Norepinephrine Content of Thoracic Duct Lymph During Tachycardia (36040)

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The storage, release and transport of endogenous and exogenous norepinephrine (NE) has been thoroughly investigated (1). NE is stored in sympathetic nerve endings and is released during stimulation of the sympathetic nervous system. Several pathways for disposition of the released norepinephrine exist. Some is bound to the receptor sites and causes a physiological response characteristic of the system involved. A small amount is enzymatically changed to less active pharmacological products. The majority of excess NE is rebound by the nerve endings, and a small amount is washed out by the blood into the venous circulation. The "washout" (2) venous blood NE is either enzymatically degraded in the lungs, liver, and kidney, or excreted in the urine unchanged, or rebound on recirculation by the storage sites at the nerve endings.

It seemed logical that some of the excess NE would enter the lymphatic system. This study was designed to determine whether the sympathetic stimulation that results from ventricular tachycardia would cause a rise in the NE content of the thoracic duct lymph.

Methods. Eight dogs, weighing between 13 and 26 kg, were anesthetized by the intravenous administration of α-chloralose (100 mg/kg). Following tracheostomy, a median sternotomy was performed and extended laterally along the left seventh intercostal space. Respiration was then maintained by a Harvard respirator. The animal was placed in a right lateral position; and the peripheral end of the thoracic duct was cannulated with a polyethylene tube to allow the lymph to be collected in a graduated cylinder packed in ice. The pericardial sac was opened and two fish hook electrodes were placed in the apex of the left ventricle for inducing ventricular tachycardia with a Grass stimulator. The left femoral artery was cannulated and the mean arterial blood pressure (MABP) was measured with a P23 AA Statham strain gauge. A polyethylene tube was placed in the right foreleg vein for the administration of a 5% glucose in water solution (250 ml/hr). The MABP and the electrocardiogram (ECG) were continuously recorded with an Electronics for Medicine DR8 research recorder.

The thoracic duct lymph (TDL) was collected before, during, and after bouts of ventricular tachycardia of sufficient degree to cause an immediate lowering of the MABP. In eight dogs, 20 bouts of ventricular tachycardia were carried out. Two bouts (T1 and T2) were completed in all dogs; and, in four, a third bout (T3) was also performed. All collection periods lasted 30 min and the sequence was control (C), ventricular tachycardia (T1), recovery control (RC1), T2, RC2, T3, and recovery (R). The rhythm was confirmed by the ECG and the measurements of the MABP and heart rate (HR) were made from the record at the midpoint in each collection period.

Following column chromatography (3), the trihydroxyindol method (4) was utilized with 6-mercaptopropionic acid stabilization (5). The fluorescence was determined utilizing a Turner Fluorometer (Model No. 111) and high-sensitivity door. The NE liberated in the thoracic duct lymph is reported as nanograms per minute (ng/min). Column recoveries for pure NE solution in this experimental range were 106.1 $\pm$ 1.2% (mean $\pm$ SEM).

Results. A rise in the NE content of the TDL was seen in 19 of the 20 bouts of tachycardia. The mean $\pm$ SEM values are shown in Fig. 1. The NE rise in T1 and T2 was similar (7.09 $\pm$ 1.06 and 7.16 $\pm$ 1.48

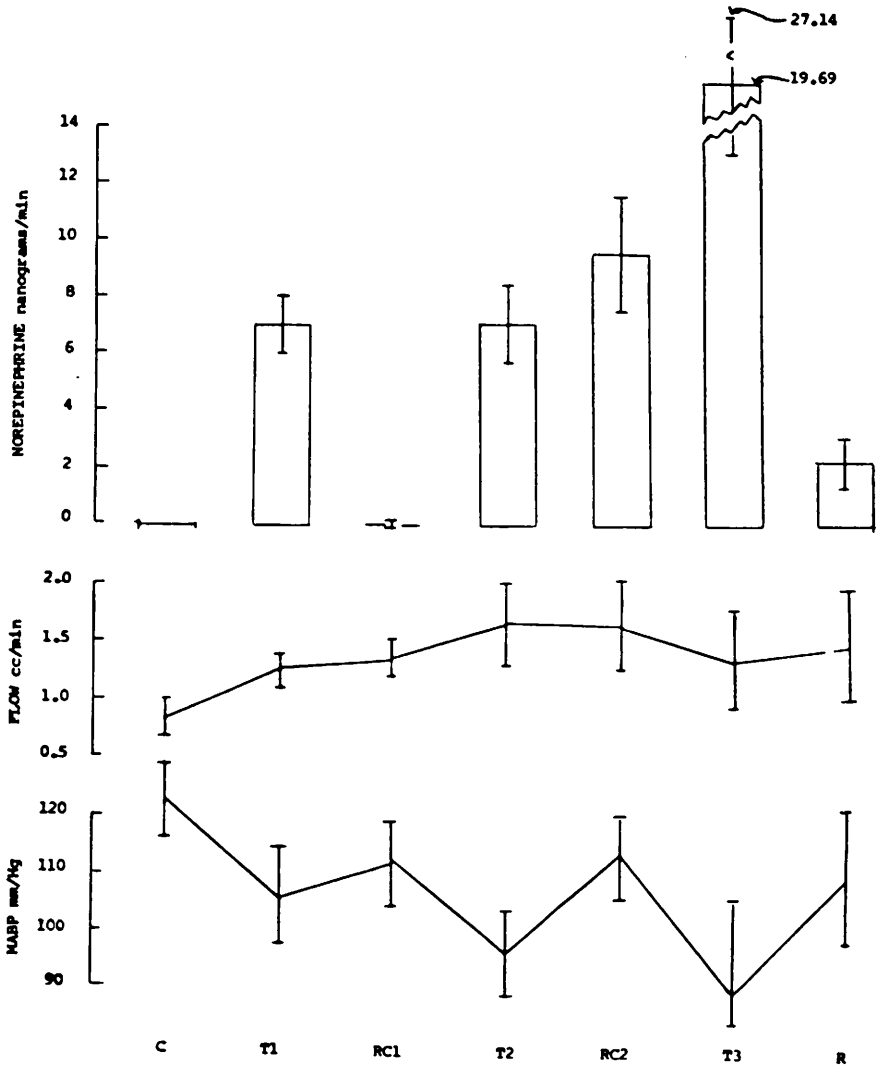

FIG. 1. The thoracic duct lymphatic content of norepinephrine (ng/min), lymph flow (ml/min), and mean arterial blood pressure (MABP) (mm/Hg) are given (mean ± SEM) during the following 30 min periods: control (C), ventricular tachycardia (T1), recovery control (RC1), ventricular tachycardia repeat (T2), RC2, T3, and recovery (R).

ng/min, respectively) and highly significant ($<.001$). The NE level failed to return to control levels following T2. The third bout of tachycardia (T3) resulted in a NE rise in three of the four animals. One animal showed a fall in NE content during T3 and this resulted in the wide variability ($<.1$). Following T3, the recovery levels again fell towards the initial control values.

The MABP immediately fell to its lowest level during each bout of tachycardia. It then partially recovered, but never rose to control levels. The mean values of the MABP taken at the midpoint of the respective periods are shown in Fig. 1. The changes in MABP were reciprocally related to the changes in NE during the periods of tachycardia. This is shown in Fig. 2, and the correlation coefficient ($r = 0.49$) was significant ($<.05$). The change in the TDL NE for all bouts of tachycardia was 6.93 ± 0.96 ng/min (mean difference ± SED) ($<.001$). The change in MABP was

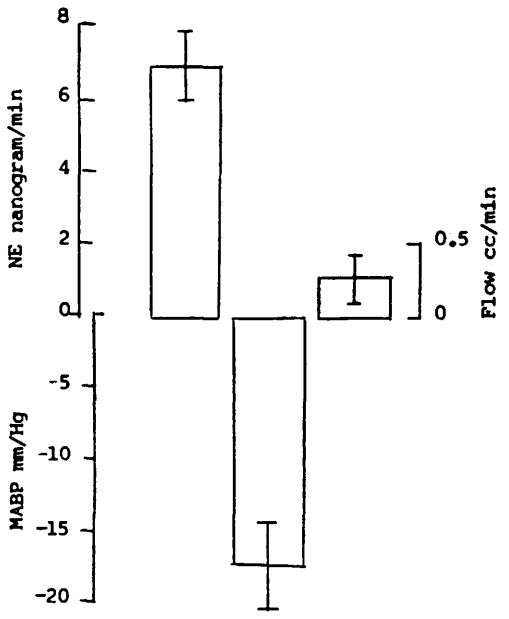

FIG. 2. The changes (mean difference ± SE of difference) in the norepinephrine (NE) content of the thoracic duct lymph (ng/min), mean arterial blood pressure (MABP) (mm/Hg), and lymph flow (ml/min) seen during 20 bouts of ventricular tachycardia in eight dogs are shown.

-17.5 ± 2.8 mm/Hg (<0.001). The change in flow was 0.28 ± 0.15 ml/min ($<.1$).

The changes induced by the first bout of tachycardia were further analyzed by a Wilcoxon Signed Rank test[1] utilizing the C and T1 data for the MABP, TDL NE, and flow. During T1, the blood pressure fell ($p < .01$), the NE rose ($p < .005$), and the lymphatic flow increased ($p < .01$).

Discussion. A significant rise in TDL NE was demonstrated during ventricular tachycardia. This most likely results from reflexogenic stimulation of the sympathetic nervous system in response to the tachycardia-induced fall in arterial pressure. Thus, the thoracic duct lymph does transport NE away from the tissue level and contributes to the "washout" phase of NE.

The importance of this newly recognized route of transport cannot be ascertained by these experiments. The TDL NE concentration is similar to the arterial NE changes induced by tachycardia (6). This would indicate that the lymphatics play a minor role in NE transport, since the difference in volume and flow of these two system is so great. The role of the lymphatics may, however, become more important under circumstances of decreased venous flow or changes in capillary filtration and reabsorption. Certain diseases such as cirrhosis (7), cardiac failure (8), and nephrosis (9) influence lymphatic drainage markedly. It has also been shown that acute changes such as a rise in systemic venous pressure (10) and acute cardiac tamponade (11) influence lymphodynamics.

Hormonal production and/or tissue uptake studies should theoretically be based on not only arterial–venous concentrations and flows, but also should take into account the lymphatic clearance. This may assume even more importance in some experimental situations wherein perfusion of organs is carried out under abnormal conditions of pressure, flow, osmotic gradients, pH, and/or oxygenation levels. Conditions such as these, which according to the Starling concept (12, 13), have long been known to influence lymphatic drainage.

The TD lymphatic system may likewise be of more significance for other endocrine glands since lymphatic systems bypass the liver and would empty these active substances directly into the venous blood. Thus, by bypassing the liver, the biological active substance would not be subjected to degradation and/or binding to proteins and, hence, be in a more active form. This would especially be true of insulin since this hormone is known to enter the general circulation through the portal vein where 50% of the insulin is removed by the liver (14, 15). Insulin is also known to enter the general circulation via the thoracic duct where no binding or degradation would occur (16).

The experiments were designed to determine if reflexogenically released NE excess would be transported away from the release site by the lymphatic system. This fact was verified in these experiments. The recovery periods were carried out to allow repeated bouts of tachycardia in the same animal. The cause for RC2 remaining high, even though RC1 and

[1] Performed by the Southern Research Support Center, VA Hospital, Little Rock, AR.

RC3 returned to or toward control, can only be speculative because of the experimental design. Time sequence alone would not seem to be the answer, since each period lasted 30 min. The cause of this phenomena remains unanswered in these experiments.

Summary. An increase in the NE content of TDL has been demonstrated during ventricular tachycardia in this canine preparation. This increase, under normal circumstances, may play a minor role in the venous washout phase. It is suggested that this lymphatic transport of biological active substances may play a more important role under various pathological states where pressure and/or flow of lymph are markedly altered.

The authors are grateful for the technical assistance of Samuel Shuler (Biochemist) and John Turner (Biological Animal Technician).

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Received July 26, 1971. P.S.E.B.M., 1971, Vol. 138.