

# Correlation of Heart Rate During Norepinephrine Infusion with Pulse Pressure Following Amyl Nitrite Inhalation

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Conway and Smith have suggested that a decrease in the pulse pressure following inhalation of amyl nitrite might be associated with loss of aortic elasticity. Studies in this laboratory have suggested that a decreased bradycrotic response during infusion of norepinephrine might also be associated with loss of aortic elasticity. It was hoped that further support might be given to such a hypothesis if both procedures gave similar results in the same patients. The present study was designed to compare the effect of inhalation of amyl nitrite on the pulse pressure and infusion of norepinephrine on the heart rate in normal, hypertensive, and arteriosclerotic subjects.

CONWAY and Smith<sup>1</sup> demonstrated a greater decrease in pulse pressure during inhalation of amyl nitrite in patients with arteriosclerotic hypertension than in hypertensive patients without arteriosclerosis or in young normal patients. Studies in this laboratory<sup>2</sup> have demonstrated a decreased bradycrotic response during infusion of norepinephrine in patients with arteriosclerosis whether the arterial pressure was normal or elevated. Both these groups<sup>1, 2</sup> have postulated independently that such procedures might be used to assess the elastic qualities of large vessels. Thus a marked bradycrotic response during infusion of norepinephrine and no significant decrease in pulse pressure following inhalation of amyl nitrite would indicate

normal elasticity of large vessels while a decreased bradycrotic response during infusion of norepinephrine or a greater decrease in pulse pressure following amyl nitrite would indicate loss of elasticity of these vessels. It was hoped that further support might be given to such a hypothesis if both procedures gave similar results in the same patients. The present study was designed to compare the effect of inhalation of amyl nitrite on the pulse pressure and infusion of norepinephrine on the heart rate in normal, hypertensive, and arteriosclerotic subjects.

## METHODS AND MATERIALS

The patients were from the wards and clinics of the District of Columbia General Hospital. Twenty-five patients were studied; 7 were male and 18 female. Six patients were without any manifest cardiovascular disease (group 1). Six patients demonstrated clinical evidence of arteriosclerosis (see below for explanation) with a normal arterial pressure (group 2), and 13 patients showed evidence of arteriosclerosis with an elevated arterial pressure (group 3).

The average age of the 6 patients without cardiovascular disease (group 1) was 38 (20 to 59) years. The average femoral arterial pressure (systolic plus diastolic divided by 2) was  $110 \pm 9$  mm. Hg. Complete physical examination with particular emphasis on the cardiovascular system was normal. The electrocardiogram, chest roentgenogram, and urinalysis were all normal.

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The average age of the 6 patients with arteriosclerosis and normal arterial pressure (group 2) was 70 (58 to 82) years. The average femoral arterial pressure was  $115 \pm 15$  mm. Hg. In no patient was there a history of hypertension. In 2 patients there was a history of cerebral vascular accident. Ophthalmoscopic examination revealed an increase in the arteriolar light reflex and tortuosity and narrowing of the retinal arterioles in 5 patients. Cataracts prevented ophthalmoscopic examination in the remaining patient. There was unilateral absence of the posterior tibial pulsation in 3 patients. The electrocardiogram was normal in 1 patient, demonstrated the pattern of myocardial ischemia in 2 patients, and old anterior myocardial infarction in 2 patients. Chest x-ray revealed an enlarged heart and widened and elongated aorta in 2 patients and a heart of normal size with elongation and dilatation of the aorta in 4 patients. Each patient demonstrated at least 3 of the above findings.

The 13 patients in group 3 had chronic hypertensive vascular disease. Their average age was 56 (32 to 72) years. The average duration of hypertension in these patients was 9 (6 to 17) years. The average femoral arterial pressure was  $168 \pm 39$  mm. Hg. Ophthalmoscopic examination revealed arteriovenous nicking plus tortuosity of the retinal vessels in 11 patients and arteriovenous nicking plus tortuosity plus exudates and hemorrhages in 2 patients. Roentgenograms of the chest revealed enlargement of the heart in the transverse diameter in all patients. The electrocardiogram was normal in 1 patient, showed the pattern of left ventricular hypertrophy and posterior myocardial infarction in 2 patients, and the pattern of left ventricular hypertrophy in 10 patients.

The patients were brought to the laboratory in the fasting state without premedication. Following local infiltration of the skin with 1 per cent procaine a 17-gage needle was inserted into the femoral artery. The arterial pressure was recorded directly by means of a strain-gage transducer and a direct-writing recorder.

Following attainment of a steady state, norepinephrine bitartrate (Levophed) was administered as an intravenous infusion in a concentration of 4  $\mu$ g. per ml. of 5 per cent dextrose in water. The rate of infusion was regulated according to the increase in arterial pressure and the decrease in heart rate and varied between 5 and 14  $\mu$ g. per minute. The endpoint of the experiment was taken as a rise of arterial pressure in excess of 25 per cent or a decrease in heart rate of more than 10 beats per minute. In those patients in whom one or the other endpoint was not reached, the norepinephrine infusion was continued for at least 10 minutes.

Following return of the arterial pressure and heart rate to control levels a crushed vial of amyl nitrite was held under the subject's nose. The patient was instructed not to sniff, but to take 2 normal inspirations. The arterial blood pressure was recorded directly throughout the entire procedure until it returned to control levels. In the measurement of the pulse pressure trends, particular care was taken to compare equivalent beats with respect to heart rate and respiration before and after the onset of the depressor effect of amyl nitrite. The experimental pulse pressure observation was noted before the development of tachycardia. The response of the arterial pressure during inhalation of amyl nitrite was tested at least twice in the same patient.

## RESULTS

The results are shown in table 1. The greater decrease in pulse pressure following inhalation of amyl nitrite occurred in the same patients who exhibited a decreased bradycrotic response during infusion of norepinephrine. Little or no overlapping occurred between the normal and abnormal responses in both procedures. A decrease of more than 10 beats per minute in heart rate occurred during norepinephrine infusion in every patient who demonstrated less than a 13 per cent reduction in pulse pressure following inhalation of amyl nitrite (groups 1 and 3A) (fig. 1). A reduction in heart rate of no more than 4 beats per minute during norepinephrine occurred in those patients who exhibited more than a 16 per cent reduction in pulse pressure following inhalation of amyl nitrite (groups 2 and 3B) (fig. 1).

## DISCUSSION

These responses in pulse pressure and heart rate were not related to the age of the patient, the control level of arterial pressure, or the percentage increase or decrease in arterial pressure. The patients in the arteriosclerotic group with normal arterial pressure (group 2) were older than the patients without cardiovascular disease (group 1). However, the ages of the patients in group 3A in whom normal responses to norepinephrine and amyl nitrite were witnessed were similar to the ages of the patients in group 3B who demonstrated abnormal responses to norepi-

nephrene and amyl nitrite. The previous studies from this laboratory, which have reported a normal bradycrotic response during norepinephrine in elderly subjects without obvious sclerosis, would also tend to minimize the importance of age as the sole cause for the decreased bradycrotic response during infusion of norepinephrine.<sup>2</sup>

The normal level of arterial pressure in groups 1 and 2 and the elevated arterial pressure in groups 3A and 3B demonstrate the lack of importance of the control level of arterial pressure in determining the heart rate response during norepinephrine and the pulse pressure response following amyl nitrite. Although a greater decrease in the arterial pressure following inhalation of amyl nitrite occurred in those patients who exhibited a greater decrease in pulse pressure, these differences are probably not significant. No correlation exists between the degree of elevation of arterial pressure and the changes in heart rate.

The mechanisms for the different responses of heart rate during norepinephrine and the pulse pressure following amyl nitrite are not known. It may be that the abnormal response to both these agents is in some way related to arteriosclerosis. Previous studies from this laboratory revealed a decreased bradycrotic response during norepinephrine in patients who demonstrated several clinical signs of arteriosclerosis.<sup>2</sup> Similarly, Conway suggested that one could predict a greater decrease in pulse pressure following amyl nitrite in patients with the arteriosclerotic type of hypertension.<sup>2</sup> The response of the heart rate during norepinephrine and the pulse pressure following inhalation of amyl nitrite could not be predicted in the hypertensive patients presented here (groups 3A and 3B). The ages of these patients, duration of their hypertension, retinal vascular changes, heart size, width of the aorta, and electrocardiographic findings all were similar.

Heymans and Neil<sup>3</sup> have shown that the response of the carotid sinus baroreceptor nerves (and presumably aortic sinus) depends on the distensibility of the carotid sinus. Loss

TABLE 1.—*Changes in Arterial Pressure and Heart Rate During Norepinephrine Infusion with Arterial Pressure and Pulse Pressure Following Amyl Nitrite Inhalation*

Group	1	2	3A	3B
Number of patients	6	6	5	8
<i>Norepinephrine</i>				
Control arterial pressure (mm. Hg)	110±9	115±15	180±52	160±16
Arterial pressure during infusion (mm. Hg)	139±10	141±19	215±53	190±21
Per cent increase arterial pressure	26±5	23±8	19±7	19±6
Heart rate (beat/min.)	70±8	75±14	74±15	66±15
Heart rate during infusion (beat/min.)	57±7	73±15	60±17	64±16
Per cent decrease heart rate	19±4	3±3	19±8	3±3
<i>Amyl nitrite</i>				
Control arterial pressure (mm. Hg)	116±13	125±21	188±51	171±18
Arterial pressure following inhalation (mm. Hg)	99±16	99±12	161±44	130±15
Per cent decrease arterial pressure	15±6	21±5	14±3	24±6
Control pulse pressure (mm. Hg)	61±6	86±20	100±18	112±32
Pulse pressure following inhalation (mm. Hg)	58±6	65±17	90±17	82±24
Per cent decrease pulse pressure	5±4	24±5	10±2	26±8

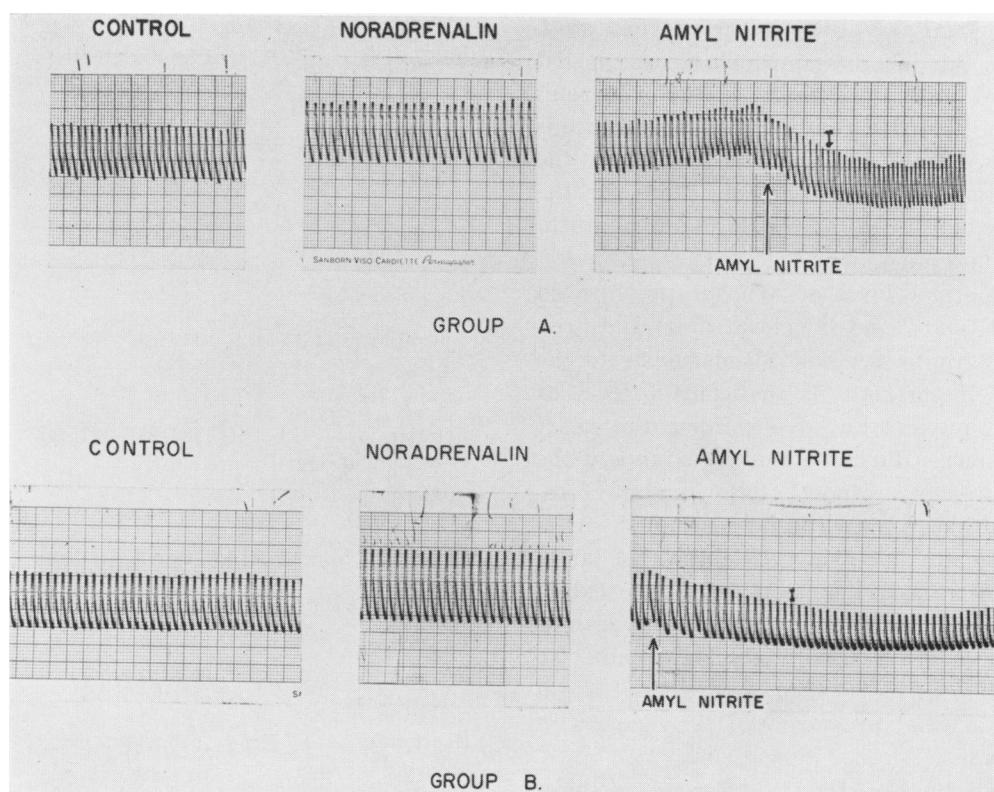


FIG. 1. Femoral arterial pulse pressure tracings of a patient without cardiovascular disease (A) and of a patient with arteriosclerosis with normal arterial pressure (B). Note the decreased bradycrotic response during norepinephrine and greater decrease in pulse pressure following amyl nitrite in B.

of distensibility due to hypertensive or atherosclerotic changes in the wall of the carotid sinus could result in decreased reactivity of the moderator nerves to elevation of blood pressure. The decreased response would be reflected in a diminished bradycrotic response. It has been postulated previously that the decreased bradycrotic response during norepinephrine might be due to an arteriosclerotic process in the walls of the aorta.<sup>2</sup> Although the data presented here furnish no further proof, a similar explanation might be offered for the decreased bradycrotic response in the patients in groups 2 and 3B presented here. It might be suggested further that the arteriosclerosis present in the patients in group 3A did not involve the walls of the aorta, whereas the arteriosclerotic process in patients in group 3B involved the walls of the aorta.

If one grants the assumption (as Conway and Smith<sup>1</sup> have done) that there is no change in stroke volume immediately following inhalation of amyl nitrite (before the development of tachycardia), it seems reasonable to postulate that changes in the pulse pressure during this period might be an index of elasticity of large vessels. The observation that a greater decrease in pulse pressure following amyl nitrite occurs in the same patients who exhibit a decreased bradycrotic response during infusion of norepinephrine suggests that both responses are a measure of the same abnormality and lends further credence to the hypothesis that such responses might serve as an index of elasticity of large vessels.

It is suggested that these procedures might be useful clinically to document the existence of large vessel sclerosis, which frequently may not be evident by the usual physical examina-



tion and laboratory procedures. Knowledge of the elasticity of large vessels would be particularly important in the evaluation of a hypertensive patient. Since a decreased bradycrotic response during norepinephrine occurs in those patients who exhibit a greater fall in pulse pressure following amyl nitrite, it would seem unnecessary to perform both procedures. The simplicity of procedure—lack of need for arterial puncture—and the ease of interpretation of results would seem to make the response of the heart rate during infusion of norepinephrine the procedure of choice. A reduction in the heart rate of more than 10 beats per minute indicates a normal response and a reduction in the heart rate of less than 4 beats per minute an abnormal response.

#### SUMMARY

The response of the heart rate during infusion of norepinephrine and of the pulse pressure immediately following inhalation of amyl nitrite was studied in normal, hypertensive, and arteriosclerotic subjects. A greater decrease in pulse pressure following amyl nitrite ( $>16$  per cent) occurred in every patient who exhibited a decreased bradycrotic response during norepinephrine ( $<4$  beats per minute). The differences in pulse pressure and heart rate response were not related to the age of the patient, the control level of arterial pressure, or the per cent increase or decrease in arterial pressure. The factors governing both these responses could not be demonstrated. It had been suggested that a decreased bradycrotic response during norepinephrine might indicate a loss of elasticity of large vessels. The abnormal response to both

procedures in the same patients presented here lends further support to this hypothesis.

#### SUMMARIO IN INTERLINGUA

Le responsa del frequentia cardiac durante le infusion de norepinephrina e le responsa del pression de pulso post le inhalation de nitrito de amylo esseva studiate in subjectos normal, hypertensive, e arteriosclerotic. Un plus importante reduction del pression de pulso post nitrito de amylo ( $>16$  pro cento) occurreva in omne patiente qui exhibiva un reducite responsa bradycrotic durante norepinephrina ( $<4$  pulsos per minuta). Le differentias in le responsas del pression de pulso e del frequentia cardiac non esseva relationate al etate del patiente, al nivello de controllo del pression arterial, o al augmento o al reduction procentual del pression arterial. Le factores que governa iste duo responsas non poteva esser demonstrate. Il existe le these que un reducite responsa bradycrotic durante norepinephrina indica possiblementemente un perdita de elasticitate in le vasos major. Le hic-presentate observation de responsas anormal a ambe procedimentos in le mesme patiente representa un supporto additional in favor del these mentionate.

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