An Attempt to Demonstrate Arterial Pressure-Volume Relationships in the Intact Dog by an Ultra-Rapid Bleeding Technic

By David F. Opdyke, Ph.D., Mary E. Zanetti, M.S., and Gordon B. Thomas

The response of arterial pressure to very rapid central venous bleeding has been utilized in an attempt to establish an arterial pressure-volume relation in the intact dog. When dogs were bled for a brief period at rates between 200 and 500 cc. per minute the arterial pressure declined as a rectilinear function of the bleeding volume. The compensatory mechanisms of cardiac acceleration and vasoconstriction do not influence this relationship. Abolition of the vasomotor pathways does, however, increase the slope of the blood pressure decline curve. This is explained on the basis of a decrease in the initial volume of the arterial reservoir.

It has been difficult to assess the true arterial pressure-volume curve in intact animals or man, such information that we do possess having been derived chiefly from in vitro experiments. Precise knowledge of the shape of the pressure-volume curve, and, even more important, how or whether the curve changes its characteristic under different conditions, is essential for the advancement of many cardiovascular problems. One of the problems which would be greatly simplified by such knowledge is how to quantitate cardiac stroke volume by analysis of an arterial pressure pulse.

The possibility occurred to us that very rapid and extensive change in circulating blood volume with simultaneous measurement of aortic blood pressure might reveal something concerning the nature of the arterial pressure-volume curve in the intact dog. Many researches have been concerned with the effect of hemorrhage on various physiological mechanisms, but the maximum bleeding rates in such experiments have rarely exceeded 50 cc. per minute. Under these conditions reflex compensatory mechanisms have time to exert a supporting effect on arterial blood pressure by initiating cardiac acceleration and vasoconstriction. Consequently, a non-rectilinear relation exists between the decline of arterial pressure and the bleeding volume. If it were possible to deplete the circulating blood volume at a much greater rate than hitherto attempted would it be possible to overwhelm or neutralize these compensatory effects? If so, what then would be the nature of the relation between the decline of arterial pressure and the bleeding volume? Would the slope of the arterial pressure decline curve under these circumstances be equivalent to an arterial pressure-volume curve for the intact animal?

Experiments on dogs were conducted in which the circulating blood volume was depleted by bleeding from the right atrium or inferior vena cava at constant rates ranging from 200 to 500 cc. per minute in a search for answers to the above questions. The decline of arterial pressure under these conditions proved to be a rectilinear function of the bleeding volume and independent of compensatory effects.

METHODS

Healthy mongrel dogs weighing 12-15 kilograms were anesthetized with 4 mg./kg. morphine sulfate subcutaneously and 200 mg./kg. barbital sodium intravenously. Since it was desired to leave the arterial system as undisturbed as possible the dogs were bled by inserting 0.115 inch O. D. polyethylene tubing into the thoracic inferior vena cava or right atrium via a femoral vein. Very rapid bleeding rates were achieved by connecting the exterior end of the tubing to a suction flask maintained at 20-40 mm. Hg negative pressure. A suitable dose of heparin administered intravenously prior to the first bleed-
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RESULTS

Figure 1 shows segments of a continuous record from a typical bleeding experiment. The bleeding rate in this experiment was 0.320 cc./kg./sec. with a total bleeding volume of 188 cc. The systolic portion of the pressure pulse curve maintained a good form throughout the bleeding period. In some experiments, however, a collapse occurred during the late systolic portion of the pressure pulse. Such a collapse is usually seen when blood volume is greatly depleted. As many as three successive bleedings in the same preparation and at approximately the same bleeding rate resulted in a consistent relation between the extent of blood pressure decline and the volume of blood (in cc./kg.) removed. Therefore, the pressure decline curve appears to be reproducible in the same preparation.

In fig. 2 the percentile changes in aortic systolic pressure and cardiac cycle length were then measured sequentially on the pressure pulses occurring just before the onset of each inspiration. The changes in systolic pressure (the reason for using systolic pressure will be discussed later) and cardiac cycle length were converted into per cent change from control value and plotted independently on rectilinear coordinate paper against the bleeding volume in cc./kg.

The best fitting regression line was calculated for each plot by the method of least squares in order to compare the various experiments and in order to make correlations between variables. This assigned a numerical value to the slope of each regression line (the regression coefficient, b) and greatly expedited the analysis and illustration of the data. The data were obtained from a total of 30 dogs.

Figure 1. Segments from a continuous record of bleeding in an intact dog. Time interval, 0.02 second. Discussed in text.
to the left hand figure, note that the systolic blood pressure decreased in a rectilinear fashion over the entire range of bleeding volume. (It may be noted at this point that both diastolic and mean aortic pressure were plotted in the same way. In both cases the points fell in a straight line, the only difference being that the slopes were slightly different. As one would expect during a hemorrhage experiment, systolic pressure fell more than diastolic, as the slope of the line for the fall in diastolic pressure was not quite as steep as that for systolic pressure. The slope of the line for fall in mean pressure appeared to be intermediate between the slopes for the decline in systolic and diastolic pressure. Since the basic observation of a rectilinear relation remained unchanged regardless of which pressure was plotted we chose for convenience and accuracy to plot systolic pressure.) The solid line marked \( b_{\text{ap}} \) is the calculated best fitting regression line. Such a rectilinear relation between the decline of blood pressure and bleeding volume was observed in all experiments. The regression line relating change in cardiac cycle length to bleeding volume (\( b_{\text{cl}} \)) is rectilinear out to only 10 cc./kg. in this experiment, however. A rectilinear regression between these two variables out to at least 10 cc./kg. was observed in all experiments. If the heart rate was rapid, as it was here, then a minimum cycle length was reached earlier during the bleeding and such a rectilinear relation could not be maintained. If, however, the heart rate was moderate or slow, cardiac acceleration continued further into the bleeding period with the rectilinear relation continuing as far along as 18 cc./kg. on the abscissa.

In the left hand illustration of fig. 2, the slopes of the pressure and cardiac cycle length decline curves are quite similar. Not so in the right hand illustration. The slopes of the regression lines for pressure and cycle length change are not necessarily related as will be shown later. To do this it is necessary to compare all the experiments one with another in order to ascertain the relation between these variables. The presentation of plots making such comparisons would be both tedious and lengthy. Therefore, the comparisons will be made by utilizing the calculated regression coefficients and regression lines.

The average slopes of the aortic systolic pressure and cardiac cycle length curves have been plotted in fig. 3. These slopes were obtained by averaging the individual regression coefficients and constructing the average regression line. In addition, the greatest and least individual declines of aortic systolic pressure and cardiac cycle length from 21 experiments on 17 dogs are shown (regression lines \( R_1 \) and \( R_2 \)).

The variation in slopes depicted in fig. 3 is sufficient to make it necessary to test the relation between the slopes and the bleeding rates. This has been done graphically in fig. 4 by plotting the numerical value of the pressure and cycle length slopes against the corresponding bleeding rate. There is no apparent correlation between the pressure slope and the bleeding rate, but apparently the steeper cycle length slopes tend to be associated with the
Fig. 4. Scattergram plots relating the slope of the blood pressure decline curve (right) and the cardiac cycle length decline curve (left) to the bleeding rate. The slopes of the curves are represented by the numerical value of the regression coefficient, \( b \), the value of the regression coefficient relating the percentage decline of systolic pressure and cardiac cycle length to the volume of blood removed (cc./KG).

Slower bleeding rates. Statistical correlation tests applied to the paired variables indicate a non-significant correlation coefficient of \(-0.08\) for the change in systolic pressure and a coefficient of \(-0.51\) for the change in cardiac cycle length which is significant at the 2 per cent level. Apparently the decline in systolic pressure is independent of the bleeding rate, but this is not true for the decline in cardiac cycle length. It is clear that, within the range of bleeding rates employed, the decline of systolic pressure is related directly to the volume of blood withdrawn and independent of the rate at which it is withdrawn. This conclusion is in accord with that made by Alexander on the basis of work with an isolated segment of thoracic aorta.

Referring again to fig. 3 we note that the average regression coefficients for the relation between the decline of systolic pressure and cardiac cycle length plotted against bleeding volume are \(-1.969X\) and \(-1.836X\) respectively. One might be tempted to conclude from the similarity of the average slopes that the decline of aortic pressure is related to the decline in cardiac cycle length. That this is an erroneous assumption can be demonstrated easily. The 21 experiments have been grouped in Table 1 according to the extent of change in cardiac cycle length. Eight experiments exhibited little decrease (group 1) while eight experiments showed marked decrease (group 3), and five experiments (group 2) resulted in a moderate decrease in cycle length. The lack of correlation between the extent of decline of systolic pressure and cardiac cycle length is obvious when one examines the individual paired values and the average paired values for each group. Although the average slope for the decrease in cardiac cycle length is more than three times greater in group 3 than in group 1 \((-0.808X\) as compared to \(-2.901X\)) the average slopes of the pressure regression lines are very similar \((-1.920X\) as compared to \(-1.844X\)). For those who like a more classical statistical treatment, none of the differences between group averages are significant and the correlation coefficient for the 21 paired values

Table 1.—Experiments grouped according to extent of decrease in cardiac cycle length. Column \( R_i \) shows the regression coefficient relating per cent decrease in cardiac cycle length to bleeding volume. The corresponding coefficient relating per cent decrease in systolic pressure to bleeding volume is shown in column \( R_s \).

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<th>( R_i )</th>
<th>Expt. No.</th>
<th>( R_s )</th>
<th>( R_i )</th>
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### Table 2

Experiments grouped according to control cardiac cycle length. Column $R_t$ shows the regression coefficient relating per cent decrease in cardiac cycle length to bleeding volume. The corresponding regression coefficient relating per cent decrease in systolic blood pressure is shown in column $R_s$.

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is $-0.1325$, a non-significant value at 19 degrees of freedom.

One other aspect of the relation between the decline of systolic pressure and cardiac cycle length must be considered. In the array of experiments it was noted that there was a considerable variation from experiment to experiment in the length of cardiac cycle before bleeding commenced. It was considered possible that the slope at which aortic pressure declined during the rapid bleeding was affected by the initial cardiac cycle length. Or, was it possible that, if heart rate was already near maximum at the beginning of bleeding, there was less chance for effective compensation and blood pressure fell more steeply? In order to test this possibility the 21 experiments were again grouped according to the control cardiac cycle length. Group 1 consisted of six experiments in which the average control cardiac cycle length was 440 msec. which was close to the average of the entire group; group 2 averaged 365 msec. and group 3 averaged 530 msec. Table 2 presents the paired regression coefficients for these three groups. Upon examining the average coefficients it can be seen, as expected, that group 2, having the shortest control cycle length also experienced the least cardiac acceleration, while group 3 with the longest control cycle length underwent the greatest cardiac acceleration during bleeding. However, the decline in systolic pressure was greatest in group 3 (slope = $-2.329X$) and least in group 1. The statistical trend is toward indicating that an initially slow heart rate, although it accelerates to a greater extent, tends to hasten the decline of systolic pressure rather than to retard it. This is, of course, contrary to our usual concept of the role of cardiac acceleration in compensation to blood loss. It is probable that the statistical trend is fortuitous and that under these conditions the control heart rate has no influence on the decline of aortic pressure.

One can safely conclude from the above data that, although both aortic pressure and cardiac cycle length decline in a rectilinear relation to bleeding volume during very rapid bleeding, the slopes of the respective regression lines are independent of each other. It follows, therefore, that cardiac acceleration plays no effective, or even demonstrable, compensatory role under these conditions.

There remains, of course, the question of what role is played by vasomotor activity during the rapid depletion of blood volume. The strict rectilinear relation between the decline of blood pressure and bleeding volume would suggest that vasomotor activity, even though intense, failed to modify this relation. If any effective compensation were to occur it would commence a few seconds after the beginning of bleeding and one might expect to see at least a temporary deviation from the rectilinear decline observed in these experiments or at least a shift to a different slope.
Such deviation or shift is conspicuously absent from all experiments.

Nevertheless, the rapid bleeding experiment was repeated in six dogs after high spinal transection. The dogs were prepared as before, except that prior to the first bleeding a spinal transection at C3 or C4 was performed. The necessity of using heparin in the bleeding process precluded a bleeding before the transection which would have been desirable for control purposes. Control systolic blood pressures for the transected group averaged 101 mm. Hg (range, 85–112 mm. Hg) which was considerably lower than in the non-transected group which averaged 141 mm. Hg. Cardiac cycle length averaged 564 msec. which was longer than in the non-transected group (435 msec.). Judging from the fact that these dogs were bled four or five times without apparent deterioration, it would appear that the lowered blood pressure was not indicative of surgical shock.

Ten bleedings were performed for this phase of the study. The average slope of the systolic blood pressure decline is shown in figure 5 (regression line R₁) as well as the least and greatest individual slopes (lines R₂ and R₃ respectively). The rectilinear relation between the decline of blood pressure and bleeding volume is fully as striking as in the non-spinal transected group. There is no indication whatsoever that the basic nature of the relationship is changed. Certain quantitative features of these responses are different, however, from those obtained from the non-spinal transected group. First, the average slope is steeper (−4.463X as compared to −1.969X) and, secondly, in the non-transected group the regression line intersects the origin at a negative value (complete regression equation: \( Y = -0.57 - 1.969X \)) whereas in the spinal transected group the line intersects the origin at a positive value (regression equation \( Y = 3.23 - 4.463X \)). The significance of the latter observation has not been analyzed.

In the spinal transected group the cardiac cycle length decreased slightly during bleeding in about one half the experiments. We interpreted this as signifying a diminishing vagal tone during bleeding. Accordingly, nine bleedings were performed in spinal transected and bilaterally vagotomized dogs. Control systolic blood pressure remained about the same as in the spinal transected preparations, but cardiac cycle length increased somewhat. Upon bleeding the relation between the decline of blood pressure and bleeding volume was unchanged (average regression coefficients before and after bilateral vagotomy in the spinal transected dogs were −4.463X and −4.464X respectively). Cardiac cycle length in these experiments either did not change or increased slightly.

Finally, chemical sympathectomy (dibenzyline*) and subsequent bleeding was done in three dogs without spinal transection. The results were very similar to those obtained in the spinal transection preparations. Apparently surgical trauma per se is not a factor in producing the steeper decline of blood pressure in the spinal transection experiments.

We conclude from these data that reflex vasmotor activity, like cardiac acceleration, when initiated after the onset of bleeding, exhibits no demonstrable compensatory effect on the maintenance of blood pressure during very rapid bleeding. Interruption of the vaso-motor pathways prior to bleeding does increase the slope of the blood pressure decline curve, however.

**DISCUSSION**

The results of these experiments clearly indicate that when the blood volume is depleted at

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* We wish to thank Dr. Paul Mattis of Smith, Kline and French Laboratories, Philadelphia, Pa. for a generous supply of dibenzyline.
a sufficiently rapid rate the arterial pressure declines as a rectilinear function of the volume of blood withdrawn. The rectilinear function in itself denies any effective compensation during the bleeding period by cardiac acceleration or vasomotor activity. Additional evidence shows that the rectilinear relation is neither altered by changes in cardiac rate nor by abolishing vasomotor reflexes. Thus, it appears safe to conclude that the arterial reservoir is acting as a simple elastic pressure-volume system during the period of rapid bleeding. The strict rectilinear response observed over the range of pressures encountered (160-40 mm. Hg) implies that the elasticity coefficient \( E \) (where \( E = \frac{dp}{dv} V \); \( dv \) being the change in volume for a given change in pressure, \( dp \) being the change in pressure, and \( V \) being the initial volume of the arterial reservoir) is a constant. If changes in arterial distensibility do occur at different pressure levels, as the data of Alexander, and Remington, Hamilton and Dow indicate, the effect of such a change is negligible and not detectable in our experiments.

These results and conclusions are in perfect agreement with the recently published data of Levy and coworkers. By a different approach they found the pressure-flow response of the systemic vascular bed to be virtually rectilinear over a pressure range of 35-179 mm. Hg when the major moderator reflexes were abolished or controlled. With the compensatory reflexes operative they observed a curvilinear relation between pressure and flow. These investigators stabilized cardiac output at various arterial pressures after denervation of the pressure-receptors in order to obtain a systemic pressure-flow curve. Our plots relate arterial pressure to bleeding volume, but under the conditions of our experiments the rapid depletion of blood volume from the venous side must have resulted in a progressive decrease in cardiac output. Therefore, our progressive bleeding volumes are an index to the progressive decrease in cardiac output. Viewed in this light, their experiments and ours are quite similar. Apparently it makes little difference in the results whether reflexes are abolished by surgical excision or controlled as Levy and co-workers did, or by simply overwhelming the compensatory effects as we have done.

The differences in the slope of the regression line relating decline in arterial pressure and bleeding volume before and after abolition of reflex pathways needs explanation. First, a point that can lead to confusion should be made clear. The rectilinear characteristic of the pressure decline curve denies any effective compensation by vasomotor activity only during the actual bleeding period. The fact that a steeper slope was observed after spinal transection indicates that the vasomotor status prior to the initiation of bleeding is an important factor in establishing the slope of the curve. The steeper slope after spinal transection or chemical sympathectomy might be due to either a change in the distensibility of the arterial system, that is, in the elasticity coefficient, or it may be that the elasticity coefficient remains constant but the initial volume of the arterial reservoir decreases. We are inclined to favor the second explanation since well known hemodynamic principles appear adequate to account for the observed facts.

If the cardiac output (inflow) into the arterial reservoir remains constant and the peripheral resistance is reduced the volume of blood within the system must be reduced due to the greater outflow. Since a reduction of peripheral resistance is characteristic immediately after high spinal transection or adrenergic blockade, these maneuvers are certain to reduce the initial volume of the arterial reservoir. In the experiments reported here, approximately the same volume of blood (in cc./kg.) was removed at each bleeding without consideration as to the initial volume of blood in the arterial system. Since the initial reservoir volume was undoubtedly smaller in the spinal transected or chemically sympathectomized preparations a larger percentage of this volume was removed from these preparations. The decline in arterial pressure would, therefore, be greater even though the elasticity coefficient remained constant. This accounts for the steeper slopes encountered after high spinal transection or adrenergic blockade.

Reviewing some of our experiments not in-
eluded here we find that every maneuver which might be expected to alter the initial arterial reservoir volume such as opening the thorax, compensated hemorrhage and epinephrine also changed the slope of the response curve, but in no case did the response curve depart from a rectilinear relation.

In the final analysis it is concluded that in these experiments the slope of the line relating decline in blood pressure to bleeding volume is determined by the relation between the initial arterial reservoir volume (which is modulated chiefly by changes in the peripheral resistance) and the volume of blood withdrawn.

REFERENCES


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Circ Res. 1955;3:86-93
doi: 10.1161/01.RES.3.1.86
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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