Diazoxide Disposition and Effect on Vascular Resistance and Compliance in Dogs

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SUMMARY The disposition and systemic vascular effects of bolus intravenous doses of diazoxide (3.75, 7.5, and 15.0 mg/kg) were studied in anesthetized open-chest dogs. Blood flow (Q) and right atrial pressure (Pra) were independently controlled by a right heart bypass. The late phase disposition halftime (beta t½) of diazoxide averaged 3.4 ± 0.5 hrs (x ± SEM) with an apparent volume of distribution at steady state of 1.3 ± 0.1 liter/kg. There was a dose-related reduction in arterial pressure (Pa) with an excellent correlation between plasma diazoxide concentrations and the reduction in Pa during the post drug-distribution phase. Diazoxide increased vascular capacitance (53 ± 16, 91 ± 10, and 134 ± 21 ml after 3.75, 7.5, and 15.0 mg/kg respectively) as determined by volume changes (V) in the bypass reservoir at a constant Q and Pra. Transient changes in blood volume following an acute decrease in Pra at constant Q showed that blood was draining from two vascular compartments with different time constants: a fast time-constant compartment with a time constant of 0.052 minutes before and 0.048 minutes after diazoxide and a slow time-constant compartment with a time constant of 0.552 minutes before and 0.501 minutes after diazoxide. The major change in arterial resistance after all doses occurred in the slow time-constant compartment without a clear dose response. Arterial resistance in the fast time-constant compartment was unchanged after diazoxide 3.75 mg/kg but was reduced by an extent similar to that in the slow compartment after 15.0 mg/kg (~42% ± 9% vs ~42% ± 4%). After diazoxide 3.75 mg/kg, venous compliance of both the slow and fast time-constant compartments was increased. Larger doses of diazoxide further increased compliance of the slow time-constant compartment but reduced compliance of the fast compartment. When the circulation was considered as a single compartment, diazoxide was 4 to 6 times more active on arterial resistance than on venous compliance. When the circulation was considered as consisting of two compartments in parallel, the major effect of low doses of diazoxide was on both arterial and venous portions of vessels with a slow time constant for flow, presumably including the splanchnic circulation. Larger doses of diazoxide were required to reduce arterial resistance of vessels with a fast time constant for flow. (Hypertension 3: 225-232, 1981)

KEY WORDS • diazoxide • pharmacokinetics • concentration response • resistance • compliance • capacitance • circulation model • anesthetized dog

DIAZOXIDE, a non-diuretic benzothiadiazine, is frequently used in the treatment of patients with severe hypertension, notably those with hypertensive emergencies. Its arterial vasodilator properties have been extensively studied in animals1-4 and man.5-11 However, there are conflicting reports of its effects on veins. Rubin et al.3 reported that diazoxide reduced resistance of small vessels without altering large vein pressure. Ogilvie and Mikulic5 observed that diazoxide reduced both pre- and postcapillary resistance of the gracilis muscle vascular bed. In hypertensive man, diazoxide reduced arterial pressure and increased cardiac output with an unaltered or increased right atrial pressure and without orthostatic hypotension.7 In both normal volunteers10 and hypertensive patients,10,11 forearm venous tone or distensibility was unaltered after bolus doses of diazoxide. However, Collier et al.12 observed an equal dilator effect in forearm arterial vessels and hand veins previously constricted with noradrenaline, during infusion of diazoxide into the brachial arteries of normal volunteers.

These conflicting results may be due to different effects of diazoxide on constricted or relaxed veins. It is also possible that the effects observed on the forearm vascular bed do not represent those on the rest of the circulation. There have been no previous studies of the effect of diazoxide on total systemic venous compliance or of the comparative effects on veins in different circulatory beds. This study in dogs reports the dose (concentration) response effects of diazoxide on arterial pressure and blood-flow distribution, venous compliance, venous capacitance, and venous return by applying a model of the circulation composed of two compliant areas in parallel.19-21
Methods

Twenty-one mongrel dogs (average weight 18.7 kg, range, 16—24 kg) were anesthetized (pentobarbital 30 mg/kg) and ventilated with 40% oxygen in nitrogen by means of a controlled-volume respiratory (end-expiratory pressure, 5 cm H2O). After a right thoracotomy, sodium heparin (500 USP units/kg) was administered. A large-bore cannula with multiple holes at the tip was introduced into the right atrium. Blood returning to the right atrium was allowed to drain into a heated reservoir previously primed with 6% dextran in saline (m.w., 70,000) through a Starling resistor that could be raised or lowered to control right atrial pressure. Blood was returned to the dog from the reservoir by a Sarns double-roller pump (Model 3500) via a rigid cannula (i.d. 10 mm) placed in the main pulmonary artery through the outflow tract of the right ventricle. A clamp around the pulmonary artery with the cannula inside allowed control of blood flow through the pulmonary and systemic circulations by control of the pump output. Blood seeping into the chest cavity was returned to the reservoir via a separate drain and peristaltic pump.

Changes in reservoir volume were continuously recorded by pressure changes at the bottom of the reservoir measured by a Statham P23BC transducer and interpreted as the inverse of changes in the blood volume and vascular capacitance. Right atrial pressure was recorded via a catheter advanced into the right atrium through a femoral vein with zero reference point for a Statham P23BC transducer at the tip of the catheter. Aortic pressure was measured via a catheter advanced into the aorta through a femoral artery attached to a Statham P23AC transducer with the midthoracic level as zero reference point. Pulmonary artery pressure was measured via a catheter in the main pulmonary artery attached to a Statham P23Gb transducer. All pressures were recorded by pressure changes at the bottom of a Grass polygraph (Model 7).

Mean pressures were obtained by electronic integration.

During 45 to 60 minutes of bypass, the body temperature was maintained at 39°C, respiratory rate and volume and acid-base balance were monitored by repeated determination of arterial pH, pO2, and pCO2, and acidemia corrected by administration of sodium bicarbonate. At this time, the preparation was usually stable, as shown by a constant reservoir volume (V) at a constant pump output (Q), mean systemic arterial pressure (Psa) and right atrial pressure (PrR). Once a steady state had been achieved, the following determinations and calculations were made repeatedly; the mathematical basis for these calculations have been previously outlined by Caldini and coworkers.

Total Vascular Compliance

We measured the ratio of changes in blood volume to changes in right atrial pressure (∆V/∆PrR) in ml/cm H2O at a constant blood flow Q by rapidly changing PrR from 6.0 to ~1.0 cm H2O and observing the change in reservoir volume at a new steady state. The PrR was changed by lowering the height of the Starling resistor. The value in ml/cm H2O was the total vascular compliance C total and was assumed to be equal to (Cp + Cs) the sum of compliances in the fast and slow time-constant compartments respectively, as described below.

Time Constant for Circulatory Flow

We determined the ratio of changes in blood volume to changes in blood flow (∆V/∆Q) in minutes at a constant right atrial pressure PrR. Blood flow was increased approximately 25% by increasing the pumping rate of the Sarns roller pump and PrR kept constant by adjusting the height of the Starling resistor. The change in reservoir volume at a new steady state was recorded. This time constant applied to a two-compartment model is equal to the sum of the time constants for each compartment times their respective fraction of total circulating flow (Fr = Rv/Cp + Fr = Rv/Cp) where Fr and Fv are fractions of the total circulating flow in the fast and slow compartments and Rp, Cp, and Rv, Cp are the time constants (product of resistance times compliance) for venous drainage of the fast and slow compartments respectively.

Overall Resistance to Venous Return (RV)

We calculated the overall resistance to venous return in cm H2O/liter · min−1 from the ratio of (∆V/∆Q) over (∆V/∆PrR).

Venous Return over Time Curve

The change in reservoir volume over time following rapid reduction of PrR from ~6.0 to ~1.0 cm H2O was plotted semilogarithmically to derive two exponentials. The plot of change in reservoir volume over time as a proportion of the total change was biphasic, indicating drainage of blood from two different regions with different time constants for flow. A representative volume over time curve during the baseline period of an experiment is shown in figure 1. Two exponentials derived by the method of residuals were used to calculate venous compliance, venous resistance and fraction of cardiac output for each of two parallel compliant regions, as outlined below. In this model it was assumed that the peripheral circulation was composed of two compliant areas in parallel, each having distinct arterial and venous resistance, venous compliance, and fraction of total cardiac output (fig. 2). One compartment was characterized by a relatively fast time constant for blood flow (Rv,Cp) and one characterized by a slow time constant (Rv,Cp). These time constants were calculated from the two exponentials in units of minutes, as outlined below. Each was corrected for the additional resistance of the right atrial cannula and tubing by subtracting the product of the cannula resistance (mean value 1.0 cm H2O/liter · min−1) and the compartmental compliance (ml/cm H2O).
The plot of the changes in reservoir volume over time could be described by the expression

$$\frac{V_i - V_{ss}}{V_i - V_{ss}} = e^{-t/R_v C_f}$$

where $V_i$ is the initial volume of the reservoir, $V_{ss}$ is the steady-state final volume of the reservoir, and $V_t$ is the volume at any time $t$. The curvilinear plot was analyzed by extrapolation of the late linear portion to $t = 0$, subtracting the derived line from the curve to obtain another straight line. The intercept of these two lines on the ordinate are equal to $C_f/(C_f + C_s)$ and $C_f/(C_f + C_s)$ respectively. The time required for the first extrapolated line to reach a value 37% of its zero time value is the time constant $R_v C_f$, and the time required for the second line to decrease to a value 37% of its zero time value is the time constant $R_v C_s$.

The values obtained from these plots were used to calculate:

1. Venous compliance: $C_f$ and $C_s$ knowing $(C_f + C_s)$ from calculations of total vascular compliance (see above).

2. Venous resistance: $R_v f$ and $R_v s$ knowing $C_f$ and $C_s$.

3. Fraction of circulating flow to each compartment: $F_f$ and $F_s$ knowing the value of $\Delta V/\Delta Q$ from calculations of the time constant for circulatory flow (see above) and the expression $(\Delta V/\Delta Q) = F_f R_v C_f + F_s R_v C_s$.

4. Actual circulating flow to each compartment: $Q_f = F_f Q$ and $Q_s = F_s Q$ in liters/min.

5. Mean systemic pressure ($P_s$) in each compartment:

$$P_{sf} = P_{fr} Q_f + P_{ra}$$

$$P_{ss} = R_v s Q_s + P_{ra}$$

in cm H$_2$O.

6. Arterial resistance ($R_a$) in each compartment:

$$R_{af} = \frac{MAP - P_{af}}{Q_f}$$

$$R_{as} = \frac{MAP - P_{as}}{Q_s}$$

in cm H$_2$O/liter $\cdot$ min$^{-1}$ where MAP was the mean arterial pressure in cm H$_2$O measured in the descending aorta.

**Change in Reservoir Volume**

We calculated the change in reservoir volume observed at a constant $Q$ during incremental increases in $P_{ra}$ of 2.5 cm H$_2$O from 0 to 10.0 cm H$_2$O. The volume change was recorded when a new steady state was attained. These values at steady state, obtained in five dogs, were used to plot a volume-pressure curve for the peripheral circulation.

All of these determinations were made repeatedly during a 60-minute period preceding the diazoxide infusion (the baseline period) and for 120 minutes after the diazoxide infusion. Diazoxide as the undiluted solution (Hyperstat, Schering Corporation) was infused intravenously at three dose levels: 3.75 mg/kg over 4 minutes in seven dogs, 7.5 mg/kg over 8 minutes in seven dogs, and 15.0 mg/kg over 16 minutes in seven dogs. The systemic vascular parameters for each dog were determined at least four times during the baseline period and six times after the drug infusion. Mean values obtained in an individual dog for each hour after the drug infusion were used to calculate group means $\pm$ SEM. Statistical analysis was
carried out using $t$ tests for paired data. The mean baseline value for each dog was compared to the mean experimental value in that dog for each hour after drug administration.

Blood samples (2 ml) were taken at baseline, the end of the drug infusion, and at appropriate intervals after the infusion in 16 dogs for subsequent determination of plasma diazoxide concentrations using a specific high-pressure liquid chromatographic technique. Plasma 100 $\mu$l was mixed with ethyl acetate 1.5 ml, centrifuged, and 1.0 ml of the organic layer removed and evaporated to dryness under nitrogen atmosphere. The residue was dissolved in 50 $\mu$l of the running solvent (1% butyl alcohol, 1% glacial acetic acid, 98% ethyl acetate v/v) and run at 60 ml/hr on a 5 $\mu$l alumina column (2.2 $\times$ 250 mm) and a detector wavelength of 268 $\AA$ for diazoxide and 254 $\AA$ for the major metabolite M1. The lower limit of detection was 0.5 $\mu$g/ml for diazoxide and 0.1 $\mu$g/ml for the M1 metabolite without detectable interference. The assay was linear up to concentrations of 500 $\mu$g/ml of diazoxide and 100 $\mu$g/ml of the M1 metabolite. Plasma diazoxide concentrations over time were subjected to a two-compartment open kinetic model analysis using an iterative least squares program on an HP9830 computer.

Results

Plasma Diazoxide Concentrations

There was a dose-related increase in plasma diazoxide concentrations following increasing doses of diazoxide (fig. 3). The calculated apparent volume of the central compartment (0.285 liter/kg ± 0.030) and the apparent volume of distribution at steady state (1.264 ± 0.117 liters/kg) were not dose-dependent. The early distribution phase had a halftime of 0.080 ± 0.007 hr whereas the slower apparent late distribution or elimination phase had a halftime of 3.36 ± 0.54 hrs over the duration of the experiment. Because plasma concentrations were followed only for a short time of ~2.5 hrs, there cannot be much confidence placed on the estimate of plasma clearance (0.317 ± 0.042 liter/k · hr$^{-1}$) calculated from the kinetic analysis of these plasma concentration-over-time curves. As can be observed in figure 3, however, the early distribution phase was largely completed at the beginning of the first estimate of blood flow distribution 15 minutes after the end of drug infusion. At this time, plasma diazoxide concentrations were considerably lower than those observed at the end of the infusion.

Arterial Pressures and Plasma Diazoxide Concentrations

The baseline arterial pressure averaged 92.5 ± 2.6 mm Hg. At the end of the 4-minute infusion of diazoxide 3.75 mg/kg, $P_a$ had decreased by 30.2% ± 3.7%. At the end of the 8-minute infusion of diazoxide 7.5 mg/kg, $P_a$ had decreased by 38.0% ± 2.2%, and at the end of the 16-minute infusion of diazoxide 15.0 mg/kg, $P_a$ had decreased by 47.5% ± 2.5%. Thereafter, the effect on $P_a$ gradually decreased over time. From 10 until 60 minutes after the end of the drug infusion, there was a good correlation between plasma diazoxide concentrations and the percentage change in $P_a$ (fig. 4). The subsequent presentation and analysis of changes in vascular function will be limited to those occurring during the first hour after drug administration. Systolic, diastolic, and mean pressures in the main pulmonary artery were unaltered during infusions of diazoxide.

![Figure 3. Plasma diazoxide concentrations (mean ± SEM) over time after infusion of 3.75 mg/kg over 4 minutes (black circles, n = 6), 7.5 mg/kg over 8 minutes (open triangles, n = 4), or 15 mg/kg over 16 minutes (open circles, n = 6).](http://hyper.ahajournals.org/)

![Figure 4. Relationship between plasma diazoxide concentrations plotted semilogarithmically during the first hour after infusion of 3.75 mg/kg over 4 minutes (black circles) or 15 mg/kg over 16 min (open circles) and percent reductions in $P_a$ at each time. Values are means ± SEM of six dogs at each dose level.](http://hyper.ahajournals.org/)
Compartments Analysis

Changes in reservoir volume over time after a sudden reduction in \( P_{ra} \) at a constant \( Q \) revealed a biphasic flow-curve (fig. 1). The analysis of this curve allowed derivation of two exponentials. One had a fast time constant for flow (0.052 ± 0.003 min) and the other had a slow time constant for flow (0.552 ± 0.022 min), indicating that blood was draining from at least two areas with different transit times. During the baseline period, it was calculated that 58% ± 2% of the total circulating flow \( Q \) of 1.30 ± 0.03 liters/min was partitioned to the vascular compartment with the slow transit time.

Arterial Resistance

In the baseline period, arterial resistance in the compartment with a slow transit time for blood flow \( R_{as} \) averaged 154.1 ± 13.6 cm H2O/liters • min\(^{-1}\), whereas that in the compartment with a fast transit time \( R_{af} \) averaged 245.3 ± 18.6 cm H2O/liters • min\(^{-1}\). Analysis of changes in arterial resistance indicated that the major change in resistance occurred in the compartment with a slow transit time for blood flow. Consideration of dose-response effects (fig. 5) reveals that maximal changes in this compartment occurred with the lowest dose so that there was no dose-response effect. In contrast, there was a clear dose-response effect of diazoxide on arterial resistance in the compartment with a fast transit time for blood flow. No change was observed with the lowest dose, and a progressively greater reduction in resistance was observed with higher doses. The reduction in \( P_a \) after the lowest dose of diazoxide was clearly due to a major effect on \( R_{as} \) whereas further reductions in \( P_a \) with higher doses was due to an increasing effect on \( R_{af} \). After diazoxide 15 mg/kg, the reduction in arterial resistance in the two compartments was similar, a -44.8% ± 8.6% decrease in \( R_{as} \) and a -42.8% ± 9.7% decrease in \( R_{af} \).

Time Constants

The ratio of changes in blood volume in the reservoir to changes in blood flow (\( \Delta V/\Delta Q \)) measured at a constant right atrial pressure of 0.344 ± 0.022 minutes during the baseline period was unchanged by any of the three doses of diazoxide. Nor was the transit time for blood flow in fast-transit areas \( R_{vt}C_v \) changed from the baseline value of 0.052 ± 0.003 minutes after diazoxide. However, the baseline transit time in slow-transit areas \( R_{st}C_s \) of 0.552 ± 0.022 minutes was reduced by 9.7% ± 4.0% (\( p < 0.05 \)) after diazoxide 7.5 mg/kg and reduced by 10.4% ± 4.0% (\( p < 0.05 \)) after diazoxide 15 mg/kg.

Circulating Flow

During the baseline period, 58% ± 2% of the total circulating flow \( Q \) of 1.30 ± 0.03 liters/min was partitioned to the vascular compartment with the slow transit time. The fraction of circulating flow apportioned to this compartment increased by 14.0% ± 6.4% (\( p < 0.05 \)) in the first hour after diazoxide 3.75 mg/kg but was not increased after the two higher doses. This redistribution of flow after the lowest dose was a consequence of the preferential reduction in arterial resistance in the slow time-constant compartment. After diazoxide 15 mg/kg there was an equal reduction in arterial resistance in the two compartments and no change in peripheral blood flow distribution from baseline values.

Venous Resistance

There were no significant alterations in overall resistance to venous return \( R_V \) from the baseline value of 12.4 ± 1.3 cm H2O/liters • min\(^{-1}\) after any dose of diazoxide. Neither venous resistance in the slow transit-time compartment \( R_{vs} \) of 27.3 ± 2.6 cm H2O/liters • min\(^{-1}\) nor that in the fast transit-time compartment \( R_{vf} \) of 7.5 ± 0.9 cm H2O/liters • min\(^{-1}\) was altered after diazoxide.

Compliance

Total systemic vascular compliance (\( \Delta V/\Delta P_{ra} \)) was unaltered from a baseline value of 32.6 ± 3.4 ml/cm H2O after any of the three doses of diazoxide. During the baseline period, venous compliance \( C_v \) of the slow time-constant compartment was 24.6 ± 3.0 ml/cm H2O whereas venous compliance \( C_f \) of the fast time-constant compartment was 8.0 ± 0.5 ml/cm H2O. After the lowest dose of diazoxide, venous compliance was variably increased in both compartments (\( p = ns \), but altered in opposite directions after the two higher doses (fig. 6). Venous compliance of the slow time-constant compartment was increased 19.2% ± 8.0% (\( p < 0.05 \)) in the first hour after diazoxide 3.75 mg/kg.
FIGURE 6. Effect of diazoxide on total systemic compliance (ΔV/ΔP_a, open circles) and venous compliance of the slow time-constant compartment (C_s, open triangles) and of the fast time-constant compartment (C_f, open squares).

< 0.05) after diazoxide 7.5 mg/kg and 20.0% ± 7.2% (p < 0.01) after 15 mg/kg, whereas that of the fast time-constant compartment was reduced 21.5% ± 7.9% (p < 0.05) after 7.5 mg/kg and reduced 16.2% ± 6.2% (p < 0.05) after 15 mg/kg.

Vascular Capacitance and Volume-Pressure Relationships

The infusion of diazoxide caused a dose-related decrease in reservoir volume (53.3 ± 16.1 ml after 3.75 mg/kg; 91.3 ± 9.7 ml after 7.5 mg/kg; 133.6 ± 21.4 ml after 15 mg/kg). The new steady state in reservoir volume was attained within 10 minutes of the end of the drug infusion. Volume-pressure relationships were determined in five animals. Although the average curve was shifted downward and to the right after diazoxide, volume-pressure relationships were not altered.

The increase in the distribution of circulating blood flow to the slow time-constant compartment after diazoxide 3.75 mg/kg combined with increased compliance of vessels in that compartment were probably responsible for the decrease in central blood volume as indicated by the decrease in reservoir volume. Maximal increases in circulating flow to and compliance of the slow transit-time compartment were observed at the time of the first determination, 10 minutes after the drug infusion when changes in capacitance were also complete. Although changes in blood flow distribution did not occur after the 15 mg/kg dose, there was a considerable increase in compliance of the slow transit compartment with this dose, and this was presumably the major cause for the increased capacitance.

Relationship between Changes in Resistance and Compliance

Calculations of ratios for decreases in P_a or arterial resistance over increases in venous compliance allowed comparison of the magnitude of the effect of diazoxide on the arterial and venous portions of the circulation (table 1). When the circulation was considered as a single compartment, diazoxide was from 3.9 to 6.0 times more active on arterial resistance than on venous compliance. When the circulation was considered as being comprised of two compartments in parallel, there was a divergence of effects. In the slow transit-time compartment, diazoxide was from 2.1 to 4.7 times more active on arterial resistance than on venous compliance. The ratio was positive in the fast transit-time compartment because higher doses of diazoxide resulted in reduced venous compliance in these areas.

Discussion

The apparent plasma diazoxide concentration half-life of 3.4 ± 0.5 hours is similar to the 3.5-hour half-life reported by Pruitt et al.\textsuperscript{16-17} using radiolabelled drug in dogs. This is considerably shorter than the 21- to 35-hour half-life observed in man.\textsuperscript{8} In the postdistribution phase after drug administration, there was a reasonable correlation between plasma diazoxide concentrations and the reduction in P_a in the present study as was previously observed in patients with severe stable essential hypertension by Nadeau et al.\textsuperscript{18} In dogs, the plasma diazoxide concentration required to reduce P_a by 25% was approximately 4.5 mg/liter (fig. 4) in contrast to ~30 mg/liter observed in hypertensive patients in this laboratory.\textsuperscript{19} The calculated free concentrations of diazoxide would be similar in the two species at ap-
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proximately 2.0 mg/liter, as 57% is protein-bound in the dog and from 90% to 96% is bound in man.8, 17, 20 These results further corroborate the earlier observation of Pearson and Breckenridge80 that the blood-pressure-lowering effect of diazoxide in patients with renal disease was related to free drug concentrations. The close relationship between plasma diazoxide concentrations and the decrease in Pa further underlines the need to analyze dose (concentration)-response effects on the vasculature, as has been carried out in the present study.

The results of this study illustrate that the vascular effects of diazoxide cannot be analyzed by considering the peripheral circulation as a single homogeneous compartment or without analysis of dose-response relationships. The major effect of lower doses of diazoxide was a reduction of arterial resistance in vascular areas with a slow transit time for blood flow. With higher drug doses, there was an increasing effect on arterial resistance in vascular areas with a fast transit time for blood flow, so that after diazoxide 15 mg/kg, the reduction in arterial resistance was approximately equal in the two vascular areas. In addition, the effects of diazoxide on venous compliance were diametrically opposed as higher doses of diazoxide were infused. Whereas the venous compliance in vascular areas with a slow transit time for blood flow was increased, venous compliance in vascular areas with a fast transit time was reduced after the larger doses of 7.5 or 15 mg/kg. It is clear that extrapolation of the effects of a drug such as diazoxide on vascular function in one area, such as the forearm vascular bed, does not allow prediction of changes in the whole system.

Recognition that peripheral blood-flow characteristics are different in different vascular areas has been important in the understanding of drug effects and control of circulating flow. It has been demonstrated that a single-compartment model of the circulation cannot be used to explain the effects of epinephrine,18 isoproterenol,87 nitroprusside,10 or nitroglycerin.18 The interrelationships between arterial resistance, venous compliance and capacitance, and circulating flow are more readily determined by application of a model of the circulation composed of two compliant areas in parallel, one with a slow transit time for flow and the other with a fast transit time.

The technique used in the present study does not record directly the circulating flow, resistances, and compliances of the two compartments. Workers in other two laboratories have physically separated the blood draining from the splanchnic circulation from that draining from the rest of the venous system31, 25 and, using different methods to estimate time constants, both laboratories demonstrated the long time-constant nature of the splanchnic circulation relative to that of the rest of the circulation. We may therefore conclude that the splanchnic circulation is a part of the compartment with the slow time constant for venous flow in the model applied in the present study.

It may be argued that the analysis used ignores the responses of the pulmonary vascular bed, systemic arteries, and large veins. The contribution of the pulmonary vascular circuit and systemic arteries to overall vascular compliance measured by these techniques is unknown but probably small. Left atrial pressure must be increased 10 times more than right atrial pressure to produce an equal reduction in venous return.13 In the present experiments, diazoxide infusions had no apparent effect on main pulmonary artery pressures. Systemic arterial compliance in the dog has been estimated to be only a very small fraction (1/30 to 1/70) of total systemic vascular compliance.31, 32, 34 and therefore alterations in arterial compliance would not invalidate the present analysis. Large veins no doubt contribute to the value of total vascular compliance25 but the contribution does not detract from the value of a model separating the circulation into two parallel compartments. The resistance function of large veins is included in the determination of the time constant for overall flow (ΔV/ΔQ) at a constant Pa.

The results of the present study using this animal model of the circulation can explain some of the previous discrepancies observed in the vascular effects of diazoxide. Bhalmann et al.11 administered a 300 mg bolus dose of diazoxide to subjects with renal or essential hypertension and measured Pa, cardiac output, forearm blood flow, and venous distensibility by plethysmography. Although Pa decreased 16%, and cardiac output increased 49% with a resultant decrease in total peripheral resistance of 50%, forearm blood flow and venous distensibility were not significantly altered. They concluded that the major effect of diazoxide must be on the splanchnic circulation. The forearm vascular bed can be considered to have, in large part, vasculature with a fast transit time for blood flow whereas the splanchnic bed is considered a major part of the compartment with a slow time constant for blood flow.13 The dose of diazoxide administered by Bhalmann et al.11 would be equivalent to the lower dose used in the present study. Thus, the absence of a reduction in arterial resistance in fast transit-time areas and a major reduction in arterial resistance in slow transit-time areas in the animal model is consistent with Bhalman's observations in man. The major effect of smaller doses of diazoxide is likely on the splanchnic circulation, whereas larger doses (and concentrations) are required to alter arterial resistance in fast transit-time areas.

In this animal model with a cardiac output fixed by the pump speed, diazoxide caused a dose-related reduction in venous return to the heart as indicated by a decrease in reservoir volume. A new steady state was reached by the time drug distribution was completed. In some dogs, diazoxide caused a redistribution of peripheral blood flow to slow transit-time channels which had increased venous compliance by a major reduction in arterial resistance in these areas. The greater portion of total circulating flow in these areas that take a longer time for transit can readily account for the decrease in central blood volume. However, the major explanation for increase capacitance after higher doses of diazoxide must have been increased
venous compliance in slow transit-time areas. Diazoxide did not alter the pressure-volume characteristics of the vasculature even though it caused an increase in the total capacitance of the circulation.

The different effects of diazoxide on veins of the two compartments may be due to different characteristics and/or control of venous tone in the two areas. The sympathetic nervous system plays a major role in controlling the capacity of the splanchnic bed and cutaneous veins whereas it is believed to have little influence on skeletal muscle veins.26-28 During experiments in which Pa is reduced by pharmacological agents, several mechanoreceptors may be activated that can induce changes in sympathetic nerve traffic from the medullary vasomotor center28 as well as result in the release of circulating catecholamines. The response of venules cannot be predicted with ease as different populations of veins respond in different ways to the same stimulus.27-28 Indirect effects resulting from decreased Pa could oppose the direct effect of the drug on veins. A larger dose of diazoxide could produce concentrations sufficient to overcome indirect effects but not predictably so, as a larger dose would also cause larger reductions in Pa with a resultant greater sympathetic stimulus that would decrease abdominal vascular capacitance.29 In the present study, the smallest dose of diazoxide increased venous compliance of both the fast and slow transit-time compartments, whereas the larger doses resulted in increased venous compliance in slow transit-time areas. The major effect of lower concentrations of diazoxide appears to be on both arterial and venous portions of vessels with a long transit time for flow, presumably including the splanchnic circulation.

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