The Effect of Nitroglycerine on the Ballistocardiogram of Persons with and without Clinical Evidence of Coronary Heart Disease

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Nitroglycerine has been given to a series of patients and its effect on the ballistocardiogram observed. Attacks of angina pectoris are accompanied by great deterioration of the record; if nitroglycerine is given at such a time, the record improves as pain passes off. Given between attacks to patients having coronary heart disease with abnormal ballistocardiograms, nitroglycerine is often followed by improvement in the record. Also given to older patients who have abnormal ballistocardiograms but no clinical evidence of coronary heart disease, nitroglycerine is often followed by improvement in the record, a fact consistent with the view that coronary heart disease is present in such cases. However, nitroglycerine is sometimes followed by deterioration of the ballistocardiogram, the possible reasons for this unexpected finding are discussed; attention is called to recent evidence indicating that serious toxic effects may follow exposure to nitrates in industry.

CLINICIANS of the physiologic school will not long be satisfied with the description of abnormalities of cardiac performance occurring under conditions of rest, although this is obviously the way to begin such studies. One can expect to gain important information by comparing the reactions of normal and diseased hearts to standard tests of many types. Thus, the response to nitrates has been used by clinicians for many years as an aid to diagnosis. The regular relief of pain in the chest after amyl nitrite or nitroglycerine is accepted by many doctors as evidence that the patient is suffering from angina pectoris and coronary heart disease; for, although it is well known that nitrates may at times relieve pains originating elsewhere than in the heart, this seldom occurs with the rapidity or with the regularity which characterizes the relief of angina pectoris by these drugs.

It is of great interest to study the association between physiologic and anatomic abnormalities even though one has no expectation that the one will be found pathognomonic of the other. So it seemed that the administration of nitroglycerine to patients on the ballistocardiograph would provide a test of importance. Such a test would enable us first to observe the effect of this agent on the cardiac performance of patients diagnosed as suffering from coronary heart disease by the usual clinical criteria, and then to discover whether this response was shared by other patients in whom the presence of coronary heart disease was unlikely or uncertain.

On the basis of such findings, we hoped to be in a position to throw light on a very interesting problem. Everyone taking ballistocardiograms in large numbers has found many persons past 50 years of age1, 3, 4 whose records were abnormal in form, although their history and clinical findings gave no clear indications of cardiac abnormality. Similar abnormalities of ballistic form have been found rarely, if at all, in healthy young adults, but they have been found frequently in persons suffering from angina pectoris and in those who have had cardiac infarction.1, 2 Both this similarity, and the fact that the increasing percentage of ballistic abnormalities, found in the living as age advances, corresponds quite well with the increasing percentage of coronary heart disease found at necropsy as age advances,8 raise the

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question whether the finding of an abnormal ballistocardiogram in an apparently healthy person does not indicate coronary heart disease at an earlier stage than that which can be identified by the appearance of the usual clinical syndromes. While the reported data are still meager, this view finds support in the necropsy findings of persons who have had abnormal ballistocardiograms during life and in the still few but increasing reports of persons having abnormal ballistocardiograms when apparently in good health, who have later developed clinical coronary heart disease. We will take this opportunity to report another such case, followed 16 years to necropsy.

Accordingly, the response to nitroglycerine has been used as a standard test in over 100 patients, and in a smaller number of healthy persons. We have found numerous instances in which ballistocardiograms, abnormal in form, have been improved, or even restored to normal during the action of nitroglycerine. Such improvement was found most frequently in patients readily diagnosed by the ordinary clinical criteria as having a coronary heart disease. But similar improvement after nitroglycerine was also found in the records of some patients in whom this diagnosis could not properly be made by such criteria. And to our surprise, deterioration of the ballistocardiogram after nitroglycerine was encountered frequently.

**APPARATUS**

A new high frequency ballistocardiograph, made for this laboratory by the Technitrol Company, employed with a Sanborn Twin-Viso recorder, proved ideal for the purpose of this study as the records could be read during the experiment as soon as they were written. The steel supporting frame of this new instrument is extremely heavily built, weighing 270 pounds. The table frame is of 635T5 aluminum alloy, the stiffening rods are of Dural. The table surface is of plywood, the total table weight being 42 pounds. The table suspension is 5 cm. in length. The pick up unit is an RCA 5734 electromechano transducer tube. The vibration properties of the table are; when unloaded, 26 cycles per second; when loaded with 100 pounds of iron bars, 14 cycles per second; with 160 pounds, 11.8 cycles per second; with 200 pounds, 10.4 cycles per second; rates slightly faster than those of our previous instruments, although the broader table of the new instrument is 15 pounds heavier than that of one of our older ballistocardiographs.

When loaded with iron bars and deflected by a force of 500 Gm., a force equivalent to those recorded in large ballistocardiograms, sudden release is followed by a return to the base line in less than 0.04 second which is not instantaneous, but rapid enough to record ballistocardiograms. There is practically no overshooting after such release. No damping has been added and that inherent in the system is insufficient to damp out the fine vibrations imparted by the perpetual motion of the building when there is no subject on the table.

The records secured by this new instrument are almost exactly similar to those obtained by our older instruments, but we have the impression that there are a few minor differences. The new records often show more definition in the early diastolic complexes, the I wave is less prominent and the M-N segment tends to be sharp and straight, so that this part of the newer records looks less like a series of waves in phase than in many of our older records. Also, we have the impression that we see short or absent K waves more frequently than in records secured by our oldest instrument, and in some healthy persons a doubled J peak is seen. So the form of the records is not very different from those secured by Talbot and his associates, and by Deuchar and co-workers by recording acceleration from a subject lying on a table floating in a pool of mercury, and those obtained by von Wittem, by Burger and by Elsbach recording acceleration from a subject lying on a low frequency table, although our records are probably not identical with any of these. Theoretically if all these instruments were perfect and if the properties of the body produced no distortion, or similar distortion, all these records should be identical, and they would record the forces; we find it gratifying that the differences are so small. Whether the gain in accuracy, expected because of the theoretical advantages of the newer techniques, will compensate for the increased complexity and cost of apparatus, and the greater difficulty of maintenance and of calibration, cannot be foretold at this moment, as the use of these new methods in routine clinical work is just beginning.

**RESULTS**

The experience with the effects of nitrates on the ballistocardiogram can best be divided into two parts.

**The Effects of Nitrates on the Ballistocardiograms of Healthy Young Adults**

For many years the senior author conducted a part of the undergraduate course in pharmacology in which familiar drugs were given to the students themselves. After receiving the drug, the subject reported his sensations while
his mates gathered around and made observations which included pulse rate and blood pressure. After our first ballistocardiograph had been constructed, these demonstrations were conducted with the subject lying on this instrument, and records were taken at intervals before, during, and after drugs' actions. From these class experiments, we have records of the action of nitroglycerine in 15 healthy young adults, and of that of amyl nitrite in 13. These records were re-examined as part of this study. Recently we tested three additional healthy young adults with nitroglycerine.

Results. The results of this experience can be summarized in a few words. All the healthy young adults gave normal ballistocardiograms before the drug was administered. After inhaling amyl nitrite, as the face flushed and blood pressure fell, the heart rate accelerated and the ballistocardiogram increased in amplitude, its form remaining normal except in two cases when a very rapid heart rate was accompanied by such fusing of waves that the I wave was diminished. One or two tablets of nitroglycerine (each 0.6 mg.), placed under the tongue, had very little effect on these healthy persons lying at rest; blood pressure diminished little, if at all, pulse rate usually increased slightly and the ballistocardiogram either showed no noteworthy change or increased slightly in amplitude, its form always remaining normal.

The Effect of Nitroglycerine on Patients and Older Persons

The patients employed in this study were secured from the medical wards or outpatient departments of the University Hospital. They do not represent a cross section of this population for we sought especially cases with abnormal ballistocardiograms, and we gave nitroglycerine to 83 such patients, most being over 50 years of age. We also gave nitroglycerine to 33 patients almost all in the latter half of life, who had normal records.

Technic. All the subjects came to the laboratory two hours or longer after their last meal. They lay supine on the ballistocardiograph for a 15-minute rest period, and then the control record was taken. This record was inspected and the decision whether to give nitroglycerine made. One tablet of nitroglycerine, 0.6 mg., was then placed under the tongue and records were taken at 2, 5, 7, 10, 15 and sometimes 20 minutes thereafter, blood pressure being determined just after each record by the auscultatory method, the points both of muffling and disappearance of sounds being recorded.

Results. Nitroglycerine caused a moderate fall in blood pressure averaging 14.9 mm. Hg for the systolic and 4.7 mm. Hg for the diastolic pressure. Our data on this response is skewed by the fact that the drug produces a greater fall of blood pressure in patients with hypertension than in those with normal pressure, as has long been known.

Some acceleration of the pulse rate was usually seen after the drug, but this change was small and transient, in the last 31 cases the maximum increase averaged 12.5 per minute. The figures give typical examples of the pulse rate and blood pressure changes. Flushing of the face was seen occasionally, and a few patients noted slight headache after the drug. Thus the typical and familiar effects of the drug regularly manifested themselves during our experiments.

Inspection showed that the maximum effect of the nitroglycerine was usually manifested in the record taken seven minutes after the administration of the drug; in that taken 15 minutes after the drug had been given this effect had largely or completely passed off. Thus the effect of the drug on the ballistocardiogram was transient.

In this study we have concerned ourselves only with large changes, so we relied on inspection of the records, and did not resort to measurement; only qualitative differences have been recorded. Improvement in the form of the record could be detected only if the original ballistocardiogram was abnormal in form; but deterioration of the record, or no change, could be detected irrespective of the character of the original record.

Examples of typical records showing the various changes which followed the drug are given in the figures. Figures 1 and 2 show ballistocardiograms and electrocardiograms secured before and during attacks of angina pectoris which appeared spontaneously, as well as records secured after nitroglycerine had
Fig. 1. Disorganization of the ballistocardiogram during an attack of angina pectoris and its restoration by nitroglycerine. Subject Dr. I. H., age 51, male. This patient had been previously tested on Oct. 2, 1951 and at that time he complained of pain in the left shoulder and the diagnosis was uncertain. In his note written at that time, Dr. Calvin Kay, the cardiac consultant, wrote, "The pain described could be of coronary origin although, if so, it is certainly atypical. It suggests more a referred pain from some structure in the region of the diaphragm, or from the spine." Indeed, an orthopedic consultant diagnosed arthritis of the cervical spine. The ballistocardiogram in 1951 was abnormal; in the smaller complexes of the respiratory cycle H far exceeded J in height and J was notched or flattened. Later he began having pain more typical of angina pectoris; although located chiefly between the shoulder blades, it was squeezing in character, brought on by exertion and relieved by nitroglycerine.

On May 24, 1954, before coming to our laboratory, he had been seen again by Dr. Kay who found a blood pressure of 132/90-88 mm. Hg. He lay quietly on our original ballistocardiograph for 15 minutes but it was noted that he seemed uncomfortable by the time the first record was taken. This is the first record reproduced above. Soon thereafter he said, "I now have the kind of pain for which I take nitroglycerine". The second tracing reproduced above was taken immediately and his blood pressure was found to be 167/110. Although lead II of the electrocardiogram was essentially unchanged during this attack one notes the marked deterioration of form in the smaller complexes of the ballistocardiogram, H far exceeding J in height and the latter wave being notched or flattened. The subject then took his usual dose of nitroglycerine (gr. 1/400). The record taken two minutes later is the third record reproduced above and it shows improvement in form and amplitude; at this time the pain was better and the blood pressure had fallen to 145/100. Pain disappeared about two minutes later and addi-

relieved the pain. Figure 3 shows the results secured in a case of angina pectoris given nitroglycerine between attacks. Figure 4 shows the maximum improvement of the records of four patients. Figure 5 is an example of a deleterious effect, figure 6 of a mixed effect.

As will be seen from the figures, no particular feature of the ballistocardiogram is affected by nitroglycerine to the exclusion of others. Many sorts of abnormalities may disappear after nitroglycerine. We are particularly impressed by the changes early in systole which may follow the drug. The abnormally large H waves so often seen in cases of coronary heart disease, frequently disappear after nitroglycerine, a fact of interest because of the uncertainty of the physiological origin of the abnormal H waves in such cases. Other changes seen frequently after nitroglycerine are the deepening of shallow I waves, and the disappearance of notches on the J wave or the H-I or I-J segments. Increased amplitude of the record is common after the drug. The figures show the variety of changes which may follow the drug better than they could be described.

Relation of the Response to Nitroglycerine and the Clinical Diagnosis

For the purposes of this study the 132 cases were subdivided into the five groups given in table 1. In the first group have been placed 48 patients who suffered from such typical attacks of angina pectoris that the diagnosis was not in doubt. They described attacks of pain, or of a sense of constriction, usually substernal, but sometimes located in other parts of the chest, brought on chiefly by exercise and relieved by rest and by nitroglycerine. Some of these cases
Fig. 2. Disorganization of the ballistocardiogram during an attack of angina pectoris and its restoration by nitroglycerine. Subject M. W., aged 63, male. This patient had suffered from severe angina pectoris for several years and ballistocardiograms had been secured at intervals during this time. He had received I\(^{131}\) in May 1953. The top record is a good representation of those usually secured, and it is rather more normal in appearance than that of most cases having such severe angina. But the record cannot be passed as normal. The amplitude is too small—49 per cent below the normal young adult mean—and the smaller complexes are abnormal in form, the I wave not penetrating the base line in many. His blood pressure was usually 120/80 mm. Hg.

On June 29, 1953 he walked into the laboratory complaining of pain. He was placed on the table and after about five minutes of rest while the amplifiers were warming, the second record reproduced above was secured. He was in pain at this time, there was S-T depression in the electrocardiogram, amplitude of the ballistocardiogram was reduced and the form completely disorganized. At this time, blood pressure was 120/80 mm. Hg. He was then given 0.6 mg. nitroglycerine and pain was relieved in a few minutes. The third record reproduced above was taken five minutes later. Marked improvement in both electrocardiogram and ballistocardiogram is obvious, although the latter record is not altogether normal. At this time the blood pressure was 110/80 mm. Hg.

This patient is being followed closely and records at subsequent times when he was not in pain have resembled the first reproduced above. In these and in records shown in the following figures, the reproductions are about one-third the actual size. They were taken by the newer technic, using a Sanborn, Twin-Viso recorder.

Fig. 3. Simultaneous ballistocardiograms and electrocardiograms taken before, during and after the action of nitroglycerine.

Subject G. B., age 42, male, weight 173 pounds. The patient had suffered a posterior wall myocardial infarction three months before this test. There had been some chest and shoulder pain since, but no typical angina. X-ray films showed the heart to be somewhat enlarged. Electrocardiogram was interpreted as indicating a well healed posterior infarct. Note the most abnormal control ballistocardiogram.

The H wave is huge and its time relations with the electrocardiogram are abnormal. The I wave only rarely penetrates the base line and often fails to reach it. The ballistocardiogram taken seven minutes after nitroglycerine shows great improvement in the record, which is now about normal. The abnormal H wave has disappeared and the J peak has moved forward, in relation to the R peak of the electrocardiogram. The I wave is normal in most complexes, although it is too shallow to be passed as normal in some. The third record shows that the effect of the nitroglycerine had passed off within 15 minutes, so the improvement was temporary.

gave a clear history of a previous cardiac infarction and some did not. Their ages ranged from 88 to 29 years, the latter a case of congenital hypercholesterolemia.

In the second group 15 cases were placed who had a clear history of previous cardiac infarction with typical electrocardiograms, but who did not suffer from angina pectoris after recovery from the acute attack.

In a third group we placed several cases who, although lacking a clear story of either angina pectoris or coronary occlusion, were
diagnosed arteriosclerotic heart disease by the clinician in charge because they were elderly persons with many signs of cardiac abnormality, and no other etiology was apparent.

B. Simultaneous electro- and ballistecardiograms of: B. S., aged 43, male. Cardiac infarction had been diagnosed from an episode in the past on doubtful grounds. The patient had atypical chest pain more recently. These pains were accompanied by shortness of breath, often brought on by exercise. They were not promptly relieved by rest. There was questionable cardiac enlargement by x-ray study. Bundle branch block was present constantly and gallop rhythm had been heard at times. The upper record is the control, the blood pressure being 126/90. The H waves are greatly enlarged, sometimes equalling J in height. K is short in many complexes and the diastolic ballistic components are clearly evident. The second record was taken seven minutes after nitroglycerine. Note that the H wave has diminished to normal size and the record would be passed as normal.

C. Ballistocardiograms of M. K., age 57, male. The patient complained only of atypical pain in his left shoulder, not usually related to exercise. It tended to be present in the morning. It had been relieved temporarily by heat and manipulations of the shoulder. The first record is the control, the blood pressure being 140/80. The form is not normal, for the J peak of the smaller complexes is notched or flattened. The second record was taken seven minutes after nitroglycerine, blood pressure being 120/80. Note that ballistic abnormality has disappeared.

D. Simultaneous electro- and ballistocardiograms of P. S., aged 68, male. The case was a confused one. The chief complaints were cough, shortness of breath and sharp stabbing pain in right chest with radiation to right upper abdominal quadrant and right shoulder. X-ray films showed rounded mass in right chest with interlobar fluid collection. The tubercle bacillus was not demonstrated in the sputum. Bronchoscopy revealed little. The urine was constantly abnormal and pyelonephritis was diagnosed. Blood urea nitrogen varied from 20 to 46 mg. per 100 ml. There was slight anemia and both a duodenal ulcer and a polyp of the colon were demonstrated by x-ray examination. Electocardiogram suggested left ventricular strain. The heart was slightly enlarged. There was no history suggestive of angina pectoris and the pain was believed to be due to the pulmonary lesion. This was never diagnosed and he was considered too sick for exploration.

The first record is the control, taken when the blood pressure was 134/94. Note the extreme abnormality of ballistic form; without the simultaneous electrocardiogram, systole could not be located. The second record was taken seven minutes after nitroglycerine; blood pressure was 112/80. Note that the improvement in the ballistocardiogram is very marked.

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Fig. 4. Ballistocardiograms before and during the action of nitroglycerine. A. Records of P. B., aged 50, a male who had had hypertension for many years and typical angina pectoris for six years, severe recently. High thoraco-lumbar sympathectomy one year ago with the aim of ameliorating the angina. In control period blood pressure was 180/110. Note high H waves in first record; they equal J in height in the smaller complexes of the respiratory cycle. The second record was taken seven minutes after nitroglycerine, the blood pressure being 140/90. Note that this record as a whole is much more normal in appearance. Note the disappearance of the abnormal H waves; K is deeper than in the control but this is not abnormal for a man of his age.
Typical Electrocardiogram

Fig. 5. Adverse effect of nitroglycerine. Subject R. A., male, Negro, aged 50, and weighing 175 pounds. Typical attacks of angina pectoris for the past two years. No history suggestive of cardiac infarction. Electrocardiogram, negative; heart, normal in size by x-ray films.

The control ballistocardiogram is normal, blood pressure at this time was 140/95 mm. Hg. The second record was taken two minutes after nitroglycerine. It is markedly abnormal, the J wave is greatly diminished and the I wave often does not reach the base line. The K wave is deep. Blood pressure was 132/95 mm. Hg at this time. In records taken 20 minutes later the normal form had been regained. This patient also showed marked deterioration of the ballistocardiogram after smoking one cigarette.

The rest of the hospital patients, those who could not be properly placed in any of the first three groups, were placed in a fourth group. These patients had little in common except the fact that neither coronary nor arteriosclerotic heart disease could be properly diagnosed by the usual clinical criteria. The primary diagnoses of these 51 cases included hyperthyroidism, diabetes mellitus, hypertension, peripheral vascular disease, chronic pericarditis, post pneumonectomy, former chest trauma, lymphatic leukemia, gastric ulcer, cirrhosis of the liver, recurrent pneumonia, diarrhea, hypercholesterolemia, rheumatic heart disease, polycythemia, chronic arthritis, and pelvic inflammatory disease. In addition we included in this group some elderly men who considered themselves to be in good health commensurate with their age. The healthy young adults, all medical students or recent graduates, were placed in the last group.

Needless to say the diagnosis of coronary

Fig. 6. A mixed effect after nitroglycerine. Subject D. L., aged 40, a woman. Formerly hypertension was present but under drug therapy the blood pressure had returned to normal. The control ballistocardiogram cannot be passed as altogether normal because H equals J in height in the smaller complexes. Two minutes after nitroglycerine the form is much more abnormal. J now exceeds H, and I is reduced to a notch on a plateau connecting J and H. However, five minutes later the record has changed its character; the I wave is too small but otherwise it is normal. The last record resembles the first, this shows that the effect of the drug has passed off.

heart disease or its absence cannot always be made with confidence during life. Especially when atypical chest pain is present, the propriety of assigning certain people to groups 1 or 4 might be long debated. We would have preferred that this decision be made without knowledge of the ballistocardiogram, but as we regularly reported our findings to the wards, this was not possible. To avoid bias, we have generally relied on the opinion of the clinician in charge; when the ward staff disagreed, we used our own judgment.
Table 1.—Ballistographic Response to Nitroglycerine in Various Clinical Conditions

<table>
<thead>
<tr>
<th>Form of Original Ballisto</th>
<th>Change of Form After Nitroglycerine</th>
<th>Number of Persons Responding in Manner Indicated in Each of 5 Groups Diagnosed as Follows</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Typical angina</td>
<td>Former cardiac infarction not followed by angina</td>
</tr>
<tr>
<td>Normal</td>
<td>No change</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Deteriorated</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal</td>
<td>No change</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Improved</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Deteriorated</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Mixed effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td></td>
<td>50</td>
<td>15</td>
</tr>
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</table>

Table 1 shows the frequency with which nitroglycerine caused improvement, deterioration or no noteworthy effect on the form of the ballistocardiograms of the patients classified as stated above.

We made no tests during the acute stage of cardiac infarction. By chance we made a test about 24 hours before such an attack and neither the ballistocardiogram nor the response to nitrates was found abnormal. A complete electrocardiographic study made at this time was also normal. The attack was a mild one and the patient made a good recovery.

**Discussion**

To those of the physiological school the reaction of the heart to a standard physiological test is of interest in itself, as it helps us to characterize and understand the physiological abnormalities encountered in our patients. So the work described in this paper was not undertaken with the primary aim of enabling doctors to make a descriptive diagnosis, such as angina pectoris, with greater confidence, though we would be glad if our work contributed to this end. Nor was the primary purpose of this study to enable doctors to increase their ability to make a pathological diagnosis, sclerosis of the coronary arteries, though we aim to learn all we can about the relationship between such lesions and the various aspects of cardiac performance. Let us, therefore, study these results for their own sake, always asking ourselves how the new knowledge can be used to the advantage of our patients.

That attacks of angina pectoris are accompanied by profound deterioration of the ballistocardiogram, is well established. Figures 1 and 2 give typical examples from our data; we have had four such cases. Others have secured similar results. At the Second International Cardiological Congress, Dr. Benjamin Baker showed a projection of a most abnormal record secured during such an attack; records secured before and after the attack were far more normal.

Kuo and Joyner in a study of the effects of high blood fat, have obtained deteriorated ballistocardiograms during 14 attacks of angina. Dr. Raymond Penneys has similar records of one spontaneous attack, one induced by smoking, one induced by exercise and several induced by breathing a gas mixture low in oxygen. Indeed there is every reason to expect that the striking deterioration of the ballistocardiogram during anginal attacks would surely aid in distinguishing pain of cardiac origin from that arising elsewhere.

Nitrites have been given to many of these patients studied during an attack and, as the pain passed off, the ballistocardiogram improved. Also, Mandelbaum and Mandelbaum subjectec patients to a mild exercise test and evoked angina in two cases; ballistocardiograms, taken by the Dock method, after nitroglycerine had brought relief, showed improvement over those taken before the exercise.
Therefore it seems well established that nitrites can bring about improvement in the abnormal ballistocardiogram found during attacks of angina pectoris.

In 84 per cent of the cases of angina pectoris tested in this study the ballistocardiogram was abnormal to some degree between attacks. That nitroglycerine, given although pain was absent, may favorably affect these records is evident from the results of this study; we found such an effect in 24 of our 42 cases of angina having abnormal records at rest, and in 8 of the 12 cases with a history of cardiac infarction not followed by angina. So it seems clear that an abnormality of myocardial function is present in these patients between attacks, and the fact that nitrites affected it favorably suggests that this abnormality has much in common with that present during an attack of angina, though doubtless it is less in degree.

One wonders if the cause of the improvement of our records after nitroglycerine is not related to the mechanism by which the drug relieves angina. For the latter, two possible mechanisms have long been known. Nitrites might aid the heart by producing coronary vasodilatation similar to that so readily demonstrated in animal experiments, and, as these drugs also lower blood pressure, they might relieve the heart by reducing its load. The sum total of these two effects would be reflected in the oxygen content of coronary venous blood, and Foltz and coworkers have shown that, in animal experiments, the administration of nitrites is often followed by a marked increase in the oxygen content of coronary venous blood. Coronary vasodilators like aminophyllin, which stimulate the heart, do not have this effect, coronary venous blood oxygen often decreasing because the increased demand exceeds the increased supply.

Clinical studies on angina have, in general, supported the view derived from animal experiments. That increased blood pressure often occurs during angina has been known for many years, so it has usually been presumed that increased cardiac work induces an attack, although blood pressure is only one factor in the heart's work. Indeed measurements of blood pressure, together with estimates of cardiac output made by an early cardiac output method, indicated that left ventricular work did increase during angina, and that this work diminished after nitroglycerine had relieved the pain. On the other hand, Wayne and Laplace studying the blood pressure during induced attacks of angina found that, while blood pressure regularly rose during attacks, there was no close correspondence between changes of blood pressure and the occurrence and relief of pain.

Our studies made between attacks likewise show no invariable correspondence between blood pressure and improvement in the ballistocardiogram, although this improvement was usually found while blood pressure was diminished. Thus our results show a few instances in which the record improved in the absence of a fall in blood pressure, some in which it regained its original abnormality while blood pressure remained down, and many cases in which a large diminution of blood pressure was not accompanied by any improvement in the record. In addition, the more rapid heart rate and the increased amplitude of the ballistocardiogram found after nitroglycerine in some of our records indicate that the heart's work per minute may not be diminished despite the lowering of blood pressure. Obviously, therefore, the available evidence does not permit us to attribute the improvement of the ballistocardiogram after nitroglycerine solely to diminution of heart work, although this may well be a factor in some cases; the coronary vasodilator action of that drug seems the more likely explanation for the improvement seen in most cases.

The 15 cases who gave no clear clinical evidence of coronary heart disease, but who had abnormal ballistocardiograms which improved after nitroglycerine, are of special interest. Of these, two belonged to the senior author's follow-up series and had been followed for 15 years. They were now 72 and 76 years of age, and the abnormality of their ballistocardiograms had developed in recent years. Both had been studied repeatedly at the hospital. The elder had an episode of precordial pain many years ago, judged by the attending physician to be due to cardiac infarction, but electrocardiographic confirmation had never been secured.
and this diagnosis was doubted by subsequent cardiac consultants.

In several others chest pain was present but it was certainly not typical of angina. In J. F., a man aged 39, it had no relation to exertion and, routine studies being negative, it was attributed to anxiety. In M. K., a man of 55 (see fig. 4c), the pain was in the left arm and increased on walking, but hypertrophic arthritis of the spine was demonstrated, and the pain was relieved by supporting the arm by a bandage; so, routine cardiac studies being negative, the diagnosis of coronary heart disease was not entertained. E. S., a man of 68, had had attacks of abdominal pain and on one occasion it was referred to the chest; a renal calculus was discovered, as well as gas in the splenic flexure, and the pain was attributed to one or both of these. D. P., a woman of 37 with advanced rheumatic heart disease, complained of attacks of severe chest pain since she was 29. Aortic valvulotomy caused only temporary improvement. Nitroglycerine failed to relieve these attacks, but Demerol gave relief and she had become addicted to this drug. D. P., a woman of 68 with hypertension for many years, had had a stroke three years before and epilepsy since. She complained chiefly of epigastric pain relieved by alkalies; x-ray films showed a large hiatus hernia, and the pain was attributed to this. She had a large variety of other complaints among them a sense of pressure under the sternum, radiating "numbness" to both shoulders; this was precipitated by excitement but not by exercise. Her electrocardiogram revealed only non specific changes compatible with hypertension, and x-ray study disclosed only a minimal enlargement. In P. S. (see fig. 4) the pain was attributed to a demonstrated pulmonary lesion.

Chest pain was no feature in the other cases. P. R., a woman aged 52, had severe myxedema. A. D., a woman aged 48 was judged to have neurocirculatory asthenia based on anxiety. S. F., a man aged 57, came in for a routine check-up which was negative. J. B., a man of 48, had congenital hypercholesterolemia and was on a low fat diet. J. C., a man aged 52, was diagnosed duodenal ulcer; routine cardiovascular studies were negative. T. I., a woman aged 46, complained of nervousness, diarrhea, shortness of breath and of being "run down;" pain in the chest was denied, but she had right sided abdominal pain often relieved by alkalies. Her heart was negative to physical examination, other cardiac studies were not made; and the final diagnosis was cirrhosis of the liver. G. M., a woman aged 49, had advanced rheumatic heart disease, and she was tested just prior to commissurotomy.

Obviously, most of these patients were of an age at which coronary heart disease is found frequently at necropsy and some had symptoms that might have been attributed to that condition. Three had diseases, myxedema, congenital hypercholesterolemia and hypertension, in which coronary heart disease is a frequent complication. Two of the younger subjects had very severe rheumatic heart disease. The abnormal ballistocardiograms and the positive response to nitroglycerine, if taken to indicate coronary heart disease, would come as a complete surprise only in a minority of the cases.

Dr. J. N. Morris, in a symposium on arteriosclerosis given at the Second World Congress of Cardiology, likened the incidence of coronary heart disease to a great pyramid of which, like a floating iceberg, only the apex was visible. According to this view the great majority of cases are not being detected during life by the clinical methods in common use. So it is certainly consistent with present knowledge to believe that the cases who have abnormal ballistocardiograms which improve after nitroglycerine belong to the submerged group whose abnormalities have not yet come to the surface and produced the familiar clinical pictures.

Proof of the presence of an anatomical lesion such as coronary arteriosclerosis can be obtained only at necropsy and our efforts to add to our knowledge by this means have continued. Our first case in which an abnormal ballistocardiogram was secured, while the subject believed himself to be in good health, has now been followed up to necropsy, and this seems an appropriate place to report it.

Case Report

C. N. was 48 years of age when his first ballistocardiogram was secured in 1937. He considered
EFFECT OF NITROGLYCERINE ON THE BALLISTOCARDIOGRAM

C. N. PROGRESSING CORONARY DISEASE

AGE B. P.

48  134/80

52  150/85

63  139/105

FORM VARIES NO NORMAL COMPLEXES

64 NECROPSY

Fig. 7. Typical large and small complexes of a case of coronary heart disease followed for 16 years until necropsy. The three ballistocardiograms were all taken on the same instrument but by three different photographic techniques. The original records would be hard to compare by inexperienced readers. Therefore, atypical large and small complexes of the respiratory cycle have been selected from each record and drawn to scale above. The case history is in the text.

himself to be in excellent health and was leading a most active life as a medical teacher and investigator. Typical complexes from this first record are reproduced in figure 7, and they attracted our attention because the H wave so nearly equaled, or exceeded the J wave in height, and because of the low amplitude of the smallest complexes of the respiratory cycle.

This patient suffered from an attack of cardiac infarction in 1940 when aged 52. The symptoms and electrocardiographic changes were typical, the course was mild and he recovered sufficiently to pass all examinations for admission to the army and he served with distinction at a job requiring desk work in Washington during the war. Six months after the acute attack the second record of figure 7 was taken. The abnormality of the H wave was found to have increased, its height equaled or exceeded that of the J wave in all complexes.

Angina pectoris on severe exertion was noted following the acute attack and as years passed his exercise capacity diminished and he began to carry and take nitroglycerine. By 1953, dyspnea on exertion as well as pain were limiting facors, although he was still carrying on most effective work at a medical school. Under these circumstances the third record was taken. The ballistocardiogram was then extremely abnormal, no normal complexes were seen in any part of the respiratory cycle, the abnormality of form varied from beat to beat, the I wave, absent or very small, failed to reach the base line in many complexes, leaving the H and J waves fused.

After this, his condition deteriorated quite rapidly. X-ray examination demonstrated that the heart had enlarged. Attacks of paroxysmal atrial fibrillation began, also attacks of paroxysmal nocturnal dyspnea, but, except for occasional short stays at home, he continued to do effective work at a medical school until a few days before his death. He then went to Washington on business, where he had an unusually severe attack of angina and returned home. He had more pain at home but after a few days’ rest seemed as well as usual. On the day of his death he arose feeling badly, collapsed and died before his physician arrived. Death took place almost exactly a year after the last ballistocardiogram.

At necropsy the pathologic lesions of importance were confined to the heart. There was severe coronary atherosclerosis with extreme narrowing of all branches. There was evidence of an old thrombotic occlusion (judged to be many years old) in the right coronary artery. The myocardium showed widespread severe damage, essentially subendocardial, but with two somewhat larger patches in the anterior and posterior walls. Of special interest were the extensive degenerative changes in the subendocardial region and the trabeculae of the left ventricle.

No definite acute muscle necrosis was present in the left ventricle though the variable staining in some areas was a bit suggestive. The finding of recent necrosis of muscle in the auricles was unexpected. No thrombi or recent obstructions were seen in any of the arteries.

The completed history of this case is certainly consistent with the view that coronary arteriosclerosis, found to such an advanced degree at necropsy was also present to some degree when the first abnormal ballistocardiogram was taken, although the subject certainly believed himself to be in good health at that time.

Let us now turn our attention to a more unexpected feature of our results, the fact that the drug, nitroglycerine, so widely used in coronary heart disease, caused temporary deterioration of the ballistocardiogram in a considerable proportion of our cases. This surprising finding has caused us to search for other evidence that drugs of this class might be cardiotonic, and to examine the records of patients showing this
unexpected response in search of a clinical difference which might explain it.

In comparison with the 91 patients who did not show this effect the group of 25, whose records deteriorated after nitroglycerine were a little older, averaging 56.6 years against 52.7 years; and their blood pressure fell a little further, the average systolic fall being 16.9 mm. Hg in contrast to 14.4 mm. Hg, the average diastolic fall being 5.0 mm. Hg against 4.7 mm. Hg. There was a high percentage of persons with hypertension among those whose records became abnormal after nitroglycerine, 38 per cent having blood pressures higher than 130/100 mm. Hg, while only 23 per cent of the contrasting group were hypertensive. However, none of these differences is significant.

Of those showing deterioration of their records after nitroglycerine, 76 per cent had been diagnosed coronary or arteriosclerotic heart disease by the ordinary clinical criteria; obviously the great majority were coronary cases. Fifty-six per cent of the contrasting group were so diagnosed, a difference just failing to be significant.

Those whose records deteriorated after nitroglycerine and who were not diagnosed coronary heart disease included: L. S., a man of 54, found to have duodenal ulcer; M. D., a woman of 38, a complicated endocrine case suspected of acromegaly; R. W., a woman aged 33, and B. P., a woman of 74, both advanced cases of rheumatic heart disease; J. M., a man aged 50, suspected of hyperthyroidism; J. R., a man aged 34, who complained only of nervousness and a fainting spell; however, smoking a cigarette caused marked deterioration of his ballistocardiogram. Others were L. S., a woman aged 54, a former case of hyperthyroidism who came to the hospital for evaluation and whose basal metabolic rate was found normal; G. R., a man aged 67, who had moderate hypertension and cholelithiasis; and D. L. whose record is illustrated in figure 6. Obviously, several of those not diagnosed coronary or arteriosclerotic heart disease were of an age consistent with such a diagnosis and the remainder fall into no particular clinical group. Certainly, this analysis has not disclosed a clinical reason for the adverse effect of nitroglycerine and another explanation must be sought.

In animal experiments, nitrates do not always increase coronary flow. Text book statements concerning the conspicuous dilator action of nitroglycerine on the coronary circulation are derived chiefly from data secured from isolated heart preparations in which perfusion pressure is kept constant by the design of the experiment. In intact animal preparations, this effect on the coronary circulation is often far less striking, doubtless because the blood pressure, which provides the perfusion pressure of the coronary arteries, so often falls after nitroglycerine. Thus in experiments on dogs, Eckenhoff and Hafkenschiel20 found that nitroglycerine caused an increase in coronary flow only so long as the amount injected was not sufficient to produce a fall in blood pressure. These authors also observed instances in which coronary flow first increased, and then, as blood pressure fell, it decreased; so it is not hard to visualize how mixed or purely deleterious effects on the ballistocardiogram might be produced in man.

In addition, there are good reasons to expect differences between the action of drugs in healthy animals and in certain patients. It has been customary to think of the coronary circulation as a single physiologic unit; in the healthy, this is doubtless true. But when an arteriosclerotic heart is examined at necropsy, one has real doubts on this point. Uniform structural abnormality of the coronary tree is seldom, if ever, seen at necropsy. The lesions of arteriosclerosis are patchy in their distribution, stretches of normal vessel as well as areas of abnormality are found in the great majority of such cases. Especially if calcified, the advanced lesions make some parts of the coronary tree incapable of dilatation; certainly one cannot stretch many narrowed vessels to normal size with a probe. Such areas of rigidity might greatly alter the effect of a vasodilator, for, if some branches of the coronary tree are fixed, and others capable of responding, it seems that under many circumstances a drug causing dilatation would increase the blood flow within the dilated branch at the expense of the flow down the rigid branch, to the consequent im-
provement of the muscle function in one area of the heart, but to its detriment in another. We are inclined to explain the increased confusion of the ballistocardiogram seen in some of our subjects on this basis.

Stimulated by the adverse ballistic effects found in some of our patients, we have searched for clinical evidence of untoward effects of nitrites. Prodger and Ayman described alarming reactions to nitroglycerine in 4 of 110 patients who had received the same doses we used, or double that dose. These reactions were characterized by a profound fall in blood pressure in two cases, heart block in one, marked slowing of the pulse in two, accompanied by weakness, sweating, nausea and faintness. But in most respects, the untoward effects described by Prodger and Ayman resemble the usual syncopeal reaction, such as might attack any person in the upright position during the action of any vasodilator drug; and except for the development of heart block in one case, this experience provides no conclusive evidence that nitrites are cardiotoxic.

At the Second World Congress of Cardiology, where our preliminary report was also given, Russek and coworkers reported that 13 of 158 patients with coronary heart disease, when given nitroglycerine before a standard exercise test, developed greater abnormalities of the electrocardiogram than were present in control records, and these authors concluded that this drug has latent potentials for adverse effects. Others have told us that they also have seen adverse changes in the electrocardiogram after nitroglycerine, but they did not consider them important. In our experiments the simultaneous electrocardiogram did not show any change when the ballistocardiogram deteriorated after nitroglycerine.

So the clinical evidence that nitrites, as given to patients, can produce real harm to the heart seems to us to be extremely meagre. Nitrites do not produce angina, although often given to patients subject to this disorder. We have no wish to emphasize unduly the importance of our findings; the effect judged to be adverse was fleeting, and our subjects had no complaints at this time. Indeed we would have been inclined to dismiss these findings as unimportant had it not been for recent evidence indicating that nitrites may have toxic potentials far greater than has been realized.

Suspicious of cardiac toxicity of a much more serious sort have been directed at nitroglycerol, a volatile nitrite not used in medicine, but identified as a hazard to those engaged in the manufacture of explosives in Europe during the last war. This deserves the attention of doctors because nitroglycerol produces effects on the human body very similar to, if not identical with, those of nitroglycerine. The cases reported by Gross occurred in workers in the explosive industry who were not elderly and who had previously been in good health. The persons affected collapsed suddenly and there were some fatalities. It is remarkable that the collapse never occurred while they were at work but took place several days after cessation of exposure, as on Sunday night or Monday morning. Writing 10 years later, Symanski collected 49 fatal accidents of the same kind in workers exposed to nitroglycerol and reported three cases he had seen himself. Previously in good health, these workers collapsed suddenly usually during moderate exertion as while walking to work. Symanski found low blood pressure, abnormal pulse rate and electrocardiographic abnormalities during the last illness. Necropsy performed in three cases did not disclose any anatomic abnormality to which death could be attributed, so the exposure to nitroglycerol was implicated.

We know of no evidence to indicate that serious cardiotoxic effects, such as those attributed to industrial exposure to nitroglycerol, ever occur in patients given nitroglycerine by their physicians. Needless to say, many cases of angina taking nitroglycerine have suffered sudden death, but the tendency of such cases to "fall down and perish almost immediately" was recognized by Heberden many years before the first use of nitrites in this disease by Lauder Brunton.

Nevertheless it is sobering to reflect that, should the nitrites be playing a role in such unhappy accidents, this would almost certainly be overlooked by the physician in charge, for death would be attributed to the underlying disease. For this reason, the increasing evi-
vidence that nitrites, used with such great benefit to most cases of angina, may disturb cardiac function under certain circumstances, must be kept in mind by the profession.

In conclusion, it is interesting to consider a possible interpretation of the adverse ballistocardiographic changes after nitroglycerine which can be tested by our results. In the majority of our patients showing such effects, coronary heart disease had been diagnosed, and so it is likely that coronary sclerosis was present. If the whole or a considerable part of the coronary arteries had become narrowed, and so rigid that dilatation was impossible, the action of nitrites by causing a fall in blood pressure in the root of the aorta, would diminish blood flow in the area supplied by the rigid vessels, since the aortic pressure provides such a large part of the driving force of the coronary circulation. So if the development and retrogression of increased ballistic abnormality after nitroglycerine coincided with the fall and rise of aortic pressure, it would suggest that the coronary sclerosis was especially severe. Most of our results are consistent with this attractive theory, for, as a rule, the blood pressure was reduced during the period of increased ballistic abnormality. But a few of our results are not consistent with this view. We have encountered instances during a period of increased ballistic abnormality after nitroglycerine, when the arterial pressures were as high or higher than during the control period. This was most often seen during recovery from the effects of the drug. We are, therefore, driven to the view that other factors must enter into the adverse effects in some cases. But whatever the complete explanation, the fact that the usual dose of nitroglycerine, though more often causing marked improvement of cardiac function, may also cause deterioration of cardiac performance, should be kept in mind by doctors prescribing it.

**Conclusion**

The effect of nitroglycerine on the ballistocardiogram has been studied in 18 healthy young adults and in 116 patients, 63 of whom had been diagnosed as having coronary or arteriosclerotic heart disease from the usual clinical evidence. Nitroglycerine had no effect on the form of the record of healthy young adults.

The ballistocardiogram deteriorated markedly during two attacks of angina pectoris. When given nitrites, as pain was relieved, the form of the ballistocardiogram improved greatly.

Most of our patients suffering from angina pectoris gave abnormal ballistocardiograms when tested between attacks. When given nitroglycerine, their records improved temporarily in about one-half of the cases tested. So the action of nitrites may bring about improvement in the record when given both during and between attacks of angina pectoris.

In patients who had had cardiac infarction not followed by angina pectoris, abnormal ballistocardiograms were improved temporarily by nitroglycerine in over half of the cases.

Patients in the latter half of life who have abnormal ballistocardiograms, but no history of angina pectoris, and no clinical evidence of coronary heart disease, showed temporary improvement in their records after nitroglycerine in two-thirds of the cases, a finding consistent with the view that they actually suffered from coronary heart disease of a form or to a degree not yet clinically manifest.

A case is reported in which an abnormal ballistocardiogram was secured while the subject believed himself to be in good health; later cardiac infarction developed, and still later advanced coronary arteriosclerosis was found at necropsy.

Despite the frequency with which improvement of the ballistocardiogram is seen after nitroglycerine, temporary deterioration of this record may follow the action of this drug when it is given in the dosage commonly employed by physicians.

The possible physiologic meaning of these untoward effects is discussed and attention is called to new evidence of serious toxic effects including collapse and sudden death, encountered in certain European workers exposed to a volatile nitrite during the manufacture of explosives.
EFFECT OF NITROGLYCERINE ON THE BALLISTOCARDIOGRAM

SUMMARÍO IN INTERLINGUA
Nitroglycerina esseva administrate a un serie de patientes, e su effecto super le ballistocardiogramma esseva observate. Attaccos de angina de pectore es accompaniate de un forte deterioration del registration: si alora nitroglycerina es administrate le registration se meliora quando le dolores subside. Administrate inter attaccos, a patientes de morbo cardiac coronari con ballistocardiogrammas anormal, nitroglycerina es frequentemente sequite per un melioration del registration. Le mesmo es ver quando nitroglycerina es administrate a patientes de etates plus avantiata qui ha ballistocardiogrammas anormal sed nulle signo clinic de morbo cardiac coronari. Iste facto concorda con le theses que morbo cardiac coronari es presente in tal casos. Del altere latere, nitroglycerina es a vices sequite de un deterioration del ballistocardiogramma. Le rationes possibile de iste inexpectate constatation es discutite. Es signalate recente datos que indica que serie effectos toxice pote sequer le exposition al effecto de nitritos in uso industrial.

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