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A Comparison of the Cardiovascular Effects of Sodium Nitroprusside and Trimethaphan

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In dogs anesthetized with pentobarbital–chloralose, cardiac output and blood flows of four regional vascular beds (superior mesenteric, left renal, left circumflex coronary and left femoral) were continuously monitered with electromagnetic flowmeters. Arterial blood pressure and heart rate were also measured. Hypotension was induced with intravenous infusions of sodium nitroprusside and trimethaphan for 5–16 min to produce comparable reductions of mean arterial pressure (32 mm Hg or 26 per cent with nitroprusside and 37 mm Hg or 31 per cent with trimethaphan). Cardiac output also decreased, but to a lesser extent (11.5 per cent with nitroprusside and 12.5 per cent with trimethaphan). Thus, total peripheral resistance was consistently decreased. Nitroprusside caused slight tachycardia, while trimethaphan produced bradycardia. Both drugs decreased mesenteric blood flow and increased mesenteric vascular resistance. Renal blood flow was maintained or increased with nitroprusside; thus, renal vascular resistance decreased; with trimethaphan, renal blood flow decreased and renal vascular resistance did not change. Both nitroprusside and trimethaphan reduced coronary blood flow; the reduction was more pronounced with the latter. Nitroprusside affected femoral blood flow minimally, with a slight reduction of femoral vascular resistance. In contrast, trimethaphan increased femoral blood flow and markedly decreased femoral vascular resistance. Redistribution of cardiac output favoring the dilated skin and muscle vascular beds appears to be an important undesirable effect of trimethaphan. (Key words: Anesthetic techniques, hypotension, induced; Heart, cardiac output; Blood pressure, peripheral vascular resistance; Heart, blood flow, myocardial; Kidney, blood flow.)

SODIUM NITROPRUSSIDE (Nipride) and trimethaphan camsylate (Arfonad) are frequently used by intravenous infusion to produce controlled hypotension during general anesthesia. The hemodynamic effects of both drugs have been well studied.[1-9] While cardiac output is usually well maintained during sodium nitroprusside infusion,[2,6-9] variable changes have been reported to occur with trimethaphan.[1,3-5] Both drugs markedly decrease total peripheral resistance. Decrease of vascular resistance probably occurs in many peripheral beds. However, changes in a given bed depend on a multitude of factors. In addition to changes in perfusion pressure and cardiac output, blood flow may be altered by a direct action of the drugs on vascular smooth muscle, by changes in sympathetic activity through baroreceptor reflexes, and by local autoregulatory mechanisms. Thus, during the hypotensive state, redistribution of blood flow in regional beds is likely to occur. Underperfusion of vital organs remains one of the major risks of controlled hypotension.[10] The present study was designed to measure changes of blood flow in some of the major regional vascular beds (coronary, renal, mesenteric and femoral), as well as the hemodynamic changes during controlled hypotension induced by nitroprusside compared with trimethaphan infusion.

Methods

The experiments were carried out on 24 mongel dogs of either sex, weighing 12–24 kg, anesthetized with sodium pentobarbital, 15 mg/kg, and chloralose, 50 mg/kg, intravenously. The animals were divided into two groups:

Thirteen animals in Group I were used for intravenous infusion studies. With artificial respiration, a left thoracotomy was performed. Electromagnetic flowmeter probes (Biotronic, model BL-610, and/or Narco, model RT-400, the latter with non-occlusive electronic zero reference) of appropriate sizes were placed around the main pulmonary artery (to record cardiac output) and at the origin of the left circumflex coronary artery. Through an incision in the left flank, the left retroperitoneal space was entered and flowmeter probes were placed around the superior mesenteric and the left renal arteries at their origins. A fifth flowprobe was placed on the left femoral artery at the femoral triangle. Arterial blood pressure was monitored with a Statham transducer (model 23 DC) via a cannulated right femoral artery. Heart rate was measured with a cardiotachometer triggered by the pressure trace. Nitroprusside or trimethaphan (0.01 per cent in saline solution) was infused intravenously with a Harvard variable-speed infusion pump (model 600–900 VDC).

Eleven animals in Group II were used for intra-arterial injection studies. In each animal, one or two vascular beds were studied. For the femoral bed, drugs were injected through an indwelling Medicut catheter inserted proximal to the flowprobe. In the

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mesenteric bed, drugs were injected through a cannulated small side branch of the artery proximal to the flowprobe. In the renal bed, the left renal artery was cannulated and perfused with blood from a cannulated femoral artery, with an extracorporeal flowprobe (Narco) interposed in the circuit. Drugs were injected into the tubing distal to the flowprobe. In the coronary bed, both the right and the left anterior descending coronary arteries were cannulated and were perfused jointly by blood diverted from an internal mammary artery. Blood flow was again recorded with an extracorporeal probe (Narco) inserted in the perfusion circuit and drugs were injected into the tubing distal to the flowprobe leading to both cannulated coronary arteries. In addition to permitting examination of the direct effects of the drugs on coronary blood flow, this preparation allowed us to study the effects of the drugs on heart rate and myocardial contractile force. The former was possible because the sinoatrial node, receiving its blood supply primarily from the right coronary artery,[11] was included in the perfusion circuit. Myocardial contractile force was recorded with a Walton-Brodie strain gauge arch sutured onto the anterior wall of the right ventricle.

All regional blood flow recordings, as well as arterial blood pressure, heart rate, and myocardial contractile force, were recorded continuously on a Beckman Dynograph Recorder (Type R). Phasic pulmonary blood flow and its integrated value were recorded on two additional channels of the same recorder but with a separate motor drive. Thus, intermittent recordings of stroke volume could be made using a fast paper speed. Minute cardiac output was calculated from stroke volume and heart rate.

Nitroprusside was prepared on the day of the experiment by dissolving sodium nitroferricyanide crystals (Mallinckrodt Chemical Works, analytical grade) in 0.9 per cent saline solution to make a 0.01 per cent solution. The same concentration of trimethaphan solution was made by diluting Arfonad (Hoffmann-LaRoche) with 0.9 per cent saline solution.

Statistical analyses of changes in arterial pressure, cardiac output, heart rate and calculated regional vascular resistance after infusion of each drug were made using the paired, two-tailed, Student's t test; data after infusion were compared with those of the control period. Changes observed after nitroprusside infusion were also compared to those after trimethaphan by analysis of variance. Differences were considered significant when $P < 0.05$.

Results

Intravenous Infusions

After completion of the surgical procedure, intravenous infusion of drugs began when all measured variables had remained stable for at least 15 min. In 13 dogs, nitroprusside, 0.4 to 1.55 mg, was infused over a 5–16 min period at rates of 4–10 μg/kg/min. In the same animals, trimethaphan, 0.4 to 2.65 mg, was infused in the same length of time at rates of 3–20 μg/kg/min. Infusion rates did not exceed 2 ml/min and the maximal volume given was 26 ml, over a 16-min period in a 16-kg animal. The sequence of infusion was varied at random. The rate of infusion was adjusted to produce a 25–50 mm Hg decrease of mean arterial blood pressure. The infusion was terminated after all measured variables had remained stable for at least 2 minutes. After complete recovery from infusion of one drug, at least 30 min was allowed to elapse before infusion of the second drug began.

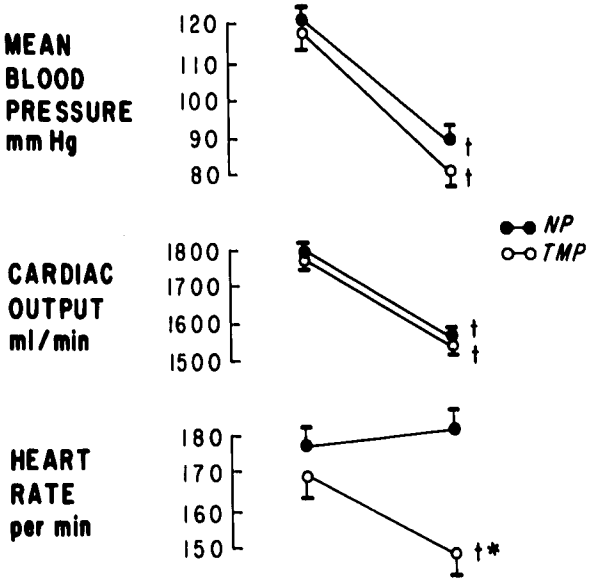

FIG. 1. Changes in mean blood pressure, cardiac output, and heart rate after intravenous infusions of sodium nitroprusside (NP) and trimethaphan (TMP) in 13 experiments. † denotes a significant change from control; * denotes significant difference of changes seen after NP compared with TMP ($P < 0.05$). Vertical bars are SE.

Arterial Pressure

With nitroprusside, a gradual decrease of arterial pressure ensued and a desirable level could be easily maintained with small adjustments of infusion rate. In 13 experiments, mean arterial pressure decreased 32 mm Hg, from 121 ± 4.39 to 89 ± 3.91 mm Hg, or 26 per cent ($P < 0.001$). Hypotension was not so easily controlled with trimethaphan. When arterial pressure began to decrease, infusion rates often had to be reduced drastically to prevent excessive hypotension. In 13 experiments, mean arterial pressure decreased 37 mm Hg, from 118 ± 3.81 to 81 ± 4.16 mm Hg, or 31 per cent ($P < 0.001$). This was not statistically significantly

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different from the decrease induced by nitroprusside (see fig. 1).

Cardiac Output

Changes in minute cardiac output were similar with the two drugs, although there was considerable variation from experiment to experiment. During the first minute or two of infusion with either nitroprusside or trimethaphan, while arterial pressure was declining, minute output increased, primarily from the increased stroke volume. Occasionally, when the onset of hypotension was gradual and the magnitude of hypotension was small (in three nitroprusside and one trimethaphan experiments), the increased output persisted throughout the infusion period. In all of the remaining experiments, outputs gradually decreased to levels below control. For all 13 experiments, at the end of infusion, cardiac output decreased from a mean of 1,787 ± 131 to 1,570 ± 120 ml/min, or −11.5 per cent, with nitroprusside ($P < 0.02$), and from 1,769 ± 176 to 1,545 ± 153 ml/min, or −12.5 per cent, with trimethaphan ($P < 0.002$). These decreases were not statistically significantly different from each other (see fig. 1).

The proportionally greater reduction in blood pressure than cardiac output led to consistent decreases in calculated peripheral resistance that averaged −15 per cent with nitroprusside and −21 per cent with trimethaphan.

Heart Rate

Heart rate responded differently to nitroprusside and to trimethaphan. With nitroprusside, heart rate changes were minimal and variable, from a mean of 177 ± 5.3 to 181 ± 5.5 beats/min, or an insignificant increase of 2 per cent. With trimethaphan, however, a decrease in heart rate was seen in every instance, from 169 ± 5.5 to 148 ± 5.8 beats/min, or a decrease of 12 per cent ($P < 0.001$; see fig. 1).

Two representative experiments are illustrated in figures 2 and 3. In the experiment shown in figure 2, nitroprusside and trimethaphan produced similar decreases in arterial pressure (30 and 35 mm Hg, respectively). Reduction of cardiac output was less with nitroprusside than with trimethaphan. Slight tachycardia occurred during nitroprusside infusion, while heart rate decreased during trimethaphan infusion. In the experiment shown in figure 3, nitroprusside also produced a 30 mm Hg reduction of

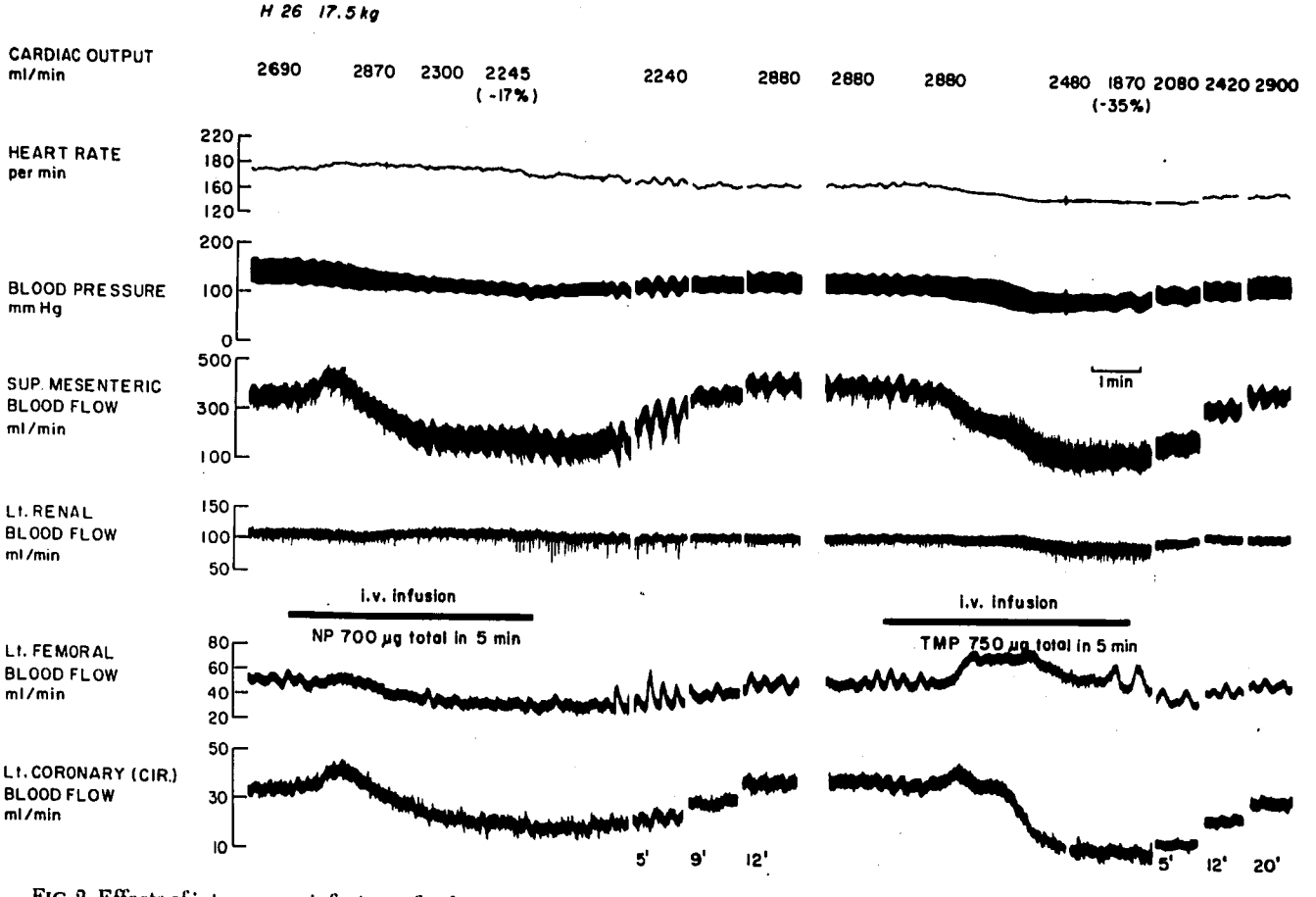

FIG. 2. Effects of intravenous infusions of sodium nitroprusside (NP), 8 µg/kg/min, and later of trimethaphan (TMP), 8.6 µg/kg/min, in a representative experiment. For description, see text.

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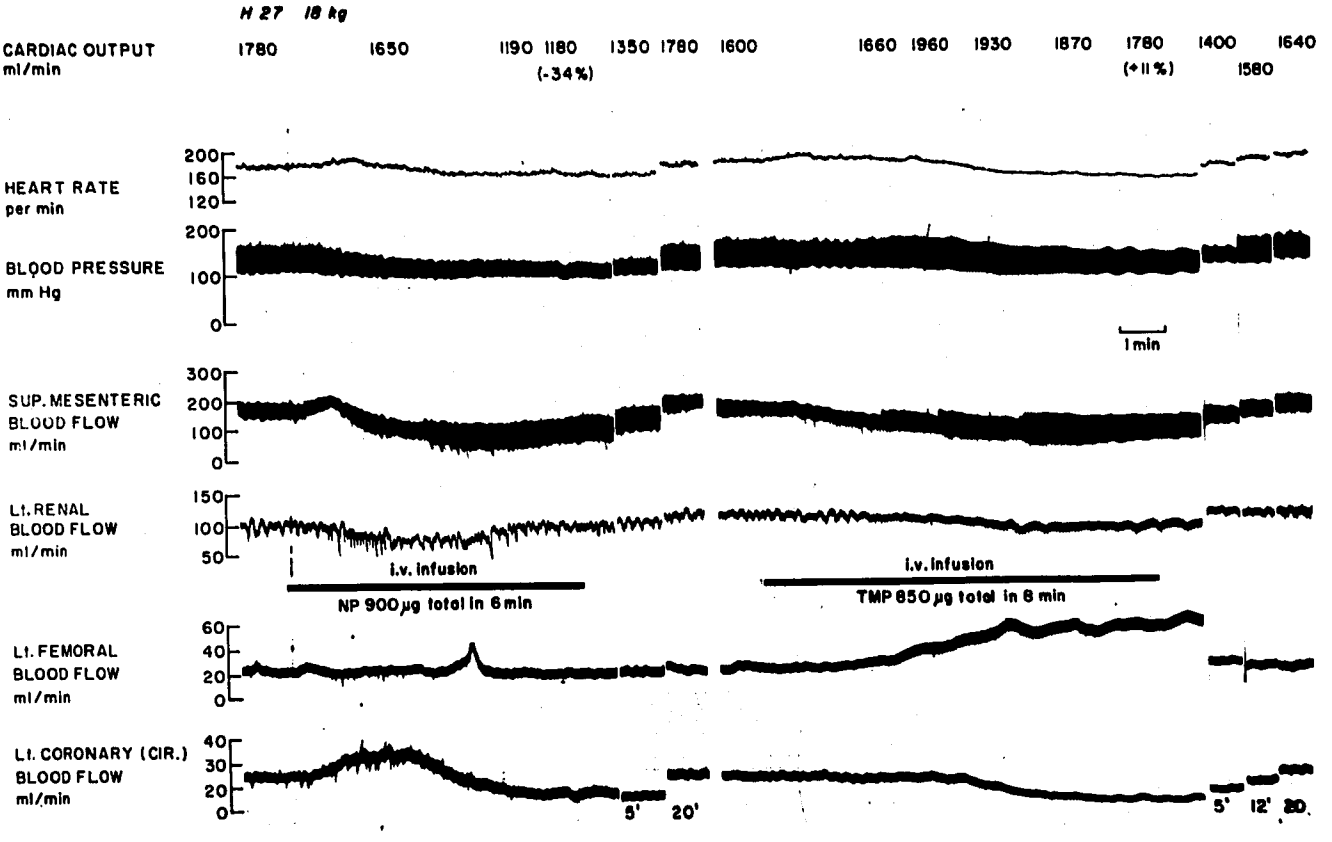

FIG. 3. Effects of intravenous infusions of sodium nitroprusside (NP), 8.3 µg/kg/min, and later trimethaphan (TMP), 5.9 µg/kg/min, in another representative experiment. For description, see text.

mean arterial blood pressure. Tachycardia was absent, and thus the minute cardiac output decreased more markedly. In the same experiment, trimethaphan was infused at a slow rate. Arterial pressure did not fall until 5 min after the infusion began, and at the end of infusion it fell only 20 mm Hg. Cardiac output increased before hypotension occurred. With the decrease of arterial pressure, output decreased to some extent, but it was still greater than control at the end of infusion. Bradycardia developed, paralleling the time course of hypotension.

Regional Vascular Resistance

Figures 2 and 3 show that during the short course of infusion, there were rather drastic changes in regional blood flows in the vascular beds studied. Redistribution of regional blood flow appeared to follow the same pattern in spite of the variable changes in cardiac output. Regional vascular resistance, calculated from mean arterial blood pressure and blood flows at the end of the infusion period, is expressed as percentage of control, shown in figure 4.

The mesenteric blood flow always decreased precipitously and markedly with both nitroprusside and trimethaphan infusions. A transient but small increase often preceded the decrease when nitroprusside was infused (figs. 2 and 3). At the time of maximal hypotension and reduction of blood flow, calculated vascular resistance always showed an increase. This increase was more pronounced with trimethaphan (131.7 ± 13.4 per cent of control, $P < 0.02$) than with nitroprusside (118.9 + 8.9 per cent of control $P < 0.02$). Because of the large scatter, however, the increased resistances during nitroprusside and trimethaphan infusions were not significantly different from each other (see fig. 4).

Changes in renal blood flow were quite different. During nitroprusside infusion, renal flow either increased (fig. 2), or remained at control level after an initial decrease (fig. 3). Thus, there was always a reduced calculated resistance (to 81.0 ± 4.1 per cent of control, $P < 0.01$). In contrast, trimethaphan always caused a reduction of renal blood flow, even when the hypotension was minimal (fig. 3). Calculated resistance increased, but not significantly, to 110.4 ± 13.5 per cent of control (fig. 4).

Femoral blood flow either remained unchanged or decreased when nitroprusside was infused (figs. 2 and 3), resulting in a slight but insignificant decrease of calculated resistance (to 93.0 ± 7.09 per cent of control; fig. 4). With trimethaphan infusion, femoral blood flow always increased in the face of hypotension. Femoral resistance decreased. This decrease

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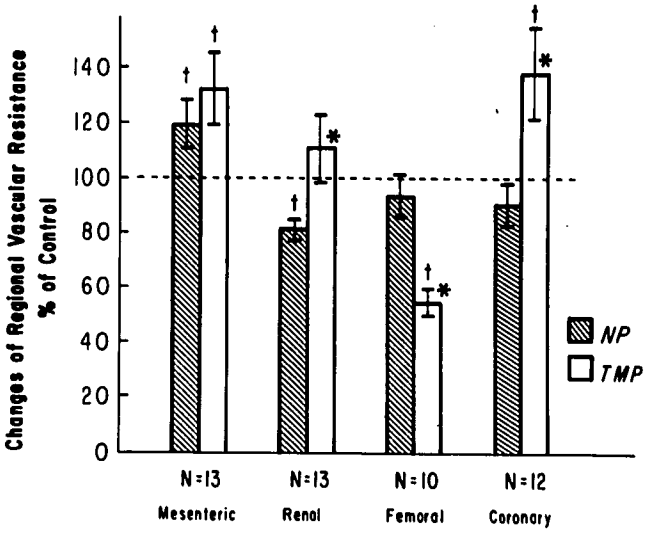

FIG. 4. Changes in regional vascular resistance, expressed as percentages of control, after intravenous infusions of sodium nitroprusside (NP) and trimethaphan (TMP). † denotes a significant change from control; * denotes significant difference of changes seen after NP compared with TMP ($P < 0.05$). Values are means ± SE from numbers of experiments shown.

was marked and consistent (to 54.1 ± 5.8 per cent of control, $P < 0.05$) and was significantly different from the decrease seen after nitroprusside ($P < 0.05$; fig. 4). When hypotension was minimal, the increase in flow was quite dramatic, as shown in figure 3. In this experiment, when trimethaphan was infused slowly and the onset of hypotension was delayed, both the decrease of mesenteric blood flow and the increase of femoral blood flow preceded the fall of arterial pressure.

Coronary blood flow usually decreased with infusions of both nitroprusside and trimethaphan, although an initial transient increase was often seen with nitroprusside infusion (figs. 2 and 3). However, trimethaphan decreased the coronary blood flow to a greater extent. The pronounced decrease in coronary blood flow during trimethaphan infusion resulted in an increased calculated resistance (to 138.0 ± 16.3 per cent of control, $P < 0.05$), compared with a slight, insignificant decrease in resistance after nitroprusside (to 90.7 ± 7.1 per cent of control; fig. 4).

INTRA-ARTERIAL INJECTIONS

In 11 experiments, nitroprusside and trimethaphan were injected intra-arterially to study their direct vasodilator effects. In each experiment, one or two vascular beds were studied. In a given bed, the same doses of nitroprusside and trimethaphan were employed. These doses ranged from 5 to 100 μg.

Although *mesenteric* vasodilation could be elicited with the lowest dose of nitroprusside employed (5 μg), the extent of vasodilation was very limited. In three experiments, doses as low as 10 μg caused maximal dilation. However, blood flow increased to only 10–25 per cent above control. Higher doses (to 100 μg) did not elicit further increase, but the duration of drug action was prolonged. The mesenteric bed was less responsive to trimethaphan; 20–50 μg elicited increases of blood flow of only 10 per cent or less. However, the duration of trimethaphan-induced vasodilation could be as long as 10 min, while the effect of nitroprusside usually lasted 1 min or less.

In four experiments, intra-arterial nitroprusside or trimethaphan injections in doses as high as 100 μg did not elicit any increase of *renal* blood flow. Usually, 50 μg or more injected into the renal artery caused a decrease of arterial blood pressure when the administered dose spilled over to the systematic circulation. When hypotension appeared, a reduction in renal blood flow often ensued.

Intra-arterial injections into the *femoral* artery were carried out in three experiments, one of which is illustrated in figure 5. Five to 20 μg of nitroprusside promptly increased femoral blood flow. The increase was dose-dependent, as much as 200 per cent above control, and evanescent, lasting about a minute. In the same experiment, trimethaphan, 5–10 μg, evoked prompt and much more pronounced vasodilation, with blood flow increases of as much as 300 per cent. The effect was also long-lasting: the vasodilating effect of a 10-μg dose lasted for 10 min. Tachyphylaxis did not develop to either drug, as these effects were reproducible in the same experiment.

In five experiments, nitroprusside and trimethaphan were injected into the coronary arteries. Figure 6 shows a representative experiment. In this, as well as the other four experiments, a small dose of epinephrine was injected first. An ensuing tachycardia verified that the sinus node was perfused by blood from the perfusion circuit. All drugs were then injected into the tubing leading to both the cannulated right and left anterior descending coronary arteries. Nitroprusside caused dose-dependent increases of coronary blood flow. Vasodilation lasted no more than a minute, like the effect of nitroprusside in the femoral bed. Further, nitroprusside had no effect on either heart rate or myocardial contractile force. Trimethaphan also caused coronary vasodilation. As in the femoral bed, the trimethaphan-induced dilation was more pronounced and longer-lasting when compared with nitroprusside. The dilation was associated with slight positive inotropy (fig. 6). The small increase in heart rate, which appeared 20 sec after injection of the 10-μg dose, was associated with a transient fall of blood pressure. Thus, tachycardia was unlikely to be the result of direct drug action on the sinus node. No tachycardia was seen in the other four experiments after intracoronary injection of trimethaphan. An interesting finding with trimethaphan was that

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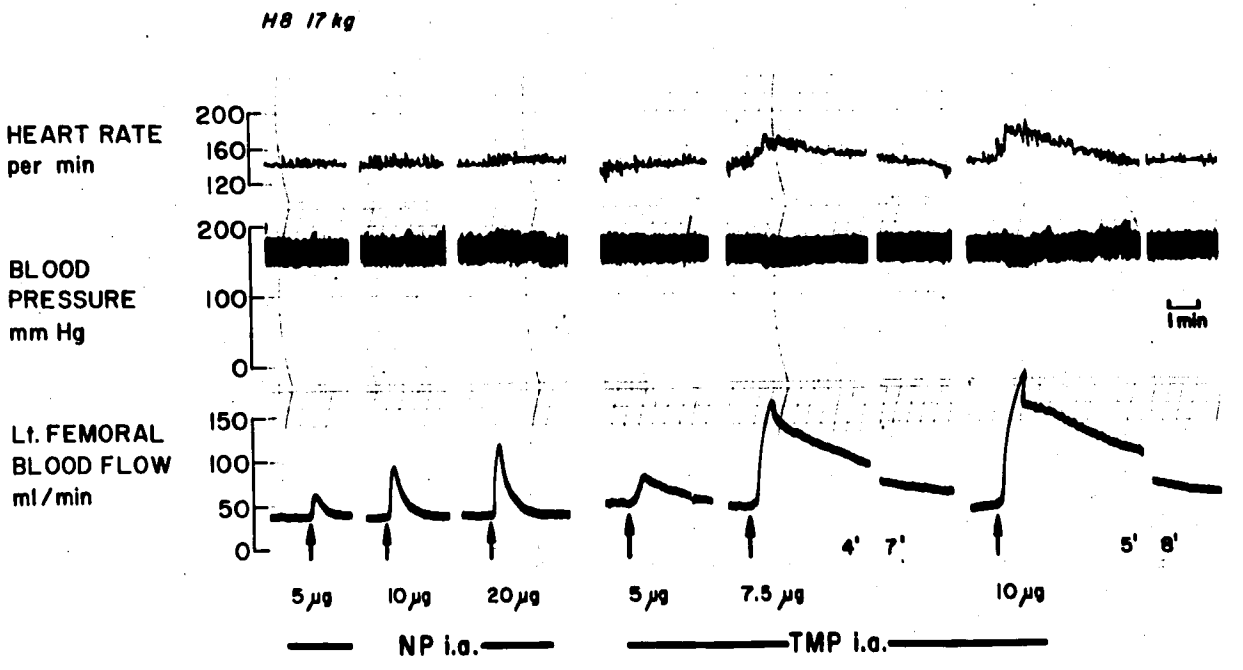

FIG. 5. Effects of intra-arterial injections of sodium nitroprusside (NP) and trimethaphan (TMP) on femoral blood flow. Note the dose-dependent increases of blood flow after either drug. Note also the more pronounced and prolonged increases after TMP injections.

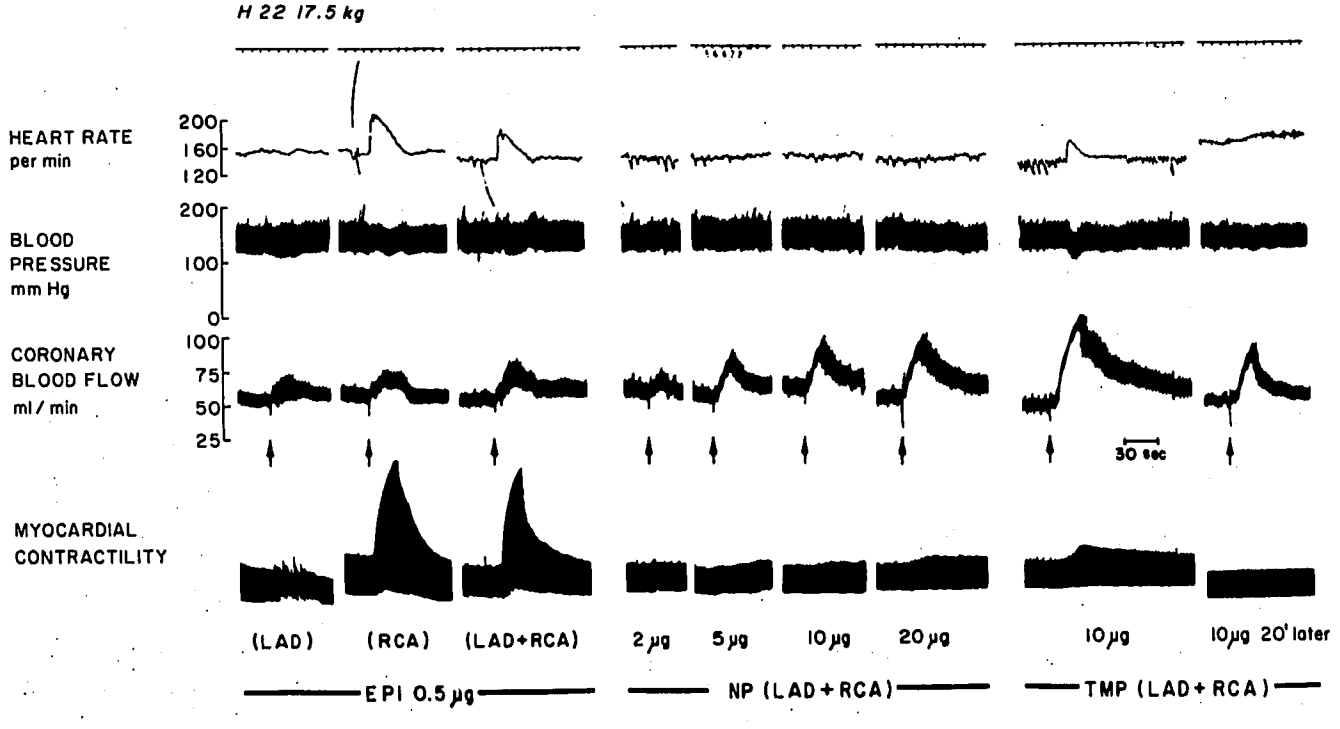

FIG. 6. Effects of intracoronary injections of epinephrine (EPI), sodium nitroprusside (NP) and trimethaphan (TMP). EPI was first injected into the left anterior descending (LAD) artery, the right coronary artery (RCA), and then into both branches (LAD + RCA) to verify that increase in heart rate was seen only when RCA, and thus the sinus node, received EPI. Note the dose-dependent increases of coronary blood flow after NP. Note also that the increases in coronary blood flow and myocardial contractility were greatly attenuated when the dose of TMP was repeated in 20 minutes.

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neither the vasodilating nor the positive inotropic action could be reproduced with subsequent injections. In the experiment shown (fig. 6), 20 min later, the vasodilating response to the same dose was halved and the positive inotropy was no longer seen. This was found to be the case in each of the five experiments. A reduced response to a given dose could be demonstrated as long as two hours after the initial injection.

Discussion

Hemodynamic Changes

The hypotensive action of nitroprusside is unquestionably due to its direct vasodilator action.[12] In the present study, vasodilation by nitroprusside was demonstrated in the femoral and coronary beds, and to a lesser extent, in the mesenteric bed. The hypotensive action of trimethaphan also has been attributed to the direct vasodilating property of the drug.[13] Although trimethaphan is a short-acting ganglionic blocking drug that liberates histamine in high doses,[14] neither ganglionic blockade nor histamine release is responsible for the decrease in blood pressure. McCubbin and Page[13] had shown that hypotension produced by small doses of trimethaphan was not affected by prior ganglionic blockade with hexamethonium, or by prior administration of antihistaminics. These authors demonstrated marked vasodilation when trimethaphan was injected into the denervated, isolated and perfused hind limb of the dog. We have confirmed this potent vasodilating action of trimethaphan in the femoral bed. However, during our short course of intravenous infusion, variable ganglionic blockade did occur, as suggested by a gradual slowing of heart rate. We verified this by injecting a small dose of a ganglionic stimulating compound, dimethylphenylpiperazinium (DMPP) intravenously before and after trimethaphan infusion in two experiments. The DMPP-induced decreases of mesenteric and renal blood flows were greatly attenuated immediately after trimethaphan infusion was terminated.

Variable changes in cardiac output, similar to those reported previously to occur in dogs and in man,[1-9] were observed during hypotension induced by nitroprusside and trimethaphan. Mean changes during nitroprusside and trimethaphan infusions, 12 per cent decreases, were quite comparable (see fig. 1). The decrease in output was perhaps more closely related to the rate of fall in arterial pressure than to the drug used. Thus, in the experiment illustrated in figure 2, the decrease in output was greater during trimethaphan than during nitroprusside infusion, while in the experiment of figure 3, output was greater than control at the end of a slow trimethaphan infusion, compared with a substantial decrease when nitroprusside was infused at a faster rate. The reduction of cardiac output was not due to a direct depressant effect of the drug on the heart. Nitroprusside had little or no effect on myocardial contraction, while trimethaphan actually caused a slight positive inotropy (fig. 6).

Tachycardia during nitroprusside infusion was minimal or absent, probably owing to the rapid heart rate prior to drug infusion. The slowing of heart rate after trimethaphan probably resulted from some ganglionic blockade in a sympathetic predominant state. This is contrary to the usual increase of heart rate seen in human subjects after trimethaphan.[4,5] The human subjects under study, either conscious or anesthetized with nitrous oxide and/or halothane, had much slower control heart rates.

Regional Vascular Resistance Changes

There were rather drastic changes in regional blood flows during the short periods of intravenous infusions of nitroprusside and trimethaphan. Despite variable changes of cardiac output, redistribution to the regional beds studied always fell into the same pattern during the hypotensive phase of each drug.

The Mesenteric Bed

The mesenteric blood flow decreased precipitously and drastically when either nitroprusside or trimethaphan was infused. Calculated mesenteric resistance increased. Net splanchnic vasoconstriction has been observed also by Ferrer *et al.*[15] after nitroglycerin administration in recumbent human subjects. There are two possible explanations for the observed decrease in mesenteric blood flow and increase in mesenteric resistance. First, as the direct vasodilating effects of both nitroprusside and trimethaphan in the mesenteric vasculature were minimal, cardiac output was redistributed to other dilated vascular beds when perfusion pressure fell, resulting in an "apparent" increase in mesenteric resistance. Second, mesenteric vasoconstriction could be also the result of reflexly increased sympathetic activity. However, the contribution of sympathetic vasoconstriction to the observed increase in mesenteric resistance was probably negligible, since the increase after nitroprusside, where reflex compensation was operative, was not significantly different from that after trimethaphan, where reflex changes were blunted by some ganglionic blockade.

The Renal Bed

While neither nitroprusside nor trimethaphan had any direct renal vasodilator effect, the change of renal vascular resistance during nitroprusside infusion was distinctly different from that seen when trimethaphan was infused. Renal resistance always decreased with nitroprusside at the end of the infusion period but remained the same or increased at the end of infusion with trimethaphan (see fig. 4). Renal vasodilation after nitroprusside was also reported by Page *et al.*[16] In our experiments, changes

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of renal resistance after nitroprusside were gradual. With the fall in blood pressure, renal blood flow either increased slowly (fig. 2), or first decreased and then returned to control level (fig. 3). This is different from the changes observed in mesenteric, femoral and coronary blood flows. In these beds, transient increases of blood flow due to the direct dilating action of nitroprusside were evident during the first minute of infusion (figs. 2 and 3), before redistribution of cardiac output began. The gradual occurrence of renal vasodilation suggests an autoregulatory mechanism. Recently, prostaglandins produced intrarenally have been implicated as the vasodilator substances mediating the renal autoregulatory response.[17] It is also known that sympathetic-nerve stimulation causes release of a prostaglandin-like substance into the renal venous blood.[18,19] Thus, it is possible that renal vasodilation during nitroprusside infusion is the result of increased intrarenal prostaglandin synthesis and release, triggered by a reflex increase of sympathetic activity when hypotension occurred. We propose that the change of renal blood flow during trimethaphan infusion can be explained on the same basis. Moyer and Handley[20] reported decreases of renal vascular resistance after single injections of ganglionic blocking compounds, including trimethaphan. In our experiments, renal resistance did not change significantly but renal blood flow decreased during trimethaphan infusion (fig. 4). The decrease of renal blood flow, however, was delayed, gradual, and moderate when compared with the immediate and precipitous reduction of mesenteric blood flow (figs. 2 and 3). It appears that autoregulation served to maintain the renal blood flow when blood pressure began to fall, until appreciable ganglionic blockade was evident. Thereafter, with decreasing sympathetic activity, autoregulation was impaired and renal vasodilation could no longer be sustained. That the decrease of renal blood flow paralleled the time course of cardiac slowing (figs. 2 and 3), an indicator of onset and progression of ganglionic blockade in our experimental setting, further supports this contention. Sivarajan *et al.*[21] found a decrease in renal blood flow in monkeys after high (T1) but not after low (T10) spinal anesthesia. Although hypotension with high spinal anesthesia was of greater magnitude, the decrease in renal blood flow could be explained also by a lack of autoregulation because of complete sympathetic blockade according to our hypothesis.

The Skin and Muscle Beds

We have confirmed that, of the four regional vascular beds studies, the femoral vascular bed is by far most responsive to the direct vasodilating actions of both nitroprusside and trimethaphan, as shown by Page *et al.*[16] and McCubbins and Page.[13] This action was particularly prominent in the case of trimethaphan. The trimethaphan-induced femoral vasodilation was not only intense but also long-lasting (fig. 5). The direct vasodilating effects of both drugs were reflected by the decreases in femoral vascular resistance when the drugs were infused intravenously. As expected, the decrease in femoral vascular resistance after trimethaphan was significantly greater than that after nitroprusside (fig. 4). While femoral blood flow usually remained close to, or decreased below, control levels during nitroprusside infusion (figs. 2 and 3), it invariably increased during trimethaphan infusion, especially when hypotension appeared gradually. Since normally about 20 per cent of cardiac output is distributed to the skin and muscle, pronounced vasodilation and increase in blood flow of the skin and muscle beds would shift a considerable portion of cardiac output to these areas.

The Coronary Bed

The dose-dependent increases of coronary blood flow after intra-arterial injections of nitroprusside reconfirmed the well-recognized vasodilating effect of nitrites on normal coronary vessels. Trimethaphan also had a direct coronary vasodilating action. This action was more pronounced than that of nitroprusside both in magnitude and in duration (fig. 6), and was quite tachyphylactic. This tachyphylaxis has not hitherto been reported, and we have no explanation for its unique appearance in only the coronary vessels. Despite the direct dilating action, coronary blood blow was not sustained during either nitroprusside or trimethaphan infusion. The reduction of coronary blood flow was so pronounced during intravenous infusion of trimethaphan that the calculated vascular resistance increased. The decrease of coronary blood flow could be secondary to reduced cardiac work and metabolism, as both arterial pressure and cardiac output were reduced. The decrease also could result from a redistribution of cardiac output, favoring areas such as the skin and muscle beds, at the expense of the coronary vascular bed.

Comparison of Nitroprusside and Trimethaphan

While both nitroprusside and trimethaphan decreased splanchnic blood flow drastically and similarly, the influences of the two agents on renal, femoral and coronary beds differed significantly. Although these changes were recorded at the end of a short (15 min or less) intravenous infusion, we assume that the same trend would apply if the infusions were continued. The hazard of major organ underperfusion during hypotension and its relationship to complications and morbidity following the procedure have been reviewed recently.[10,22] Despite marked hepatic underperfusion during controlled hypotension, which is illustrated clearly in our study

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also, impairment of hepatic function has not been reported.[10] Warner *et al.*[23] compared renal functions in patients undergoing prolonged surgical procedures with and without hypotension induced by trimethaphan. Although patients in the hypotensive group had normal renal function tests, they all had significantly reduced urinary outputs during the surgical period. Our findings of decreased renal blood flow during trimethaphan-induced hypotension, but maintained or increased renal blood flow during nitroprusside-induced hypotension, suggest that renal function is better preserved with nitroprusside. In patients who have compromised renal function, this difference may be important. Both nitroprusside and trimethaphan decreased coronary blood flow. The decrease was more pronounced when trimethaphan was infused. It cannot be predicted whether the reduced coronary blood flow was always adequate for the myocardial oxygen needs, as the latter also decreased parallel to the fall of blood pressure. A precipitous reduction of coronary blood flow is always hazardous, especially in patients who have ischemic heart disease. The hazard would be greater during trimethaphan- than during nitroprusside-induced hypotension. Myocardial infarction, although relatively uncommon, has been reported to occur after controlled hypotension by ganglionic blockade in both Little's [24] and in Grace's [25] series. Decreases of femoral resistance were seen during both nitroprusside- and trimethaphan-induced hypotension, but the decrease was far greater with the latter, often associated with marked increases of femoral blood flow. This "inappropriate" vasodilation undoubtedly contributes to shifting of blood away from vital organs and represents a true undesirable property of trimethaphan. In a study reported by Didier *et al.*,[3] in which hypotension induced by trimethaphan was used for radical mastectomy, controlled hypotension was found not always to provide a satisfactory surgical field. Bleeding in the area being operated on may have been related to the vasodilation in skin and muscle caused by trimethaphan.

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