Non-Respiratory Oscillations in Systemic Arterial Pressure of Dogs

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The maintenance of systemic arterial pressure depends upon a control system containing multiple feedback loops. Systems of this type are potentially capable of oscillating and oscillations in pressure can be produced in the circulation under various conditions. Such oscillations may be of sustained amplitude (Mayer waves) or may consist of trains of damped waves following a transient disturbance; initiated, for example, by sudden inflation and deflation of the lungs.

These waves contain considerable information about the intact blood pressure control system and this paper describes their use in an investigation of cardiovascular regulation.

Methods

Twenty-four mongrel dogs weighing 15 to 20 kg were anesthetized intravenously with thiopental sodium (20 mg/kg) or pentobarbital (30 mg/kg). A cuffed endotracheal tube was inserted and, after inflation of the cuff, respiration was maintained with an interrupter type positive pressure respirator fed by compressed oxygen. The respirator was adjusted to maintain a rate sufficient to suppress spontaneous respiratory movements. From time to time small additions of anesthetic agent were given to maintain the required degree of surgical anesthesia. All animals received heparin (2 mg/kg). One femoral artery was exposed and a large cannula inserted which was subsequently used both for blood pressure measurement and for bleeding the animal. A femoral vein was exposed and cannulated for the infusion of drugs either instantaneously or from a continuous infusion pump.

Pressure in the endotracheal tube was measured through a needle passed into its lumen; pressure in the femoral artery through a polyethylene cannula. Both were connected to Statham strain gauges, type P23Db which were connected to a UV recorder.

Before any observations were made thirty minutes were allowed to elapse after the induction of anesthesia. A transient disturbance in the systemic arterial blood pressure was induced by stopping the interrupter of the respirator thus allowing the lungs to inflate to a pressure of approximately 40 mm Hg over a period of about five seconds and then suddenly allowing them to deflate. The subsequent changes in blood pressure were recorded during the following five minutes.

The effect of graded haemorrhage on the response of the transient systemic blood pressure disturbance was determined in 17 experiments. After the control data had been obtained and the systemic arterial blood pressure had returned to normal the animals were bled through the femoral artery cannula in aliquots of 2 to 4 ml/kg. Following each bleeding and when the systemic arterial blood pressure had initially stabilized (after approximately three minutes) the transient change in blood pressure was again introduced as outlined above.

The effect of drugs on the response of the transient systemic blood pressure disturbance was investigated in 13 experiments. Pentolinium tartrate (Ansolysen, May and Baker Ltd., England) was administered slowly, intravenously, in graded doses in 4 experiments. Epinephrine tartrate (Adrenaline, David G. Bull Laboratory Pty. Ltd., Australia) and norepinephrine bitartrate monohydrate (Levophed, Winthrop Laboratories, Australia) were infused continuously intravenously by a Harvard constant rate infusion pump in 7 experiments. Angiotensin II (Hypertensin, Ciba Ltd., Switzerland) was given slowly intravenously as a single dose in 2 experiments.

Results

The cycle of inflation and sudden deflation of the lungs was associated with an initial small rise in femoral systolic arterial blood pressure (SBP) followed by a fall of 10 to 60 mm Hg with a mean fall of 28 mm Hg.

*Consolidated Electrodynamics Corporation, type 5-124.
The SBP then returned to the control level usually with overshoot and subsequent oscillation. It was this return of SBP to control levels and oscillation that was analyzed in these experiments and the initial fall in blood pressure was not considered in detail. The systolic blood pressure was chosen because of ease of analysis, but the results were approximately the same when based on mean or diastolic pressures.

Experiments Showing Overshoot

In these experiments, following inflation and deflation of the lungs, there was a series of damped oscillations. In most cases the oscillations were approximately sinusoidal in form, but in some they were obviously distorted, particularly after severe blood loss and when respiratory efforts were present.

In the absence of significant nonlinearity a damped wave train of this type can be expected to have a sinusoidal form, which can be described in terms of the damping ratio and undamped natural frequency. Deviation from a sinusoidal form indicates...
that nonlinearity is present in the system and its description by damping ratio and natural frequency is only an approximation whose validity depends on the degree of distortion present.

The damping ratio is calculated from the rate at which the oscillations subside, and may also be described by the subsidence ratio. This is the ratio between the amplitudes of each successive oscillation and in these experiments the ratio was approximately constant in each case. (Armstrong and Irby have used the reciprocal of this figure to describe the same term.) The subsidence ratio was measured directly from the last discernible oscillations in order to minimize the effects of nonlinearity. Because the deflections were small, accurate measurement was difficult, and no attempt was made to distinguish between subsidence ratios of 0.1 or less. The damping ratio was obtained from graphs showing plots of subsidence ratio against damping ratio.

The undamped natural frequency is defined as the frequency at which the system would oscillate if its damping were reduced to zero,
and it differs from the frequency of the damped oscillations by a factor dependent on the degree of damping. In our experiments the frequency of oscillation was determined from the period of the last two positive over- 
swings, and was determined only when at least two overswings could be detected. Under these conditions (corresponding with a subsidence ratio of approximately 0.1 or greater) the frequency of oscillation was within 7% of the natural frequency and no correction was made. In most experiments the frequency did not change appreciably during a train of damped waves, but in some, particularly those with distortion of the wave form, the oscillations became faster as they subsided (fig. 2 below).

Experiments Not Showing Overshoot

In those experiments which did not show detectable overshoot after restoration of the SBP the shape of the rise was approximately exponential; although there were a few small superimposed oscillations. Regarding these curves as exponential they can be described by the time constant which is defined as the time taken to change by 63% or 100 (1 – 1/e) of the difference between initial and final SBP.

CONTROL DATA

Following the cycle of inflation and deflation of the lungs 19 of the 24 animals showed an oscillatory change in SBP and 5 returned to control levels without overshoot. In those with an oscillatory response the natural frequency had a mean of 0.039 cycle/sec (range 0.030 to 0.060) which corresponds with a period of oscillation of 26 seconds. In this group the subsidence ratio had a mean value of 0.25 (range 0.1 to 0.5), corresponding with a damping ratio of 0.2.

In those 5 experiments in which there was no overshoot during the recovery phase the time constant of the exponential rise ranged from 15 to 25 seconds, in all these experiments the record showed damped oscillations superimposed on the simple exponential rise. The frequency of this oscillation varies from 0.038 to 0.059 cycle/sec.

In one experiment (no. 11) spontaneous oscillations (Mayer waves) with a frequency of 0.067 cycle/sec were present at the commencement of the experiment. When the cycle of inflation and deflation of the lungs was carried out against the background of this oscillation, a damped wave with a lower frequency (0.050 cycle/sec) was produced and when this disappeared it was replaced by the original Mayer waves. Both these frequencies are plotted in figure 1, no. 11.

Fifteen of the 24 dogs showed spontaneous variations in SBP of 2 to 10 mm Hg amplitude. These were irregular in form and had a frequency of 0.20 to 0.67 cycle/sec (5 to 15 sec period). They appeared to merge into large irregular swings in SBP with frank respiratory efforts consisting of diaphragmatic and abdominal movements and were not classified as Mayer waves.

All the experiments showed variations of approximately 5 mm Hg amplitude in SBP synchronous with the intermittent positive pressure respirator.

EFFECT OF GRADED HAEOMORRHAGE

Figure 1 shows the data obtained from 17 experiments and figure 2 shows the changes recorded in one experiment in which these changes were the most obvious (experiment 11). The amount of blood loss necessary to cause an appreciable fall in arterial blood pressure varied. Excluding experiment 20, in which the animal was only bled to a loss of 14 ml/kg, the animals can be conveniently divided into those requiring a loss of more than 20 ml/kg (11 animals), and those requiring a blood loss of less than 20 ml/kg (5 animals, experiments 4, 9, 10, 16, 17).

The natural frequency of the recorded oscillations of SBP in most experiments remained approximately constant during haemorrhage until the blood pressure began to fall. At this stage the natural frequency fell to about 0.020 cycle/sec.

The subsidence ratio of these oscillations in all but one experiment at first increased and later fell with continued haemorrhage. In the group of 11 animals which held their blood pressure until 20 ml/kg blood loss there was a rise in subsidence ratio before the
blood pressure began to fall. In those animals with the earlier fall in blood pressure (5 animals) the rise in subsidence ratio tended to come after the fall in arterial blood pressure. Mayer waves were present in all animals except two which maintained their arterial blood pressure until 20 ml/kg blood loss. These waves were not seen in those animals in which the blood pressure fell with smaller blood losses.

**EFFECTS OF PHARMACOLOGICAL AGENTS**

Pentolinium tartrate was investigated in 4 animals after varying amounts of blood loss. The results (table 1 and fig. 3) show that this drug produced a fall in arterial blood pressure, a decrease in natural frequency and a decrease in subsidence ratio. In experiments 20 and 21 the natural frequency fell after only small changes in blood pressure.

Thiopentone sodium or pentobarbitone in increments of 10 mg/kg were investigated in 5 animals (fig. 4). These drugs had a similar effect to pentolinium tartrate and caused a fall in blood pressure and decrease in both the natural frequency and subsidence ratio. The effect of thiopentone sodium usually passed off in 15 to 30 minutes but pentobarbital required one-half to one hour before its effect decreased appreciably allowing a return
TABLE 1

Effects of Pentolinium Tartrate After Blood Loss

<table>
<thead>
<tr>
<th>Expt.</th>
<th>Dose of pentolinium (mg/kg)</th>
<th>Arterial pressure (mm Hg)</th>
<th>Natural frequency (cycle/sec)</th>
<th>Subsidence ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>0.0</td>
<td>200/125</td>
<td>0.040</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>0.3</td>
<td>155/100</td>
<td>0.017</td>
<td>0.3</td>
</tr>
<tr>
<td>20</td>
<td>0.0</td>
<td>135/95</td>
<td>0.040</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>0.4</td>
<td>130/85</td>
<td>0.031</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>1.7</td>
<td>100/80</td>
<td>0.018</td>
<td>0.3</td>
</tr>
<tr>
<td>21</td>
<td>0.0</td>
<td>140/85</td>
<td>0.043</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>65/40</td>
<td>0.020</td>
<td>0.1</td>
</tr>
<tr>
<td>24</td>
<td>0.0</td>
<td>130/85</td>
<td>0.038</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>120/80</td>
<td>0.030</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>100/50</td>
<td>0.020</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>100/50</td>
<td>0.017</td>
<td>0.1</td>
</tr>
</tbody>
</table>

FIGURE 3

Effect of 0.4 mg/kg of pentolinium tartrate on the response of blood pressure to the cycle of inflation and deflation of the lungs following a blood loss of 13 cc/kg. Top, before; bottom, after administration of the drug.

FIGURE 4

Effect of 3 mg/kg of thiopentone sodium on the response of blood pressure to the cycle of inflation and rapid deflation of the lungs. Top, before; bottom, after the administration of the drug.

of natural frequency and subsidence ratio to control levels.

Norepinephrine was administered in 7 experiments in doses of 1 to 40 μg/min to animals at various stages of exsanguination. The effect of this drug on the transient oscillations appeared to be related to the level of arterial blood pressure achieved by the infusion. When the blood pressure was high (above 200 mm Hg) the response to a cycle of inflation and deflation of the lungs was an immediate rapid return to the pretransient level with no overshoot. In a partially exsanguinated animal, norepinephrine restored the arterial blood pressure to the normal range and decreased the natural frequency and subsidence ratio (fig. 2). The effect of epinephrine was similar. Mayer waves could not
be produced by the infusion of either epi-
nephrine or norepinephrine.

Angiotensin II was used in 2 experiments
in doses of 1 μg and produced an immediate
rise in blood pressure to levels exceeding 200
mm Hg followed in about five minutes by the
appearance of Mayer waves with a large am-
plitude (exceeding 20 mm Hg) and frequen-
cies of 0.043 cycle/sec in one experiment and
0.025 cycle/sec in the other.

Discussion

The results presented here are in substan-
tial agreement with the previous work of
Guyton and Harris and Armstrong and Irby
and may be interpreted on the basis that the
system controlling systemic arterial pressure
consists of a number of interconnected feedback loops. Figure 5 is a simplified diagram
of the major components.

In relating these results to the characteristics
of the individual portions of the system con-
tained within the blocks illustrated in figure
5, two major problems are encountered. These
are 1) the multiple control loops involved
and 2) nonlinearities between the input and
output of the various blocks. The first
difficulty can be resolved by the considera-
tion that because of their restricted sensitivity
ranges, the carotid and aortic baroreceptors
are effective over the upper pressure ranges,
with a maximum sensitivity around 120 mm
Hg, while the chemoreceptors and cere-
bral ischemic response are increasingly effec-
tive as the arterial pressure decreases below
an upper threshold of approximately 50 mm
Hg. Of these latter receptors the cerebral
ischemic response is the more important.

Nonlinearity however presents a more dif-
ficult problem in analysis and is manifest in
these experiments by deviation of the oscilla-
tions from a sinusoidal form, and changes in
the subsidence ratio and frequency during
damping of the oscillations. In analysing these

![Diagram of major control loops involved in the regulation of systemic arterial pressure.](http://circres.ahajournals.org/)

*Figure 5*

*Diagram of major control loops involved in the regulation of systemic arterial pressure.*

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results the effect of nonlinearity has, however, been minimized by studying the smallest possible amplitude oscillations of the damped trains.

Inflation and sudden deflation of the lungs is analogous to a Valsalva manoeuvre and introduces a transient disturbance into the circulation by direct alteration in intrathoracic blood flow and changes in sympathetic neural activity. The response obtained depends on the open loop characteristics of the control loop involved at that particular input pressure.

Since in most experiments the closed loop response is oscillatory, the open loop characteristics must be described by a system which is at least second order. The closed loop response of these systems will show an increasing tendency towards oscillation, i.e., decreased damping, as the open loop gain increases. Decreasing the gain will lead to a response that approximates an exponential one as was seen initially in five experiments. Increasing the gain can also be expected to increase the natural frequency. The rate at which these parameters change is dependent on the complexity of the system.

The decrease in damping and appearance of spontaneous oscillations in systemic blood pressure during the course of haemorrhage all suggest that an increase in open loop gain has occurred. One cause of this phenomenon may be nonlinearity in the baroreceptors, causing alterations in input pressure to be reflected in changes of gain at the receptor. That this is only part of the explanation is suggested by the observation that the decreased damping was frequently associated with only slight change in arterial blood pressure. Although the release of catecholamines during the bleeding phase might produce such an increase in gain, we were unable to demonstrate this, since the administration of epinephrine and norepinephrine did not produce any change which could be separated from their effects in altering the systemic arterial blood pressure and thence the sensitivity of the baroreceptors. Angiotensin II, on the other hand, did appear to produce spontaneous oscillation in the two experiments in which it was used. This is in accord with the findings of Holybauer and Vogt.

The decrease in overshoot following pentolinium, pentobarbital and thiopentone could be due to a decrease in gain produced by pharmacologic effects on the afferent and efferent portion of the reflexes involved. Nonlinearity of the baroreceptor response is unlikely to be the basis for these changes for in some experiments the systemic arterial blood pressure remained almost steady following the administration of the drugs while the damping and natural frequency of oscillation changed.

The behaviour of the natural frequency of the system can be explained on the basis of two factors:

1) Resonance effects have been demonstrated in the peripheral vascular beds at frequencies around 0.025 to 0.030 cycle/sec. Since these represent a component of the control system it is to be expected that they would pull the natural frequency of the system towards the value, and diminish the expected rise in frequency with increasing gain.

2) As the arterial pressure falls, the operative receptors change from the baroreceptors to the cerebral ischemic response and probably to a lesser extent the chemoreceptors. Open loop studies by Sagawa et al. have suggested that the expected closed loop natural frequency for the cerebral ischemic loop is 0.022 cycle/sec (a period of 45 seconds). This figure corresponds closely with the natural frequency obtained in our experiments after the reduction of blood pressure that accompanied exsanguination.

In the cardiovascular system, blood loss represents a continued stress to the blood pressure control system. In any control system of this type the resulting deviation (change of blood pressure) is inversely related to open loop gain. This is illustrated by those experiments in which animals with low open loop gain (shown by the absence of both overshoot and spontaneous oscillation) did not maintain their blood pressure at or near control level, whereas those with high gain.
(the presence of overshoot and spontaneous oscillation or Mayer waves) held their blood pressure despite large blood losses. In any control system, unless complex techniques are used, good control requires high open loop gain with the potential hazard of instability whereas a low open loop gain system, while stable, has the disadvantages of poor compensation. Both these features are seen in these experiments. In the majority of our experiments the open loop gain appeared to rise during haemorrhage, thus aiding compensation at no cost to stability at normal blood pressures. The mechanism through which this rise in open loop gain is obtained has not been elicited in our experiments and it seems likely that some other receptors may be involved.

Summary

In dogs the condition of the cardiovascular control system was investigated quantitatively during haemorrhage, by using a system of transient inputs and by recording arterial blood pressure. The analysis of our results using standard control system techniques demonstrates a probable increase in open loop gain and a reduction of natural frequency. The implications of these findings are discussed.

Acknowledgment

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References

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