

# Effect of *l*-norepinephrine on left ventricular diastolic pressures in man<sup>1</sup>

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Left ventricular systolic pressure, left ventricular diastolic pressure, left ventricular end-diastolic pressure, left ventricular cardiac output, systemic vascular resistance, and central blood volume were specifically measured in seven patients with normal cardiovascular systems before and during the tenth minute of an infusion of *l*-norepinephrine and the emergence of a 'square wave' pattern in the peripheral arterial blood pressure during Valsalva's manœuvre. At that time point the mean left ventricular systolic pressure exceeded the resting level. The mean left ventricular diastolic pressure rose by 6 mm. Hg, and the mean left ventricular end-diastolic pressure rose by 5.5 mm. Hg. The left ventricular output remained unchanged. A reduction in the heart rate of 13 beats/minute was found, and the calculated mean systemic vascular resistance, mean left ventricular stroke volume, and left ventricular stroke work continued to be above resting levels. No change was apparent in the central blood volume. The results indicate that the left ventricular diastolic pressure and left ventricular end-diastolic pressure rise significantly in the course of a prolonged infusion of *l*-norepinephrine coinciding with left ventricular after-loading. The magnitude of this elevation affects all diastolic pressures passively throughout the lesser circulation, including the central venous pressure. *l*-Norepinephrine is markedly inotropic when released within the myocardium. In the usual clinical dose and during a period of 10 minutes' infusion its efferent vagal, peripheral, arteriolar constrictor, and left ventricle after-load effects reduce the initial inotropy.

Previous investigations in man have shown that the resting right atrial pressure (R.A.P.) rises from a mean of 6.7/2.7 to 15.8/10.3 mm. Hg. ( $P < 0.01$ ) during the tenth minute of an infusion of *l*-norepinephrine. This elevation in R.A.P. coincides with the emergence of a 'square wave' in the arterial blood pressure pattern during Valsalva's manœuvre (O'Neill and Cudkowicz, 1965). Subsequently, in 12 patients free from heart failure, right ventricular (R.V.), pulmonary artery (P.A.), and pulmonary wedge (P.C.P.) pressures were observed under similar conditions (Cudkowicz and O'Neill, 1964). With the emergence of a 'square wave' peripheral arterial blood pressure pattern at a mean time of 9.5 minutes of *l*-norepinephrine infusion, identical 'square wave' patterns emerge throughout the pulmonary circulation. Significant changes from the resting phase were noted in the following:

Mean heart rate fell from 91 (S.D.  $\pm$  18.5) to 76 (S.D.  $\pm$  17.3).

Mean R.V. diastolic pressure rose from 0.4 (S.D.  $\pm$  0.9) to 7.0 (S.D.  $\pm$  3.8) mm. Hg.

Mean R.V. end-diastolic pressure rose from 3.5 (S.D.  $\pm$  1.7) to 8.7 (S.D.  $\pm$  4.5) mm. Hg.

Mean P.A. diastolic pressure rose from 18.3 (S.D.  $\pm$  15.2) to 27.0 (S.D.  $\pm$  16.5) mm. Hg.

Mean P.C.P. rose from 12.0 (S.D.  $\pm$  5.8) to 17 (S.D.  $\pm$  10.5) mm. Hg.

These differences were statistically significant. The cardiac output, total pulmonary vascular resistance, oxygen consumption, and minute ventilation did not change. It was then suggested that the 'square wave' response throughout the lesser circulation during *l*-norepinephrine infusions of not less than 10 minutes is dependent upon a passive elevation in all diastolic pressures of the lesser circulation attending on a similar rise in diastolic pressures of the left ventricle (Cudkowicz and O'Neill, 1964).

Central venous and right atrial pressure elevations during *l*-norepinephrine infusion were first observed by Fowler, Westcott, Scott, and McGuire (1951) and attributed to an increase in

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venomotor tone. Landis and Hortenstine (1950) suggested that widespread venous constriction raises the central venous pressure only if the left heart fails to elevate its output at the same time. The mechanism by which *l*-norepinephrine elevates right atrial pressure continues to be speculative, and the current study was undertaken in order to follow the effects on the left ventricle of a continuous infusion of *l*-norepinephrine. At the same time information was sought concerning left ventricular output, left ventricular stroke work, systemic vascular resistance, and central blood volume before and coincident with the emergence of the 'square wave' phenomenon to Valsalva's manoeuvre.

### METHODS

Observations were derived from seven patients undergoing left heart catheterization in recumbency. All these patients were free from cardiovascular disease, and in every instance the resting arterial blood pressure responses to Valsalva's manoeuvre were normal.

All seven studies were carried out in the unanaesthetized, fasting basal state. The left heart was catheterized by the retrograde arterial route using the Seldinger (1955) technique. The continuous infusion of *l*-norepinephrine, 4 µg. base/min., was effected via an intravenous polyethylene catheter threaded to the superior vena cava. Pressures from the superior vena cava and left ventricular catheters and a femoral artery needle were continuously inscribed on a direct-writing Sanborn recorder through Sanborn pressure transducers. Left ventricular pressures were not corrected for increments of intrathoracic pressure during airway straining. Interest was focused entirely on differences in resting and post-Valsalva pressures. The abolition of the 'overshoot' in phase 4 of Valsalva's manoeuvre constituted an additional guide to the emergence of a true 'square wave' response.

Airway strain during Valsalva's manoeuvre was maintained with the glottis open by forced expiration from the mid-inspiratory position against a mercury manometer at a marked pressure of about 80 mm. Hg and lasted 15 seconds.

On completion of the resting pressure observations the resting cardiac output was determined by the dye dilution technique using Coomassie blue (0.5 mg./kg.). The dye was rapidly injected via the polyethylene catheter, while blood was withdrawn from the aorta through the Seldinger catheter and a densitometer.<sup>1</sup> During the dye studies the tip of the Seldinger catheter was withdrawn above the aortic valve. This provided additional central aortic pressures.

For the second part of this study, *l*-norepinephrine was infused in 0.9% NaCl through the intravenous catheter at 6 ml./min. with an average dose of

4 µg. base/min. and a range of 3.8 to 4.6 µg./minute. Central venous arterial and left ventricular pressures were constantly monitored at a slow speed and the Valsalva manoeuvre was repeated every two minutes. With the establishment of an unequivocal 'square wave' all previous measurements were repeated.

The integrated sample plasma concentration of dye in density units was obtained from a model DU Beckman spectrophotometer at a wavelength of 585 µ. The final calculation of cardiac output from the inscribed dye dilution curve on a Honeywell strip-chart recorder followed the outlines of McNeely and Gravalles (1954).

Systemic vascular resistance was calculated as a ratio of mean systemic pressure to the cardiac output. Stroke work of the left ventricle in grammeters was derived from the difference between the mean arterial pressure (cm. H<sub>2</sub>O) and the left ventricular end-diastolic pressure, multiplied by one-hundredth of the calculated stroke volume.

Central blood volume was calculated by the Stewart-Hamilton technique.

### RESULTS

All measurements during the *l*-norepinephrine infusion were carried out after a persistent 'square wave' response to Valsalva's manoeuvre had emerged in two consecutive arterial blood pressure records taken at intervals of two minutes each. The average time of infusion required for this was 9.5 minutes (S.D. ± 2.7 minutes).

The maximum elevation in systemic blood pressure, however, was seen at a mean time of 3.5 minutes of the infusion, and a decline from this maximal level was quite frequent by the tenth minute. All present comparisons with the baseline values were derived after the tenth minute of *l*-norepinephrine infusion. The Table indicates that during 10 minutes of *l*-norepinephrine infusion the mean reduction in heart rate was 13/minute. The central venous pressure is significantly elevated. No difference could be demonstrated in the cardiac output as measured by the dye method, but the calculated mean stroke volume was increased. The mean aortic pressure at the tenth minute of the infusion remained significantly elevated as well as the systemic vascular resistance.

Figure 1 compares the contours of the left ventricular pressures during the tenth minute of the *l*-norepinephrine infusion. Bradycardia and the elevations in both diastolic and end-diastolic pressures are apparent. The systolic pressure peak is above that found before the infusion. Figure 2 shows the effects of the Valsalva manoeuvre on

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TABLE  
EFFECTS OF L-NOREPINEPHRINE DURING THE TENTH MINUTE OF A CONTINUOUS INFUSION

	Heart Rate/ min.	Central Venous Mean Pressure (mm. Hg)	Mean Aortic Pressure (mm. Hg)	Cardiac Output (Dye) (l./min.)	Systemic Vascular Resistance (dynes/sec./ cm. <sup>2</sup> )	L.V. Diastolic Pressure (mm. Hg)	L.V. End- diastolic Pressure (mm. Hg)	L.V. Systolic Pressure (mm. Hg)	L.V. Stroke Vol. (ml.)	L.V. Stroke Work (g./m.)	Central Blood Vol. (ml.)
Control (N=7)											
Mean .. ..	91	4.5	126	5.98	1,680	0.5	3.6	154	66	8.11	775
S.D. ± .. ..	16.8	1.5	30.4	2.09	741	0.3	1.8	48.9	28.3	6.6	298
During l-norepinephrine (N=7)											
Mean .. ..	78	11.5	157	5.82	2,110	6.5	9.0	219	74	10.87	862
S.D. ± .. ..	15.4	3.2	38.3	2.06	851	3.4	6.0	71.2	23.6	7.2	321
Significance of difference	<0.05	<0.01	<0.01	>0.1	<0.05	<0.01	<0.05	<0.05	<0.05	<0.01	>0.1

L.V. = Left ventricular.

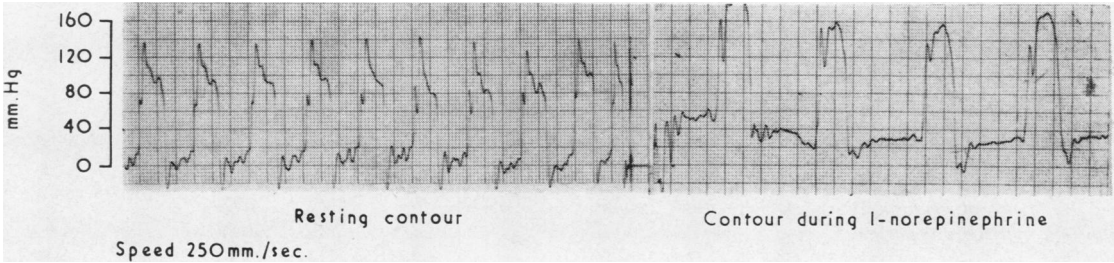


FIG. 1. Left ventricular diastolic pressure.

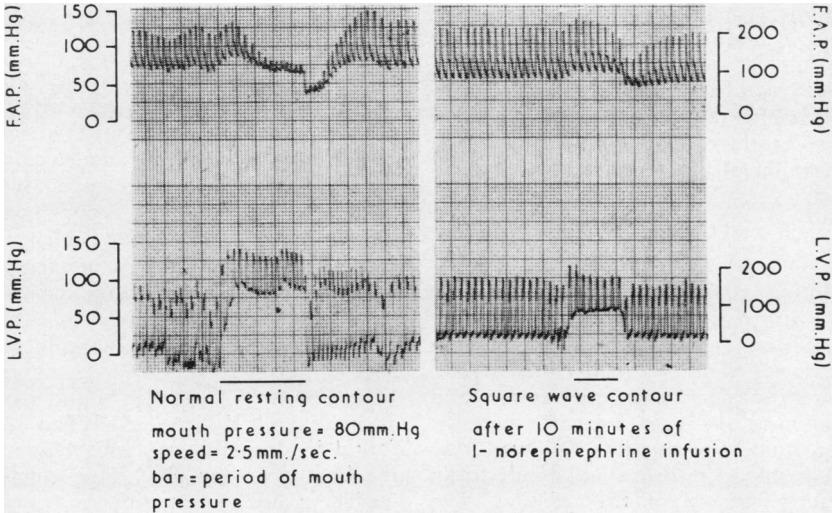


FIG. 2. Effects of Valsalva manœuvre on left ventricular (L.V.P.) and femoral artery (F.A.P.) pressures.

the left ventricular and femoral artery pressures before and during the tenth minute of *l*-norepinephrine infusion.

The Table shows the means of the seven studies and reveals a significant rise in mean left ventricular diastolic pressure (6.0 mm. Hg) and mean left ventricular end-diastolic pressure after *l*-norepinephrine. The difference between the latter pressures is 5.5 mm. Hg. The mean left ventricular systolic pressure also exceeded that found at rest. The left ventricular stroke volume was greater than at rest but principally as a function of the reduced heart rate.

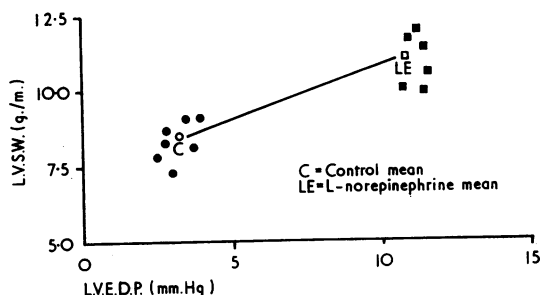


FIG. 3. Left ventricular stroke work curve after 10 minutes' infusion of *l*-norepinephrine.

Figure 3 shows the left ventricular stroke work in relation to left ventricular end-diastolic pressure and indicates an obvious shift to the right arising from the uniform elevation in left ventricular end-diastolic pressure.

The Table also provides the means concerning left ventricular stroke work which is increased in the presence of a significant rise in mean left ventricular end-diastolic pressure. There was no change in the central blood volume after 10 minutes of *l*-norepinephrine infusion.

#### DISCUSSION

The slow evolution of the 'square wave' response in the patients infused with *l*-norepinephrine in the present series is identical with that noted in a previous study (O'Neill and Cudkowicz, 1965). Approximately 10 minutes' infusion was required before unequivocal 'square wave' patterns emerged, and this consistently followed the maximum rise in blood pressure and bradycardia during the fourth minute of the infusion. The current study also shows that during the tenth minute of the infusion not only the central venous pressures but also the left ventricular diastolic

and end-diastolic pressures were significantly higher than before the infusion, whereas no change was demonstrable in the cardiac output. Systemic vascular resistance and left ventricular stroke work were still above the resting level. The slight mean increase in the central blood volume was statistically not significant.

These findings accord with observations concerning the action of *l*-norepinephrine on the lesser circulation as previously reported and show a possible back pressure effect between the left ventricular end-diastolic pressure and the right atrial diastolic pressure (Cudkowicz and O'Neill, 1964). The total mean diastolic pressure elevation across the lesser circulation at the end of the tenth minute of *l*-norepinephrine infusion is 6.1 mm. Hg (see Fig. 4) (Cudkowicz and O'Neill, 1964).

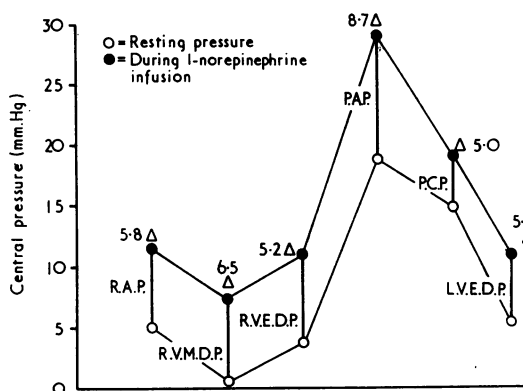


FIG. 4. Changes in central diastolic pressures during infusion of *l*-norepinephrine.

The time component seems critical in the conversion of the normal arterial blood pressure response to Valsalva's manoeuvre during *l*-norepinephrine infusions in man. It appears that haemodynamic changes occur in the course of such a continuous infusion which may yield conflicting results unless measurements are made at definite time intervals. Dunér and von Euler (1957) noted a decline in systemic blood pressure during prolonged infusion of *l*-norepinephrine in cats; and similar observations were reported by Lever, Mowbray, and Peart (1961) and more recently by Weglarz and Killip (1963). The latter observers found in dogs that systemic blood pressure rises maximally in the first four minutes and then begins to fall. The peripheral vascular resistance at the end of the tenth minute of the infusion was lowered by a mean of 22%. More recently Moss, Vittands, and Schenk (1966), Schenk and Moss



(1966), and Schenk, Galbreath, and Moss (1966) showed in dogs that cardiovascular performance was augmented for the first 15 minutes of an *l*-norepinephrine infusion, but this effect was not sustained. Thereafter there was a dose-related decline in cardiac output, systemic pressure, and left ventricular work, and an increase in the calculated peripheral vascular resistance. At the highest *l*-norepinephrine dose rate employed, significant left ventricular failure developed by the second hour. These same authors also demonstrated cardiac lesions consisting of focal degenerative necrosis of myofibrils and sub-endothelial haemorrhages. In addition, in dogs infused with *l*-norepinephrine, 1 to 4  $\mu\text{g./kg./min.}$ , a rapid and dose-related increase was observed in serum lactic dehydrogenase (LDH) and specifically of the LDH isoenzymes normally present in the heart.

The slow rise in the right atrial filling pressure accompanying the continued infusion of *l*-norepinephrine over at least 10 minutes and the emergence of a 'square wave' pattern during Valsalva's manoeuvre suggest a change in myocardial contractility following the maximum constriction of the peripheral arterioles. This is evidenced by the elevation in right atrial and left ventricular end-diastolic pressures in the presence of a minor increase in stroke volume. Sonnenblick and Downing (1963) have shown that, at a constant blood pressure, norepinephrine increases the work performed at any left ventricular end-diastolic pressure by augmenting the stroke volume. Yurchak, Rolett, Cohen, and Gorlin (1963) reported that during an infusion of *l*-norepinephrine in man the left ventricular end-diastolic pressure rises progressively with increasing after-loading. A prolonged infusion of *l*-norepinephrine, producing a bradycardia and probable efferent vagal effects on human myocardial contractility, appears to differ in its effect from that obtained experimentally by stellate ganglion excitation where the heart rate is kept constant by independent pacing. This leads to a shift to the left of the left ventricular work curve. A comparable state in man may occur during effort, but there is no satisfactory evidence of an elevation in the right or left ventricular diastolic pressures, and the associated 'square wave' response to Valsalva's manoeuvre during the *l*-norepinephrine infusion seems to depend on a net effect of the infused catecholamine and the efferent action of the vagal baroreceptor reflex. The elevation in systemic blood pressure following peripheral arteriolar constriction at the inception of the infusion exerts a powerful stimulus

on the vagal and glossopharyngeal baroreceptor afferents of the aorta and carotid sinus respectively, which is similar to that operative in phases 1 and 4 of the normal Valsalva response. The efferent effect is principally an early and significant bradycardia. Apart from this chronotropic vagal effect, actions on the myocardium need clearly to be considered. Little information is available concerning the myocardial effects of efferent vagal excitation in man, but experimentally the vagi have recently been shown to exert a negative inotropic effect on ventricular contractility (Sarnoff and Mitchell, 1961; DeGeest, Levy, and Zieske, 1964; and DeGeest, Levy, Zieske, and Lipman, 1965).

Sarnoff and Mitchell (1961) provided some information concerning vagal efferent effects on the myocardium by stimulating the cardiac end of the cut vagus in dogs. This brakes the cardiac rate, depresses atrial contraction, and elevates both the right and left mean atrial pressures; the cardiac output falls and the plot of the mean left atrial pressure against the left ventricular stroke work shifts to the right. A shift to the right of the left ventricular work curve obtains in man as soon as the left ventricular end-diastolic pressure rises significantly in the course of a prolonged infusion of *l*-norepinephrine.

It is probable that during a prolonged infusion of *l*-norepinephrine efferent vagal effects other than the chronotropic alter myocardial contractility. The net effect on the myocardium of such an infusion over 10 minutes and more indicates some decay in initial positive inotropy with a predominantly negative inotropic action (Dunér and von Euler, 1957) at the time of the emergence of a 'square wave'. The 'square wave' response to Valsalva's manoeuvre pin-points these net effects and provides indirect evidence of a critically elevated left ventricular end-diastolic pressure.

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