Influence of Levarterenol on Portal Venous Flow in Acute Hemorrhage

By MATTHEW N. LEVY, M.D.

With the collaboration of Arthur F. Flatley II, B.S. and Harrison Zieske, Jr.

In anesthetized dogs, the effects of hemorrhage alone upon the mesenteric circulation have been compared with those of hemorrhage plus l-norepinephrine. With norepinephrine, the portal venous flow is slightly less than in the case of untreated hemorrhage.

In view of the significantly higher blood pressure during the norepinephrine infusions, however, the mesenteric resistance is considerably greater during infusions of this agent than in untreated hemorrhage.

It has recently been demonstrated that during hemorrhagic hypotension, infusion of l-norepinephrine (levarterenol) increases cardiac output to or toward control levels.1-3 This change is associated with a considerable redistribution of the systemic blood flow.4 Furthermore, evidence has been accruing which indicates that, in certain vascular beds, this agent may exert an action upon blood flow opposite to that observed with normal blood volumes. For example, although norepinephrine ordinarily reduces renal blood flow, it may actually improve the flow appreciably during hemorrhagic hypotension.5-7

The effects of norepinephrine upon the splanchnic circulation in normovolemic animals has been investigated extensively, but adequate data relative to hemorrhagic conditions are scanty. In their studies of hemorrhagic shock, Frank and his collaborators4 determined the influence of norepinephrine upon hepatic venous outflow in 6 experiments. Four of these measurements were made during the post-transfusion phase of shock, and only two during the oligemic stage (personal communication). In view of the critical role played by this region in hemorrhagic shock, further information concerning flow during hypovolemia was deemed desirable. In the present study, the influence of norepinephrine infusions upon mesenteric blood flow was determined during a standardized bleeding procedure, and the observed changes were compared with the effects induced by hemorrhage alone.

METHODS

Fourteen experiments were performed upon mongrel dogs anesthetized with sodium pentobarbital (30 mg./Kg.). Mean arterial pressure was recorded optically from a femoral artery by means of a Gregg manometer. Portal venous outflow was measured from a cannula inserted into the portal vein at a point midway between the liver and the junction with the splenic vein. Just prior to insertion of the cannula, the portal vein was ligated on the hepatic side of the point of cannulation. Heparin* (350 units/Kg. initially, and 500-1,000 units every half hour thereafter) was administered to prevent clotting. Wide-bore plastic tubing was used to connect this cannula to a glass L-tube which was placed just above the open mouth of an aspirator bottle. This bottle, which was equipped with a side arm near its bottom, was supported by a platform which rested upon the actuating pin of a Statham strain gage. In this manner, venous outflow was recorded optically by the method of Alexander,5 except that a carrier amplifier was employed to drive a Hathaway galvanometer. The side arm of the aspirator bottle was connected by plastic tubing to a polyethylene catheter which was inserted into the superior vena cava via the right external jugular vein. A solenoid valve was inserted into this line, and was actuated by the carrier amplifier in such a manner that the line was closed when the bottle became almost empty.

*Supplied through the courtesy of Dr. W. B. Kirtley, Lilly Research Laboratories.
The line was reopened when 50 to 60 ml. of blood had accumulated in the reservoir. Thus, portal flow could be recorded during the filling phase of this cycle. The pressure drop in the cannula and tubing was negligible at the rates of flow obtained. Therefore, the portal venous pressure remained virtually constant throughout each experiment, and was measured as the hydrostatic column from the tip of the L-tube to the level of the portal vein.

In 10 animals, the experiments were organized according to the following sequence: (a) a control period of at least 30 min. duration, (b) first hemorrhage, 20 to 30 min., (c) first recovery period, 30 min., (d) second hemorrhage, 20 to 30 min., and (e) second recovery period, 30 min. Records of pressure and flow were obtained at 3 to 5 min. intervals throughout the experiment. In each bleeding period, 20 ml. of blood per kilogram body weight were removed over a 5 min. interval. In the odd-numbered experiments, an infusion of norepinephrine was given intravenously during the first hemorrhage at a rate just sufficient to maintain the arterial pressure at the control level. The norepinephrine infusion was composed of 8 mg. 1-norepinephrine bitartrate monohydrate* (4 mg. 1-norepinephrine base) dissolved in 500 ml. of 5 per cent glucose solution. During the second hemorrhage, a 5 per cent glucose solution was given which was equal in volume to the norepinephrine solution previously administered. In the even-numbered experiments, the norepinephrine was infused during the second hemorrhage. During the first hemorrhage, therefore, the volume of isotonic glucose to be administered was computed on the basis of the average employed in the preceding experiments. During the recovery periods, all infusions were discontinued, and the blood was returned rapidly by vein after having been warmed to body temperature.

Four additional experiments are described briefly below.

**RESULTS**

In each experiment, a gradual tendency toward a diminution in portal flow was manifest, despite the maintenance of arterial blood pressure. The portal flow averaged 283 ml./min. during the control period, 262 ml./min. during the first recovery period, and 230 ml./min. during the final recovery period. The corresponding values for mean arterial pressures were 101, 98, and 102 mm. Hg, respectively. This progressive deterioration of portal flow is undoubtedly the result of the considerable surgical intervention involved in exposing the portal vein and inserting the cannula, as well as of the experimentally induced hemorrhages. In order to compare the effects of hemorrhage plus norepinephrine with those of hemorrhage alone upon the mesenteric circulation, this progressive impairment of flow must be taken into consideration. A chart was therefore prepared (fig. 1) in which all values of arterial pressure (P), portal venous flow (Q), and mesenteric resistance (R) are presented in terms of the per cent of the average of the preceding control (or first recovery) value and the succeeding recovery value. Each point in the figure represents the average of several determinations made after stabilization had occurred following hemorrhage or reinfusion.

In 7 of the 10 experiments the animals were quite sensitive to the action of norepinephrine. These experiments are represented by solid circles; horizontal solid lines in each column depict the average of these values. A hemorrhage of 20 ml./Kg., in animals not treated with norepinephrine, resulted in a reduction in pressure to 76.1 ± 9.2 per cent (mean ± S.D.) of the average control and recovery values. In the norepinephrine-treated animals, the arterial pressure was 98.1 ± 8.0 per cent, since the criterion guiding the rate of administration after bleeding was the maintenance of control blood pressure.

During the hemorrhage, there was an appreciable reduction in portal venous flow. When only isotonic glucose was given, flow fell to 76.4 ± 17.5 per cent. With the administration of norepinephrine, resulted in a reduction in pressure to 76.1 ± 9.2 per cent (mean ± S.D.) of the average control and recovery values. In the norepinephrine-treated animals, the arterial pressure was 98.1 ± 8.0 per cent, since the criterion guiding the rate of administration after bleeding was the maintenance of control blood pressure.

When these data are considered in terms of resistance to flow (pressure gradient from artery to portal vein divided by portal flow), the action of norepinephrine during hemorrhage is contrasted more clearly with the effects of hemorrhage alone. Although the differences in flow rates were not statistically

*The 1-norepinephrine was generously supplied by the Sterling-Winthrop Research Institute in the form of 4 ml. ampules of Levophed.
significant, the mean arterial pressure was significantly greater \((p < 0.001)\) during treatment with norepinephrine. With hemorrhage alone, there was no appreciable change in mesenteric resistance \((101.8 \pm 32.0\) per cent). This corresponds with the findings of other investigators. When norepinephrine was infused during the hemorrhage, on the other hand, there was a virtual doubling of resistance \((189.8 \pm 87.6\) per cent). This is significantly different \((p = 0.03)\) from the level in the untreated hemorrhage.

In 3 experiments of this series (open circles in the figure) the animals appeared to be quite refractory to the action of norepinephrine. In the 7 experiments described above (solid circles), the mean infusion rate was 2.13 \(\mu\)g./min./Kg., with a range of from 0.36 to 3.82. In the remaining 3 experiments however, the norepinephrine solution had to be infused at rates of 5.69, 6.81 and 9.30 \(\mu\)g./min./Kg., respectively, in order to prevent a drop in mean arterial pressure. In each instance, the portal flow was actually increased appreciably above control during the norepinephrine infusion. This is probably not a result of overtreatment with norepinephrine, although this is suggested by arterial pressure values of 108, 109 and 115 per cent for the open circles in the norepinephrine column in figure 1. Actually, in 2 of these 3 experiments, the arterial pressure during the infusion was identical with that during the preceding control period. In the subsequent recovery period, however, pressure fell significantly, thereby accounting for the fact that the experimental values exceeded the average control and recovery levels.

The increase in portal flow in these 3 experiments is probably attributable, in large part, to the considerable volume of isotonic glucose solution which accompanied the norepinephrine. In 2 of these experiments the hemorrhage treated with norepinephrine happened to precede the untreated hemorrhage. In these 2 cases, the same volume of fluid was given during the second hemorrhage period; in each case, it resulted in an elevation of portal flow above control. In the third in-
The lowest open circle in the portal flow column). The flow fell significantly during hemorrhage, within the range of values observed in the experiments portrayed by solid circles.

Four additional experiments were performed which further justify the conclusion that mesenteric vasoconstriction is the more typical response to norepinephrine during hemorrhage. In these experiments, dogs were bled 35 ml./Kg., and their mean arterial pressures were sustained at control levels with concentrated infusions of norepinephrine (4 mg base per 50 ml isotonic glucose in 2 dogs, and twice this dilution in the other 2 animals). Thus, only negligible volumes of fluid were administered, but very large quantities of hormone had to be employed in order to sustain pressure (12 to 28 µg./min./Kg.). Under these conditions, mesenteric flow virtually ceased in 2 experiments, and diminished to only 10 to 15 per cent of control in the other 2 experiments.

Discussion

The observation that norepinephrine improves cardiac output appreciably during hemorrhagic hypotension might lead one to predict a salutary influence of this agent upon the course of hemorrhagic shock. Furthermore, studies upon individual vascular beds have indicated that, during oligemia, norepinephrine may enhance flow through the kidneys, myocardium, brain, and adrenals. However, independent investigations upon experimental animals have consistently failed to demonstrate any significant improvement in recovery rates unless the infusions are continued for inordinately long periods of time.

The splanchnic circulation has been repeatedly shown to be of crucial importance in the development of irreversibility to shock. The present study, as well as the data reported by Frank and his colleagues, reveals that norepinephrine does not enhance splanchnic blood flow during hemorrhage. This may account for the failure of norepinephrine to improve survival rates from hemorrhagic shock, despite its salutary influence upon total systemic flow and flow through certain individual components of the systemic circulation.

Summary

Infusions of 1-norepinephrine were administered to anesthetized dogs subjected to hemorrhage amounting to 20 ml./Kg. These infusions were given at a rate just sufficient to maintain arterial pressures at control levels. In 7 out of 10 cases portal venous flow was reduced to an average of 61.4 per cent of control. This was somewhat less than the reduction in flow engendered by an equivalent hemorrhage, but treated only by isotonic glucose infusions of comparable volumes. The mesenteric resistance was not altered during the hemorrhage periods not treated with norepinephrine. With infusions of this agent, however, a twofold increase in mesenteric resistance was observed during hemorrhage. The remaining 3 dogs appeared to be refractory to norepinephrine during hemorrhage. In these cases, such large volumes were infused in an effort to sustain mean arterial pressure that an actual increase in portal flow was produced.

In 4 additional experiments, very concentrated infusions of norepinephrine were administered during hemorrhage amounting to 35 ml./Kg. Under these conditions, portal flow was severely reduced or stopped completely.

Summary in Interlingua

Infusiones de 1-norepinephrina esseva administrate a canes anesthesiate subjicite a un hemorrhagia amontante a 20 ml per kg de peso corporee. Le infusiones esseva administrate a nivello de intensitate justo suficiente pro mantenere le pression arterial al valores de controlo. In 7 ex 10 casos le fluxo in le vena portal esseva reducite a un magnitudo medie de 61,4 pro cento del magnitudo de controlo. Iste reduction esseva alique minus marcate que le reduction effectuate sub le conditiones del mesme grado de hemorrhagia quando le infusiones consisteva de comparabile volumi-nes de glucosa isotonic. Le resistencia mesen-teric non esseva alterate durante le hemor-
LEVATERENOL AND PORTAL VENOUS FLOW

rhagia non trattata con norepinephrina. Tamen, quando norepinephrina eseva infundite, un duplication del resistenza mesenteric eseva notate durante le hemorrhagia.

In le 3 remanente canes del serie de 10, il pareva haber refractorietate a norepinephrina durante hemorrhagia. In iste casos, le volumines infundite pro mantente le pression arterial medie eseva si grande que le fluxo in le vena portal eseva de facto augmentate.

In 4 experimentos additional, multo concentrate infusiones de norepinephrina eseva administrate durante hemorrhagias amontante a 35 ml per kg de peso corporee. Sub iste conditiones le fluxo portal eseva reducute severmente o stoppava completemente.

REFERENCES
Influence of Levarterenol on Portal Venous Flow in Acute Hemorrhage

MATTHEW N. LEVY

Circ Res. 1958;6:587-591
doi: 10.1161/01.RES.6.5.587

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1958 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/6/5/587

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/