as to how the circulation of the individual hypertensive patient is affected beyond that afforded by blood pressure determinations. As a corollary, the ability of a particular heart to respond to the new milieu created by the various drugs allows further functional evaluation of that heart.

5. In view of the unfavorable prognosis that has been established for patients with abnormal ballistocardiographic patterns, consideration of the ballistocardiographic improvement achieved may rank in importance with the hypotensive response in selection of a hypotensive drug.

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Sumario Español

Cambios agudos balistocardiográficos producidos por cinco drogas hipotensoras han sido evaluados en 15 pacientes con hipertensión esencial en conjunción con los efectos depresores. En la mayoría de los experimentos mejoría balistocardiográfica cualitativa y cuantitativa fue paralela a la reducción en presión. En ocasiones el reverso ocurrió. Inferencias se dedujeron de estas reacciones basadas en la farmacodinámica de las drogas. Por la naturaleza de un record balístico, se concluye que la capacidad del corazón hipertenso a responder balistocardiográficamente a agentes depresores permite la evaluación provechosa de la reserva funcional y ayuda en la selección de un agente hipotensor de un modo más fisiológico.

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DAN C. ROEHM, ROSS C. KORY and GEORGE R. MENEELY

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