Studies on Cardiac Dimensions in Intact Unanesthetized Man

V. Effects of Nitroglycerin

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Although nitroglycerin has been used in the treatment of angina pectoris since 1879, the precise mechanism by which it relieves this symptom has not been clearly defined. It has been suggested that the drug enhances oxygen delivery to the ischemic myocardium by a direct dilating effect on coronary vessels. On the other hand, the possibility has also been considered that nitroglycerin lowers myocardial oxygen requirements, and in this manner reestablishes a more normal relationship between the demand for and availability of oxygen. Considerable experimental evidence has been obtained to support the view that the tension which the ventricles develop plays an important role in determining myocardial oxygen requirements, and it is also clear that the tension of the myocardium is determined not only by the intraventricular systolic pressure, but also by the volume of the ventricular cavity. The finding that the sublingual administration of nitroglycerin results in dilatation of forearm veins and peripheral pooling of blood suggested the possibility that this drug reduces ventricular size and thereby reduces myocardial oxygen requirements. It was possible to evaluate this possible action of nitroglycerin by means of a cineradiographic technic which permits the measurement of changes in ventricular dimensions in intact human subjects over relatively long periods of time.

Methods

The technic employed consisted of suturing small silver-tantalum markers to the external surfaces of one or both ventricles at the time of cardiac operation, and following the patients' recovery from operation exposing cineradiograms at 30 frames per second before and after nitroglycerin. The distances between the markers on individual frames of the cineradiograms were then measured, providing information concerning the changes that had occurred in ventricular dimensions throughout the cardiac cycle.

The effects of nitroglycerin were studied in 11 patients, nine women and two men, ranging in age from 17 to 51 years. The operative procedures at which the markers were applied were mitral commissurotomy in three patients, closure of atrial septal defects in four patients, correction of congenital aortic stenosis in one patient, pulmonary valvotomy and closure of an atrial septal defect in one patient, correction of total anomalous pulmonary venous return and an atrial septal defect in one patient, and mitral valve replacement with a Starr-Edward prosthesis and insertion of a radiofrequency pacemaker for complete heart block in one patient. This latter patient also had partial anomalous pulmonary venous return which was not corrected at the time of operation. In the other patients the operation successfully corrected the anatomic defect and the hemodynamic improvement was verified in eight of the patients at cardiac catheterization carried out postoperatively. No patient had clinical evidence of coronary artery disease. Five patients had markers sutured to the right ventricle, four to the left ventricle, and two patients had markers on both ventricles. The patients were studied 2 weeks to 17 months after operation.

The technic has been described in detail previously. All observations were made with the patient in the supine position. The only ventricular dimensions measured were those between markers which had been placed in a fashion so that the line which joined them was parallel, or nearly parallel, to the frontal plane so that errors resulting from rotational changes of the heart within the thorax could be minimized. Radiopaque markers were also placed on the
anterior chest wall of each patient and if the position of these markers on the cineradiogram was altered by thoracic rotation or displacement, the data were discarded. The motion of a mechanical indicator, triggered by the electrocardiogram and recorded on the cineradiograms, and simultaneously recorded on a multi-channel photographic oscillograph, together with the arterial pressure, pneumogram, and electrocardiogram. Use of this indicator made it possible to synchronize the ventricular dimensions in each specific frame of the cineradiogram with the variables recorded on the photographic recorder. To eliminate the respiratory effects on ventricular dimensions, all measurements were made at end-expiration.

Cineradiograms and photographic recordings were made before the sublingual administration of 0.6 mg of nitroglycerin and at 2-minute intervals thereafter for 12 to 20 minutes. In two patients it was possible to eliminate any changes in ventricular dimensions due to alterations in heart rate. The latter was controlled in one patient by continuously stimulating the right atrium through an electrode catheter. In the second patient the left ventricle was stimulated continuously with a radiofrequency pacemaker that had previously been inserted for the treatment of complete heart block with atrial fibrillation. In six patients cardiac output was determined by the dye-dilution technic as described previously. Measurements were made during the control period and 3 to 5 minutes after nitroglycerin administration, the time at which the maximal decrease in arterial pressure had occurred.

**Results**

Following the administration of nitroglycerin, a decrease in both end-systolic and end-diastolic dimensions occurred in every patient, the maximum decline occurring between the second and sixth minutes. In the six patients in whom it was measured, left ventricular end-diastolic length decreased by an average of 6.2 per cent (range 3.4 to 9.8 per cent), while left ventricular end-systolic length decreased by an average of 5.9 per cent (range 2.9 to 14.3 per cent) (fig. 1). In seven patients right ventricular end-diastolic length decreased by an average of 5.0 per cent (range 2.2 to 7.7 per cent), while right ventricular end-systolic length decreased by an average of 3.6 per cent (range 1.2 to 7.9 per cent) (fig. 2). In the two patients whose heart rates were maintained constant by electrical stimulation, at rates of 80 and 85 per minute, respectively, the changes in ventricular dimensions and excursions after nitroglycerin were quite similar to those observed in the patients whose rates were permitted to change (fig. 3). Since, following nitroglycerin, the end-diastolic dimensions decreased more than the end-systolic ones, the

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**Figure 1**

Effects of nitroglycerin on the relative distances between two markers sutured to the surface of the left ventricle. The distances during a complete cardiac cycle during the control period are shown on the left and the distances after nitroglycerin are shown on the right. LVEDL, left ventricular end-diastolic length; LVESL, left ventricular end-systolic length; H.R., heart rate/min., Art. B.P., systemic arterial pressure.

**Figure 2**

Effects of nitroglycerin on the distances between two marks sutured to the right ventricle. RVEDL, right ventricular end-diastolic length; RVESL, right ventricular end-systolic length.
excursions of the markers, i.e., the decrease in the distances between them during systole, diminished. The systolic excursions of the markers on the right ventricle decreased in all instances, with an average fall of 13.3 per cent. Similarly, a decrease, averaging 18.4 per cent, occurred in four of the six patients with left ventricular markers; a small increase in systolic excursions occurred in one patient and the excursions were unchanged in the other patient.

Prior to nitroglycerin the systolic, mean, and diastolic arterial pressures averaged 116, 85, and 68 mm. Hg. At the time the changes in ventricular dimensions were recorded, the pressures had declined in every patient and the average levels were 103, 76, and 64 mm. Hg, respectively. Nitroglycerin resulted in a fall in cardiac output in all six patients in whom it was measured, from an average of 5.6 to 5.0 L./min. Stroke volume also decreased in all of them, from an average of 65 ml./beat during the control period to 55 ml./beat after nitroglycerin. In the nine patients in whom the heart rate was not controlled, this variable increased by an average of 8/minute.

Discussion

In previous investigations, both in experimental animals12-14 and in patients,7, 18-21 it has been shown that nitroglycerin lowers systemic arterial pressure, and our findings are in agreement with this observation. On the other hand, there is considerable dispute concerning the effects of this drug on cardiac output, which has previously been reported to rise22, 23 to remain unchanged20, 24 or to decline slightly.19 In this study, although the changes were not large, they were consistent; in all six patients in whom cardiac output and stroke volume were measured, both of these variables diminished at the time of the maximum decline of arterial pressure, 3 to 5 minutes after the sublingual administration of the nitroglycerin. Thus, in view of the fall in arterial pressure, cardiac output, and stroke volume, the calculated external work performed by the left ventricle (per minute and per stroke) diminished in every patient.

The major objective of this study was to determine the effects of nitroglycerin on ventricular size. It was observed that both the end-diastolic and end-systolic dimensions of both the left and right ventricles decreased. The diminution of end-systolic dimensions was usually of lesser magnitude, thereby resulting in a fall of the stroke excursion, a finding which is in agreement with the observed decline in stroke volume. In view of the known effects of respiration and heart rate on ventricular dimensions,6, 10 attempts were made to control both of these variables. Thus, the dimensions were always measured at end-expiration, and in two patients the effects of nitroglycerin were determined at a constant heart rate. Since the decreases in ventricular dimensions during systole, i.e., the systolic excursions, ranged from 15 to 20 per cent of the control end-diastolic dimensions, the average decreases in ventricular end-diastolic dimensions following nitroglycerin (5.9 per cent for the left ventricle and 5.0 per cent for the right ventricle) approximate one third of a stroke volume, i.e., 20 ml. These decreases in end-diastolic dimensions are comparable to those which have previously been observed to occur during induced tachycardia10 and muscular exercise,25 but are greater than those noted during the infusion of isoproterenol.26

At any given level of ventricular pressure,
the tension developed by the myocardial fibers is a function of the ventricular volume.\textsuperscript{5, 6} Thus, the decline in ventricular size resulting from nitroglycerin administration, which was observed in this study, indicates that even had systolic pressure remained unchanged, intramyocardial tension would have diminished. Inasmuch as the tension which the myocardial fibers are called upon to develop is an important determinant of their oxygen requirements, the simultaneous decrease in ventricular size and systolic pressure indicates that nitroglycerin reduced the heart’s oxygen demands. As reported in the companion paper,\textsuperscript{7} it appears that nitroglycerin dilates both the systemic arteriolar and venous beds and it seems likely that these actions of the drug on the peripheral circulation are responsible for the reductions in ventricular dimensions described in this report. In conclusion, although the present investigation was not designed to answer the question of whether nitroglycerin, in the doses used clinically, actually dilates the coronary vessels in patients with coronary atherosclerosis, it does provide evidence for one mechanism by which the drug so remarkably interrupts the pain of angina pectoris.

**Summary**

The objective of this study was to determine the effects of nitroglycerin on ventricular dimensions. At the time of corrective cardiac operations, silver-tantalum markers were sutured to one or both ventricles of 11 patients without clinical evidence of coronary artery disease. Following recovery, cineradiograms were exposed at 30 frames per second and distances between markers were measured before and after 0.6 mg. of nitroglycerin. In all patients, end-diastolic and end-systolic dimensions decreased within 2 to 6 minutes. Right ventricular end-diastolic and end-systolic lengths decreased by an average of 5.0 per cent and 3.6 per cent of control values, respectively, while left ventricular end-diastolic and end-systolic dimensions declined by an average of 6.2 per cent and 5.9 per cent of control, respectively. The diminutions of end-diastolic ventricular dimensions approximated 30 per cent of the stroke volume. Systolic excursions decreased by an average of 13.3 per cent of control for the right ventricle, while left ventricular excursions decreased in four of the six patients. Systolic, mean, and diastolic arterial pressures decreased in each patient after nitroglycerin. Cardiac output fell from an average of 5.6 to 5.0 L./min., decreasing in each of the six patients in whom it was determined, while stroke volume fell from an average value of 65 ml./beat during the control period to 55 ml./beat after nitroglycerin.

Thus, nitroglycerin reduces both arterial pressure and ventricular dimensions and in view of the relationship between ventricular size, myocardial tension, and oxygen consumption, this action tends to reduce cardiac oxygen requirements and may explain, at least in part, the effectiveness of the drug in angina pectoris.

**References**


9. **Goldblatt, A., Harrison, D. C., Glick, G., and Braunwald, E.**: Studies on cardiac dimensions.

*Circulation, Volume XXXII, November 1965*


Galen 131-201 A.D.

An enthusiastic and outstanding investigator during his youth, Galen later became dogmatic and prone to invoke unverifiable forces and teleological concepts in order to explain natural phenomena, and ended by praising Divine Providence for the marvels of its creation. Hence, his authoritative pronouncements in all fields of medicine were readily acceptable to theologians, whether Moslems, Jews, or Christians.—ANDRE COURAND, M.D. Circulation of the Blood. Edited by Alfred P. Fishman, M.D., and Dickinson W. Richards, M.D. New York, Oxford University Press, 1964, p. 15.
Studies on Cardiac Dimensions in Intact Unanesthetized Man: V. Effects of Nitroglycerin

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Circulation. 1965;32:767-771
doi: 10.1161/01.CIR.32.5.767

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