Cardiac output and total peripheral resistance in carotid sinus reflex

ROBERT M. SCHMIDT, MAMORU KUMADA, AND KIICHI SAGAWA
Department of Biomedical Engineering, Schools of Engineering and Medicine, and Department of Surgery,
School of Medicine, Case Western Reserve University, Cleveland, Ohio 44106

Schmidt, Robert M., Mamoru Kumada, and Kiichi Sagawa.
Cardiac output and total peripheral resistance in carotid sinus reflex. Am.
J. Physiol. 221(2): 480-487. 1971.—The sensitivity of the carotid
sinus baroreceptor reflex to step change in sinus pressure was
studied in anesthetized dogs, with emphasis on the relative con-
tributions of cardiac output (CO) and total peripheral resistance
(TPR) in bring about a lowering of mean arterial pressure
(MAP). Changes in MAP, CO, and TPR were determined after
successive 25-mm Hg step increases in intrasinus pressure (ISP)
from 50 to 200 mm Hg. Arterial pressure fell significantly with
each step from 75 to 175 mm Hg ISP; CO showed a slight but
consistent reduction throughout this range of sinus pressure.
However, TPR was sensitive to altered sinuses pressure only between
100 and 150 mm Hg ISP. In this latter range, where the greatest
blood pressure reduction occurred, a reciprocal relationship be-
tween ΔCO and ΔTPR was evident in individual dogs. Vagotomy
influenced the magnitude of all three response variables. Step
increase in carotid sinus pressure brought about a fall in MAP
through either ΔCO or ΔTPR, or both. The magnitude of arterial
pressure change appeared to be influenced by the aortic baro-
receptor reflex, but it did not seem to influence the effec-
t mechanisms through which that change was brought about.

intrasinus pressure; carotid sinus pressure; vagotomy

THE CAROTID SINUS baroreceptor reflex is a multiinput,
multioutput system which exerts a significant control over
arterial pressure. While investigating the quantitative im-
portance of the two input factors of the reflex system
(namely, the mean and pulsatile components of intrasinus
pressure) in the recovery of arterial pressure after mild
hemorrhage (12), we became aware that there has been no
systematic investigation of the reactivity of cardiac output
and peripheral resistance at different carotid sinus pressures.
Thus, we undertook the present study of cardiac and vascu-
lar responses to small step elevations of intrasinus pressure
over the range from 50 to 200 mm Hg to gain quantitative
information on these mechanisms over a wide range of
operating pressures of the reflex. Although the effect of
pulsation with different frequencies and amplitudes about
various mean sinus pressures has also been studied, we con-
centrate, in this report, on the results of altering static sinus
pressure. The responses in heart rate, stroke volume, arterial
pressure, and venous pressure were recorded, and the
steady-state values occurring 1–2 min after the step change
in sinus pressure were analyzed. Repeating the study in the
same group of dogs after vagotomy allowed us to estimate
the buffer effect of the aortic arch barostatic reflex system
on the carotid sinus responses.

METHODS

Nineteen conditioned, mongrel dogs weighing 7–26 kg
were used in this study. After sedation with morphine sul-
fate (2 mg/kg), each was anesthetized with α-chloralose
(60 mg/kg) and urethan (400 mg/kg). Morphine was
given about 2 hr before the experimental run. Its predomi-
nant effect was slowing of the pulse, although no systematic
examination of this drug’s effect on the carotid sinus reflex
was done in this study. The trachea was intubated to assure
unobstructed respiration. Supplemental anesthesia was
given as needed using doses of one-third the initial amount.
Both carotid sinuses were isolated as completely as possible;
namely, the internal carotid and occipital arteries and all
other visible vessels from the bifurcation were ligated. How-
ever, in order to perfuse the sinuses with arterial blood when
the experiment was not running, the external and common
artery, and a servo-controlled pressure source which gen-
crated the desired intrasinus pressure (ISP). Mean and
phasic systemic arterial pressures were recorded from a
thermocouple in the right common carotid artery, and central
tibial venous pressure from the caval vein near the right atrium.
Intrasinus pressure was controlled through a servo-
amplifier, syringe-pump system diagramed in Fig. 1. For
operation of the system a hemostat was removed from tube 1
and placed across tube 2, thereby isolating the carotid
sinuses from the systemic circulation. The desired ISP could
then be obtained by adjusting the reference voltage.
Through the comparator (no. 3), servo amplifier
motor-driving system (no. 4), and syringe pump (no. 5),
pressure was exerted on a rubber diaphragm in the
pressure-transmission chamber (no. 6). The latter contained
saline but the sinuses remained filled with arterial blood
during the experiment because of their complete isolation.
Two thousand units of sodium heparin were given intra-
venously at the time the sinuses were isolated; this dose was
repeated after 2–3 hr.

In each dog an electromagnetic flow transducer (Bio-
tronex series 5000 or in vivo metric FT-Q) was implanted
FIG. 1. Schematic diagram of pressure-generating system for servo control of carotid sinus pressure. See text for description.

around the ascending aorta 6-10 days prior to the experiment. The flow signal, integrated per beat, was calibrated during the experiment using Cardiogreen (Hynson, Westcott & Dunning), densitometer (Gilford model 103-1R), and a formula for abbreviated measurement of the dye-curve area (18).

Once the pulse rate, arterial pressure, and stroke volume appeared stable for more than 5 min, servo control of ISP was begun with reduction of that pressure to 50 mm Hg. Recordings of mean systemic arterial pressure, venous pressure, heart rate, and stroke volume were obtained at 1-2 min after the institution of this intrasinus pressure. Thereafter, ISP was raised in steps of 25 mm Hg to 200 mm Hg and the recordings repeated. Because there was frequently respiratory variation in heart rate and stroke volume, mean values for these two variables were determined over two entire respiratory cycles. Cardiac output per minute was calculated and corrected for body weight. Total peripheral resistance was determined from the data of mean arterial pressure and normalized cardiac output, and is expressed in mm Hg/(ml/min per kg). This presentation allowed us to compare the reflex changes in cardiac output and total peripheral resistance among dogs with widely varying sizes. Otherwise, a large dog, which naturally has a larger control cardiac output and a smaller total peripheral resistance than a small dog, would give an erroneous impression that its heart or vessels respond more greatly to the reflex than those of a small dog. On the other hand, if we had expressed the data in percentile change from the control values, we would be unable to detect the relationship between the absolute magnitude of these variables and their variations by the reflex. It appeared to us that the normalization with body weight meets our demands in this study. Since venous pressures were small, they have been neglected in the calculation of total peripheral resistances. In 16 animals the measurements were repeated after both vagal nerves were severed.

With this preparation (13) we cannot distinguish between the effects of chemoreceptor and baroreceptor stimulation. However, with change in intrasinus pressure we saw no responses characteristic of the carotid chemoreceptors (5, 6). Thus, we feel it is unlikely that chemoreceptor influence affected our results.

RESULTS

General observations. To estimate the variation in mean arterial pressure, heart rate, cardiac output (CO), and total peripheral resistance (TPR) during apparent steady-state conditions, paired determinations obtained at 1 and 2 min after step change in carotid sinus pressure were compared. The findings of this comparison, presented in Table 1, show that the mean steady-state difference for each is less than 1%. Thus we are certain that we recorded actual steady-state changes.

The mean venous pressure was 1.2 mm Hg in the intact and 1.8 mm Hg in the vagotomized groups at 125 mm Hg ISP. Variations in a given dog and for the group as a whole were small and did not bear any consistent relationship to intrasinus pressure.

The results of changing carotid sinus pressure are illustrated in a composite fashion in Figs. 2 and 3. When the vagal nerves were intact, stepwise elevation of ISP caused no appreciable reduction in mean heart rate, although the changes in a given dog were variable and inconsistent. However, there was a slight but continuous fall in stroke volume as ISP was raised from 75 to 175 mm Hg; a 2-5%
reduction in CO accompanied each step change in ISP over this range (Fig. 3). Significant sensitivity of TPR to change in ISP was seen only between 100 and 150 mm Hg ISP. While the individual changes in cardiac output and total peripheral resistance were small in the 75–100 and 150–175 mm Hg ranges, the overall effect on mean arterial pressure was still statistically significant in those ranges.

Severing of the vagal nerves resulted in a monotonic decrease in heart rate as well as in stroke volume and a more precipitous fall in cardiac output as ISP was increased. On the other hand, TPR continued to show little response to changing ISP below 100 mm Hg. Blood pressure alterations reflected those in cardiac output and total peripheral resistance, showing significant reductions over all the ranges of ISP.

Statistical analysis of changes. The absolute changes in each variable with every step increase in ISP were analyzed using the paired t test. Heart rate did not change significantly in the vagal intact dog. The 0.08 ml/min per kg fall
Accordingly, the fall in CO was significant throughout. Sensitivity to altered ISP existed only from 100 to 175 mm Hg for total peripheral resistance in the vagotomized dog. Of the 16 dogs, 7 showed a peak change in TPR in one of the three steps (range 10–50%).

Open-loop static gain. The mean overall open-loop static gain of the carotid sinus baroreceptor reflex has been determined for the different levels of intrasinus pressure by dividing the mean change in blood pressure by 25 mm Hg (ΔISP). These data, presented in Fig. 5, demonstrate a wide range of the reflex sensitivity with broad peaks between 100 and 150 mm Hg ISP for both intact and vagotomized dogs. Most dogs had a broad range of sensitivity; curves for individual animals resembled the mean curves for the entire group in shape and region of peak gain.

Relative contribution of CO and TPR. In order to evaluate the relative contribution of changing CO and TPR in lowering blood pressure, the changes in each variable were normalized for the value at ISP of 125 mm Hg (Fig. 6). From the mean systemic pressure graph of Fig. 3 it is evident that this represented an equilibrium pressure between ISP and systemic pressure under the closed-loop condition for the group of dogs studied. With intact vagal nerves the dogs showed 3.0–5.1 times greater reduction of TPR than of...
CO with increasing ISP in the range from 100 to 150 mm Hg. Above and below this range, changes in these effector mechanisms were small and variable. In contrast, when the vagal nerves were severed, the reductions in TPR and CO were similar in magnitude as ISP was elevated within the range from 100 to 175 mm Hg. At low intrasinus pressures, change in CO appeared to be primarily responsible for the lowering of systemic arterial pressure.

The average response pattern of CO and TPR in the reflex may be inferred from Fig. 6. However, there was great variability in relative strength of CO and TPR responses among individual dogs. To illustrate this variability among dogs, the percent change in TPR was plotted against the respective percent change in CO for each dog during the two separate step elevations of ISP from 100 to 125 mm Hg and from 125 to 150 mm Hg (Fig. 7). The relationship between changes in BP, CO, and TPR can be written as:

\[(BP - ABP) = (CO - ACO) \cdot (TPR - ATPR)\]

The use of percent values reduces the above equation to:

\[\Delta TPR(\%) = 100[\Delta BP(\%) - ACO(\%)]/[100 - ACO(\%)]\]

which was used for calculating \(\Delta TPR\) with different \(\Delta CO\)’s.

The hyperbolic curves in Fig. 7A–D are plots of the above equation for the mean pressure changes which occurred in this experiment. This figure illustrates that when the vagal nerves were intact (Fig. 7A and B), the points are scattered very closely along the curve, indicating that variation in \(\Delta BP\) was indeed small, though the contributing mechanisms were variable in magnitude. When the vagal nerves were severed, there was much greater variability in the blood pressure response with both CO and TPR tending to participate more equally in the blood pressure fall (Fig. 7C and D), although in an unpredictable manner.

**Influence of control level of CO and TPR.** To see whether the control level of CO and TPR influenced the effector
mechanism through which arterial pressure was lowered, the dogs were first grouped on the basis of their control values for these variables at a given ISP and then analyzed for the predominant response mechanism which lowered arterial pressure on step elevation of ISP from that level. The steps from 100 to 125 mm Hg and from 125 to 150 mm Hg ISP, with vagi intact and severed, were studied in this manner. The latter step with the vagal nerves intact has been selected to illustrate the quadrant grouping on the basis of the control values which have been plotted on a CO-TPR plane (Fig. 8); the horizontal and vertical axes represent the mean values for control CO and TPR, respectively. The dogs were divided into four separate groups, depending on whether the control cardiac output or total peripheral resistance was higher or lower than the mean value. The response of each dog to the 25-mm Hg step in arterial pressure on step elevation of ISP from that level. If the changes in CO and TPR were both less than 5%, the dog was designated as exhibiting a response of neither effector mechanism. When the percent reduction in either CO or TPR was larger than the other by a factor of 2 or more, the mechanism predominating was designated as the effector mechanism. When the change in CO and TPR were both greater than 5% and similar in magnitude, the animal was judged to have both CO and TPR contributing to the lowering of arterial pressure. The same quadrant grouping and response grading were done for the step responses from 100 mm Hg ISP, vagi intact and severed, and from 125 mm Hg, vagi severed. The results are presented in Table 2. At 100 mm Hg ISP, vagi intact, there was no apparent relationship between the control values of CO and TPR and the effector mechanism of blood pressure reduction on elevation of ISP. At 125 mm Hg a high control TPR favored a reduction of arterial pressure by that mode, but those animals with high CO and low TPR responded through either or both mechanisms. The vagotomized dogs at 100 mm Hg ISP tended to react through cardiac output when that variable was high, and through TPR when CO was low. In contrast, at 125 mm Hg ISP, the magnitude of CO was only of slight predictive value in determining the predominant effector mechanism.

A few general observations may be made from this analysis. Of those dogs with high CO-low TPR control values, 52% showed a reduction (greater than 5%) in CO, while 60% showed a reduction in TPR on step elevation of ISP. On the other hand, of the low CO-high TPR group, only 27% showed a reduction of CO, while 69% showed a reduction in TPR. This suggests that when control CO is high, it may participate in blood pressure change on sinus nerve stimulation; but when CO is low, it is less likely (P < 0.10, χ² test) to change. However, TPR shows an equal likelihood for response whether its control value is high or low.

**DISCUSSION**

Our data contain many findings which were not evident from previous studies on the circulatory effects of altered carotid sinus pressure. One of those findings is the broad range over which cardiac output showed slight reduction with elevation of intrasinus pressure. Although the fall in cardiac output was not statistically significant for any single step elevation of intrasinus pressure between 75 and 175 mm Hg, the sum of two or more step changes in this variable resulted in a significant fall (0.05 < P < 0.01). Using the direct Fick or dye-dilution techniques, Brind, Bianchine, and Levy (1) and Polosa and Rossai (15) did not find a significant change in cardiac output with bilateral carotid occlusion which elevated systemic pressure by 40-60 mm Hg. However, using electromagnetic flowmeters the latter authors did record a 4.5% elevation of cardiac output in six dogs, with a significance level of P < 0.1; if they had studied a greater number of dogs, it might have been shown that there was a statistically significant change in cardiac output with carotid occlusion. Similarly, Epstein et al. (8) have shown that carotid sinus nerve stimulation in awake humans caused an 8% reduction in cardiac output (P < 0.05) with a 23% fall in systemic arterial pressure. Thus, it would appear that small changes in cardiac output do indeed occur with changes of carotid nerve excitation.

Another important finding of this study is the narrow range of carotid sinus pressure (100-150 mm Hg) within which alteration of pressure induced a significant change in peripheral resistance. Most studies on the vascular effects of carotid sinus nerve stimulation, carotid perfusion, or carotid occlusion indicate that significant changes in peripheral resistance occur. However, it has not been appreciated that this change in resistance results from alteration of intrasinus pressure in a critically sensitive range; namely, 13 of the 19 animals had a definite peak change in TPR following one of the two steps in the above range.
The absence of significant heart rate response in the vagi intact dogs is not in agreement with some of the previously reported studies on carotid sinus nerve stimulation or carotid occlusion (10-16). However, Corcodillas et al. (4) noted an insignificant change in heart rate from control during the 2nd min after carotid artery occlusion. Also, Heymans and Neil (11) point out that the heart rate response is usually poorly maintained. We did, indeed, note an initial reduction in heart rate on step elevation of ISP 25 mm Hg, but this change was transient, lasting only 10-30 sec. A recent study on carotid sinus nerve stimulation in unanesthetized dogs (17) also indicates absence of persistent effect on heart rate, which often increased above the control level after the initial decrease of 20-30 sec duration in the presence of continued stimulation. Since the duration of ISP changes from 50 to 200 mm Hg usually exceed 20 min in our experiment, it is not surprising that there was an apparent escape from the carotid sinus nerve control of heart rate.

Aside from differences in magnitude, the vagotomized animals generally showed responses similar to those with intact vagal nerves. A notable exception is the heart rate response which decreased monotonically on elevation of intrasinus pressure. This finding is consistent with a reduction in sympathetic discharge to the heart, known to occur with carotid sinus nerve stimulation (2, 3). Our data disagree with the conclusions of Glick and Braunwald (9) who state that the sympathetic nervous system plays no detectable role in the reduction of heart rate as blood pressure is elevated in the atropinized or vagotomized dog. However, their own data reveal a mean reduction of 2 beats/min with elevation of systemic pressure 10-20 mm Hg and of 6 beats/min with a 25-50 mm Hg elevation from a mean pressure of 134 mm Hg. For an unexplained reason heart rate response was variable when blood pressure in their experiment exceeded 200 mm Hg, which apparently led them to the above conclusion. We have no data for comparison at that high level of carotid sinus pressure.

Olmsted et al. (14) noted in unanesthetized dogs that common carotid occlusion caused a significant increase of cardiac output only in those dogs which originally had a relatively low cardiac output per body weight. On the other hand, dogs with relatively low total peripheral resistance and high cardiac output before occlusion responded mainly through augmentation of the resistance with little increase in cardiac output. As opposed to Olmsted’s occlusion experiment, our anesthetized dog’s sinus pressure was elevated stepwise; there was a tendency in those dogs with originally high cardiac output to respond with a reduction in cardiac output as well as a decrease in vascular resistance, while those dogs with originally low cardiac output tended to respond merely through reduction in vascular resistance (Table 2). No other investigators studied this interesting aspect of the reflex system behavior. As a matter of approximation, our results are a mirror image of Olmsted’s observation suggesting a basically similar tendency. Although the grouping of control state cannot be very precise because of the limitation of the dye-dilution technique (7), further confirmation of the suggested tendency seems worthwhile from the standpoint of systems analysis of biological variations.

In an attempt to eliminate the antagonistic effect of the aortic baroreceptor, we sectioned the vagus nerves. Since vagotomy interrupts a number of other afferent and efferent nerves, we cannot ascribe all the differences observed after vagotomy to elimination of the aortic baroreceptor reflex alone. However, Olmstead et al. (14), who eliminated only the aortic afferents, observed a mean increase of 34% in both cardiac output and total peripheral resistance after carotid occlusion. We also observed in the vagotomized dogs a similar magnitude (about 40%) of decrease in both cardiac output and total peripheral resistance as intrasinus pressure was raised from 100 to 150 mm Hg. The agreement suggests that the predominant effect of vagotomy in our experiment is removal of the buffer action of the aortic baroreceptor reflex. Also, the comparable response between the unanesthetized dogs used by Olmsted’s group and our anesthetized dogs may indicate that the effect of the anesthesia was relatively small.

This work has been supported by Public Health Service Grants GM 01588 and HE 13040. Present address of M. Kumada: Dept. of Surgery, University Hospitals, Cleveland, Ohio 44106. Present address of M. Kumada: Dept. of Physiology, University of Tokyo, Tokyo, Japan.

Received for publication 21 October 1970.

REFERENCES


