REGULATION OF CARDIAC OUTPUT DURING TRANSITION FROM REST TO EXERCISE

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THE cardiovascular system is a branching network with distensible tubes fed by a constant pressure pump whose output is highly dependent on the impedance presented to the pump by the arteries. In turn the distribution of flow through the parallel paths is determined primarily by the state of dilatation of the small arteries, which in turn, is a function of the rate of metabolism of the individual tissues, as well as the reflex control mediated through the sympathetic nervous system.

Figure 1 shows a block diagram of the system which I will refer to repeatedly throughout this paper.

Let us first consider the operation of this system in response to the most important forcing function to which it is exposed, namely, muscular exercise.

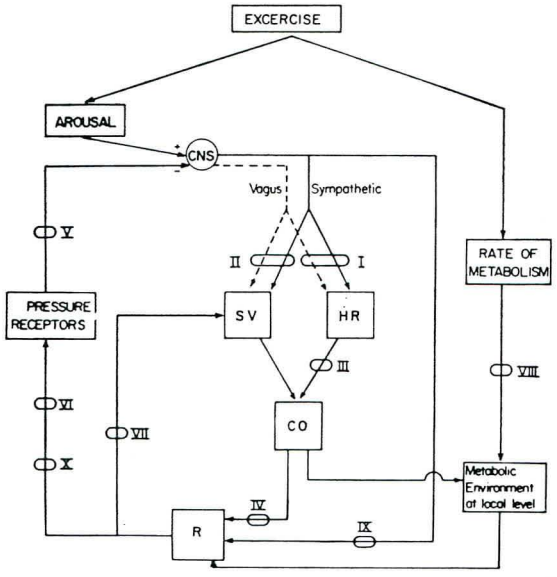

FIG. 1. Block diagram of model of cardiac output control during exercise (see text).

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Exercise acts on at least two places in the system. First, there are direct psychological effects which accompany exercise and which I have called by the term arousal. Second, of course, exercise increases the rate of metabolism in the working muscles. This change in metabolic rate, which will produce a change in metabolic environment at the local tissue level with increased carbon dioxide concentrations and concentrations of other acid metabolites, as well as decrease in pO_2 at the tissue level, brings about a vasodilatation or a fall in resistance to blood flow.

If cardiac output has not changed, this will result in a fall in arterial pressure, which is the product of cardiac output and resistance. This fall in pressure has a direct effect on the impedance into which the left ventricle ejects on the next systole and also has an effect upon the arterial baroreceptors. The reflex effect of this fall in pressure will decrease the activity of the carotid sinus nerve. This, when combined with the increased discharge from the higher centers of the central nervous system due to the arousal, results in a decreased vagal efferent activity and an increased frequency of action potential of the sympathetic nerves both to the heart and to the smooth muscle of blood vessels.

Sympathetic activity will have an effect on stroke volume and heart rate as well as on resistance to blood flow while the vagus activity acts primarily on heart rate. Resulting changes in cardiac output will tend to bring the arterial pressure back to normal and the metabolic environment back to its control level.

With this diagram as a point of reference, I would like to discuss several elements of this system about which we have some quantitative experimental data as well as some theoretical relationships between input and output. Also I will discuss briefly experimental techniques which have been used to test these concepts.

Each of the points in Fig. 1 labeled with Roman numerals represents a place in the system where the control loop has been opened and a transfer function determined. Number I is the relationship between the frequency of action potential on the sympathetic and vagus efferent nerves as input and the heart rate as output.

Figure 2 shows data obtained from a dog with sympathetic and vagus nerves to the heart cut bilaterally and distal ends of these nerves stimulated supramaximally at the frequency indicated. The control heart rate is approximately 145 per minute.

Stimulation of the stellate ganglion at 10 per second causes, after a short delay, a gradual increase in heart rate to a new plateau which is maintained until vagal stimulation is begun at 10 per second. This produces a prompt drop in heart rate within one heart beat to its minimum value at approximately 80 per minute and heart rate remains at this level except for a few fluctuations. When sympathetic stimulation is later discontinued, the heart rate remains at

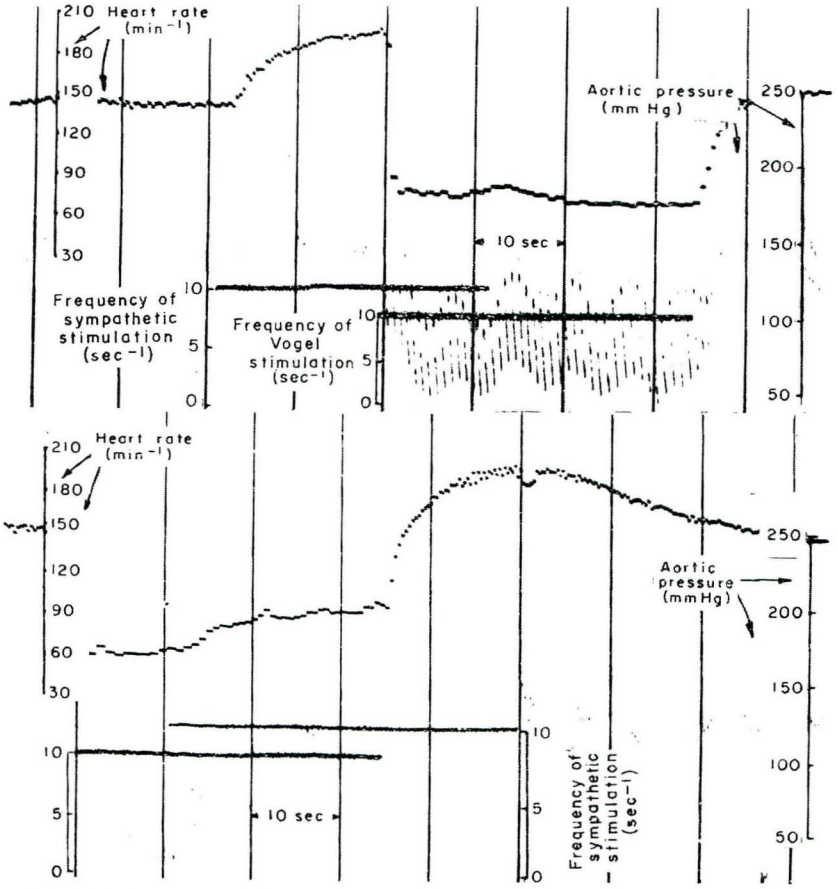

FIG. 2. Time-course of heart rate as a function of sympathetic and vagal nerve stimulation. Both sympathetic and vagus nerves are cut.

essentially the same level but when vagus stimulation is discontinued, the heart rate rises back to its control level. The blood pressure fluctuations in this recording are exaggerated by the respirator.

In the bottom part of Fig. 2 is shown the opposite sequence. The control rate again is approximately 150 per minute. When vagal stimulation is begun, heart rate drops immediately to 60 per minute. With the onset of sympathetic stimulation heart rate increases to approximately 90 per minute. This is a variable response and not necessarily characteristic of the sequence of stimulation. A complete lack of response to sympathetic stimulation may also be seen when vagal stimulation is begun first but, as shown here, discontinuing the vagal stimulation will cause a rise in heart rate to the same level expected from sympathetic stimulation alone, approximately 210 per minute. Discontinuing the sympathetic stimulation causes a slow return of heart rate to

the control value. A model[1] relating both the frequency of sympathetic and vagal stimulation to the heart rate has been developed but this will not account for the interesting phenomenon of an essentially complete control by the vagus when both are stimulated simultaneously.

Recent experiments with much the same kind of preparation have been performed to study the effects of sympathetic and vagal stimulation on cardiac output measured beat-by-beat using a pressure pulse method calibrated against a flowmeter. This transfer function relating sympathetic stimulation to stroke volume is represented at point II in the model shown in Fig. 1. Stimulation of the sympathetic efferent nerves to the heart results in an increase in cardiac output but a decrease in stroke volume. The time-course of increase in cardiac output is the same as the increase in heart rate just shown following sympathetic stimulation. The effects on stroke volume are undoubtedly related to the frequency effects of the stimulus on the force of contraction as well as the indirect effects of decreasing filling time as the heart rate increases. Stimulation of the vagus nerve results in a decreased cardiac output of about the same magnitude as one would expect from the decrease in heart rate alone.

In a dog with complete atrioventricular block, however, in whom heart rate is controlled by ventricular driving, vagal stimulation has no effect on cardiac output. Even more interesting, however, is the data shown in Table 1 obtained

TABLE 1

Stimulus	S.V.	H.R.	C.O.	$\bar{P}$	R
None	16.3	154	2.5	112	45
RS_{10}	13.5	223	3.0	133	45
RS_{10} RV_{10}	20.5	85	1.75	105	60
RV_{10}	22.7	84	1.90	90	48
None	15.3	137	2.1	94	45
RV_{10}	16.2	105	1.7	87	51
RV_{10} LS_{10}	17.2	102	1.75	99	57
LS_{10}	14.5	159	2.3	104	45

from a dog whose chest was closed and in whom both sympathetic and both vagus nerves to the heart were cut. With no stimulation the resting heart rate is 154 per minute, cardiac output 2.5 l./min, mean pressure 112 mm Hg, resistance 45 mm Hg min/l. and stroke volume 16.3 ml. During stimulation of the right sympathetic at 10 per second, heart rate increases to 223 per minute. Cardiac output does increase but certainly not dramatically.

With the sympathetic stimulus still on, stimulation of the right vagus at 10 per second is begun. Heart rate falls immediately to 85 per minute and the cardiac output falls to 1.75 l./min and there is an increase in stroke volume.

Now when sympathetic stimulation is discontinued, heart rate and cardiac output are unchanged.

Performing the same experiment but reversing the sequence of nerve stimulation again shows surprisingly little effect on cardiac output of sympathetic stimulation when heart rate is held at control values by vagal stimulation. This time the control heart rate is 137 per minute and the control cardiac output 2.1 l./min. Stimulation of the right vagus lowers heart rate to 105 per minute and lowers cardiac output to 1.7 l./min.

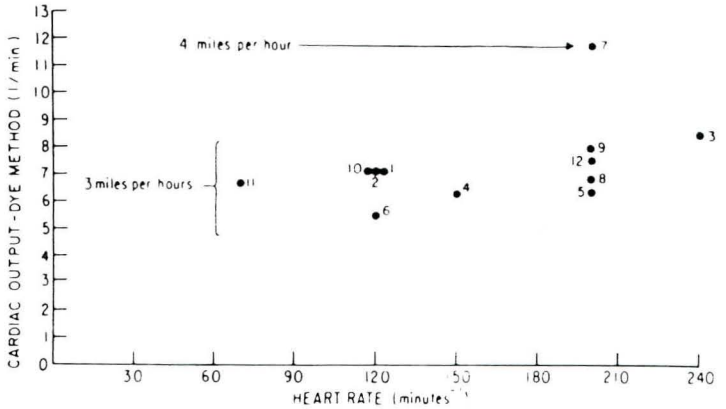

FIG. 3. Cardiac output as a function of heart rate measured by the dye dilution technique in a dog with complete heart block.

Combined stimulation has essentially no effect on heart rate or cardiac output and yet the effect of the sympathetic stimulation is very obvious on the contour of the aortic pressure curve which showed the very rapid initial rise in aortic pressure that is characteristic of sympathetic stimulation. When vagal stimulation was discontinued, sympathetic stimulation alone resulted in heart rate rising to 159 per minute. This is characteristic of the response to left sympathetic nerve stimulation which has a less pronounced effect on heart rate than the right. So it does appear from these studies that the sympathetic stimulation has little or no effect on cardiac output if heart rate is held constant at a low value. It is obvious from examination of the contour of the aortic pressure curve, however, that the sympathetic stimulation has a marked effect on the rate at which the maximum ventricular tension is developed but the duration of systole is shortened. This more rapid ejection would, of course, have a salutory effect on stroke volume if heart rate were increasing and arterial resistance were decreasing as is the case during exercise.

Studies were carried out in our laboratory three years ago on the effects of heart rate *per se* on cardiac output.[2] Although cardiac output is depressed at

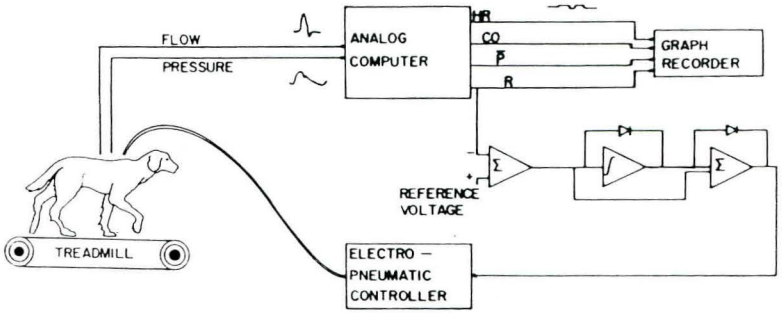

FIG. 4. Diagram of experiment for controlling resistance during exercise.

rates less than about 75 per minute, cardiac output is relatively uninfluenced by heart rate over a wide range as shown in Fig. 3.

These data were obtained from a dog exercising on a treadmill. The dog had previously been subjected to surgery and a complete atrioventricular block produced. The ventricle was stimulated from implanted electrodes in the right ventricle and cardiac output was measured by dilution method on successive exercise runs. With each run the heart rate was set at a different level. It can be seen that cardiac output was fairly independent of heart rate over a rather wide range of heart rates from approximately 70 to 240 per minute. In some experiments the cardiac output decreased when heart rate fell to levels of 70 and 75 per minute. Although there was a slight trend in this particular dog, in general this trend certainly was not impressive.

This reponse would be expected if cardiac output were controlled through some closed-loop mechanism such as the one shown in Fig. 1. in which blood flow is regulated by the metabolic requirements of the tissues and modulated by the reactions of the animal to its external environment.

A series of experiments was done in which cardiac output, heart rate, stroke volume, mean pressure and resistance were measured beat-by-beat during the transition from rest to exercise in a dog. In these studies it was observed that the fall in resistance appeared to lead the rise in cardiac output and heart rate. For this reason an experiment was devised in which the loop could be opened at the location marked with IV in Fig. 1 by controlling independently the resistance to blood flow that the left ventricle pumps into on each beat.

Figure 4 shows the experimental arrangement that was used. Flow and pressure were sensed in the ascending aorta using an electromagnetic flowmeter and a strain gauge manometer. These signals were fed to an analog computer where they were averaged over each heart cycle. The ratio of the mean pressure to the mean flow was calculated and compared to a reference resistance. The difference signal actuated one or the other of two solenoid valves which controlled the air flow into and out of a balloon. This balloon

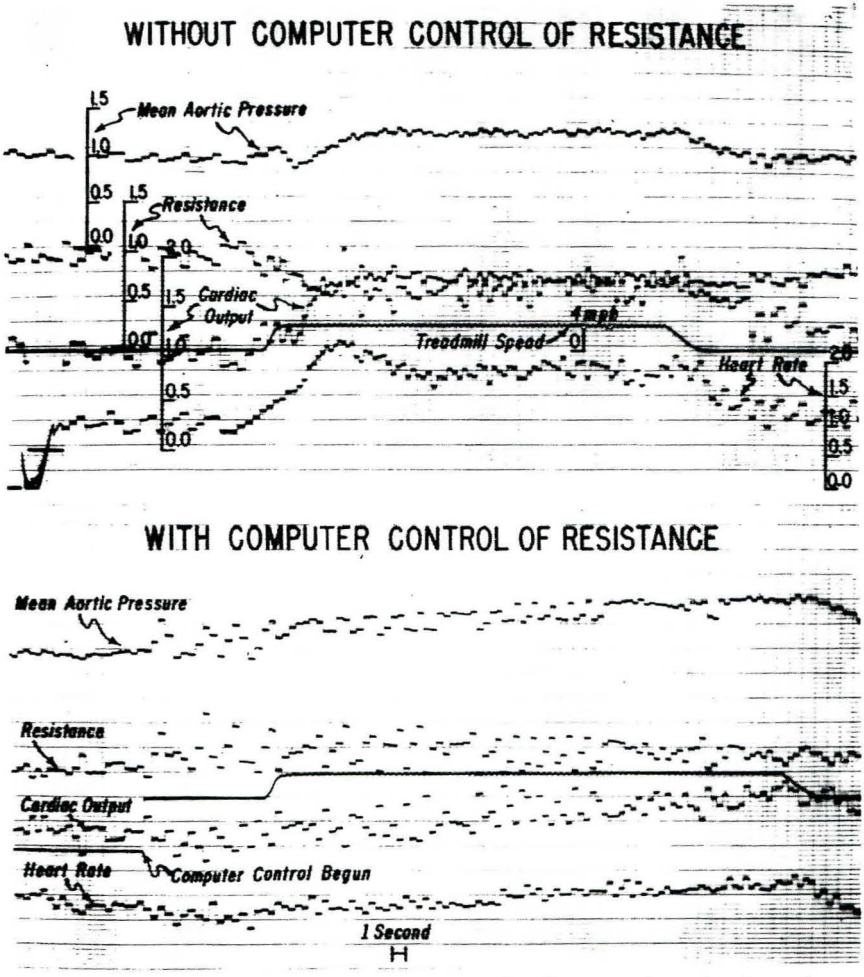

FIG. 5. Top—response to exercise measured as fraction of resting value for each variable. Bottom—similar data obtained during computer control of resistance.

was placed around the descending aorta at the diaphragm and enclosed in a cloth cuff. Inflation of the balloon increased resistance to blood flow out of the left ventricle. Thus, with this mechanism it was possible to control aortic resistance as seen by the left ventricle and to test whether the increase in cardiac output that normally occurs on exercise is dependent on a fall in peripheral resistance.

Figure 5 shows the results of such an experiment. Mean aortic pressure, resistance, cardiac output and heart rate are plotted by the computer as a fraction of their control value. In the top record, in which the computer was not controlling resistance, the onset of exercise resulted in an initial transient

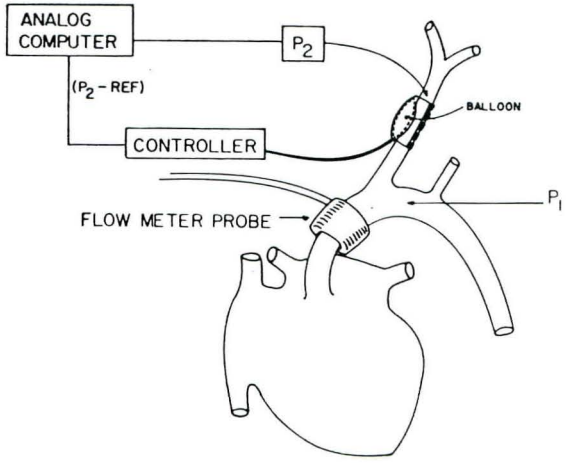

FIG. 6. Diagram of experimental arrangement for controlling carotid sinus pressure during exercise.

fall in pressure followed by a rise above the control level, a fall in resistance to about half of its initial value, a rise in cardiac output to 170% of its resting value and a rise in heart rate with a little overshoot. This overshoot is variable from one dog to the next but it was a rather common response. Within a relatively short time heart rate plateaus and remains constant until exercise is discontinued, in this case approximately 1 min later.

About 3 min after this run the dog was exercised again but just before starting the treadmill the computer took over control of resistance. When this occurs there is considerable variation in resistance which is due to the hunting of the control mechanism in the computer. It is unstable because of the fact that resistance is defined over a minimum period of one heart cycle since it is measured as the ratio of the average pressure to the average flow. Thus, after a correction has been put into the system by the computer at the end of one heart cycle, it has to wait until the next heart cycle to see whether that correction was enough or too much and a certain amount of hunting will occur. In spite of this, mean resistance is held essentially to a constant value and there is no systematic fall in resistance during the course of exercise. With the onset of exercise under these conditions only a very gradual rise in cardiac output occurs. This increase is approximately 15% above the resting level compared to a rise of 70% in the control run. Heart rate, likewise, has only a very minimal increase during the exercise when resistance is controlled. Thus, it appears that resistance does play an important role in bringing about the increase in cardiac output that occurs with exercise. Furthermore, changing resistance under computer control during an exercise run produces reciprocal changes in cardiac output.

Since it seemed possible that the effects of resistance on cardiac output were mediated through the arterial baroreceptors, an experiment was performed in which the control loop was opened at the point marked VI on Fig. 1. (Point V, of course, is the transfer function of the baroreceptors themselves and this will be dealt with explicitly in another paper from this laboratory contained in this volume (Christensen, B. N., Warner, H. R. and Pryor, T. A., "A Technique for the Quantitative Study of Carotid Sinus Behavior").) The experimental arrangement is shown in Fig. 6. We attempted to control carotid sinus pressure independent of the systemic artery pressure in a dog running on a treadmill. The operative procedure consisted of implating a pneumatic controlling cuff around the brachiocephalic artery after having stripped the adventitia from the aortic arch and attempting to preserve as far as possible the efferent vagus and sympathetic fibers to the heart and still destroy the baroreceptor activity from the aortic arch.

Flow and pressure were sensed in the ascending aorta and the pressure measurement was made in the brachiocephalic artery beyond the constrictor. This pressure was compared to a reference signal in the computer and the deviations of this pressure from the reference signal drove the controller to inflate or deflate the cuff. Thus, the carotid artery pressure could be controlled independent of the pressure in the rest of the arterial bed by arbitrary manipulation of the reference signal in the computer. We recorded these five variables from the analog computer and calculated from the pressure and flow signals.

Figure 7 shows the results of one such experiment. A step decrease in the reference signal causes a rapid fall in carotid sinus pressure. Although heart rate and resistance rise gradually to new levels, cardiac output does not change systematically. That the rise in aortic pressure is the result of reflex vasoconstriction and not the direct mechanical effect of occlusion of a major arterial branch is apparent from the time required for the pressor response. From this result it appears that the baroreceptor mechanism is not the important mechanism in controlling cardiac output under these circumstances, but is over-ridden by the direct effects of the reflexly induced increase in resistance.

The time constants for the element of the control system marked VIII in Fig. 1 represent the relationship of the onset of exercise to the change in metabolic environment at the tissue level. It is apparent from the recording in Fig. 5 that the fall in resistance occurs very quickly after exercise is begun. Within two to three heart beats the resistance has fallen down to a new level where it remains throughout the exercise run. To test whether the rate of change of tissue environment is sufficiently fast to account for this, measurements of oxygen saturation of the venous blood from the exercising limb were made as a function of time during transition from rest to exercise. Indeed, oxygen saturation of venous blood falls to a new lower plateau level within five seconds. This is about as fast as could be expected even if a square wave

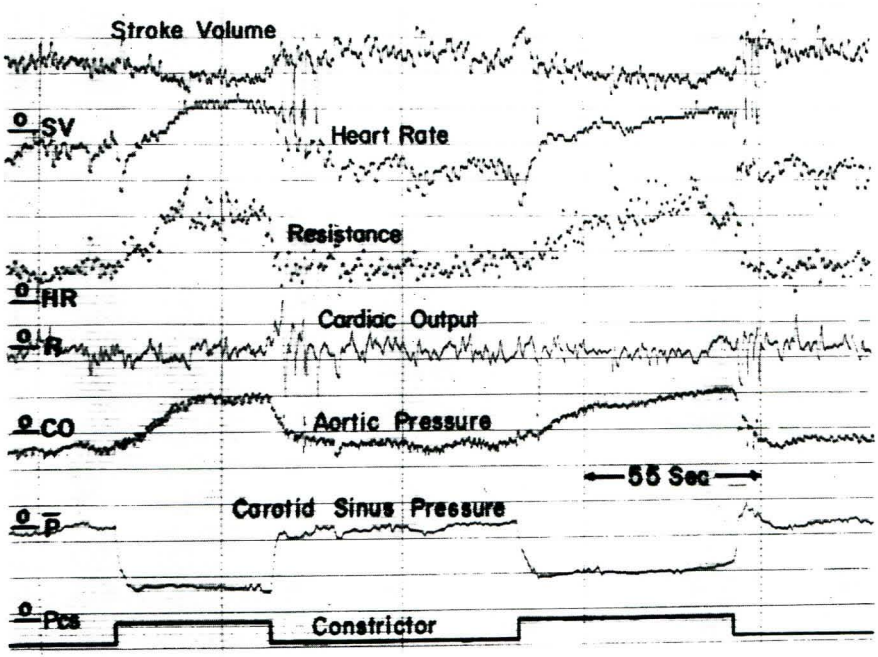

FIG. 7. Cardiovascular response to step changes in carotid sinus pressure in awake dog.

change in oxygen tension had occurred at the tissue level due to the smearing effect of transmitting through the venous system such a concentration gradient. This rapid response results from the fact that the stores of oxygen in the tissues are not at all big compared to the rate of turnover of oxygen. This, of course, does not imply that lowered pO_2 is the only mechanism responsible for the vasodilatation but it does indicate that the time constants are consistent with the hypothesis that the tissue environment is playing an important role in controlling the state of dilatation during exercise.

The reflex effects on resistance have been studied by several workers (point IX of Fig. 1). Allen Scher[3] has looked at the time constant for this element of the loop in the system. It is approximately the same, that is, from 10 to 20 sec, as the time constants that were observed in the heart rate response to sympathetic stimulation.

Kjellmer[4] has shown that the sympathetic stimulation in the presence of muscular exercise will produce only a transient increase in resistance through the blood vessels in the exercising limb and this appears to be rather rapidly returned to the vasodilated state apparently due to the build-up of metabolic end-products at the local level.

Finally, Dr. Scher and other people have quantitative data on the over-all transfer function of the baroreceptor mechanisms (point X of Fig. 1). The

overall gain of the system was found to average somewhere around 2 but varied all the way from 0.8 to 8 in animals under chloralose anesthesia.

Finally, the venous side of the circulation and its role in controlling cardiac output through the Starling mechanism has been restudied and nicely refined and quantitated in the isolated heart by Sarnoff and co-workers.[5] Although such mechanisms undoubtedly play an important role in maintaining a balance between the left heart and the right heart output and the systemic and pulmonary blood volume, their role in controlling cardiac output during exercise is probably less important since only minor variations in left and right heart filling pressure have been observed.

Endocrine effects are also of potential importance but their effects are mainly limited to longer term control since the delays in transport through the blood system between the point of secretion and the point of action places a real limit on their effectiveness in responding to sudden changes in state of the animal.

It seems likely that the papers to follow will shed considerable light on some of the mechanisms I have discussed and perhaps bring to our attention several new areas which need our intensive study.

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DISCUSSION

PETERSON: This is an intriguing approach to the problem of the mechanisms which relate the response of the cardiovascular system to stress and how the body senses the requirements and effects of the changes that are known to take place.

HEYMANS: In my opinion, increase in carotid sinus pressure induces a reflex decrease in the peripheral resistance while decrease has the opposite effect. Do you agree with this Dr. Warner? I thought I heard you say the opposite.

WARNER: I think you misunderstood me Dr. Heymans, my point was that it was the transient fall in pressure that brought about the changes in exercise. Our working concept at the moment is that it is not the absolute level of activity coming on the afferent fibers from the carotid sinus that determines what happens on the efferent side, but that there is some interaction or simply a difference detector of some kind in the central nervous system which is balancing what comes from the carotid sinus against, say, this vague thing we have called arousal level, which essentially sets a level.

This is a tough thing to prove, and yet it is a pretty obvious thing to anybody who has worked with animals on a treadmill, for instance. Rushmer a long time ago pointed out,

that it is a common experience with a dog on a treadmill as you reach for the switch the dog's heart rate and cardiac output increase before he starts to exercise.

So I think it is essentially an interaction of the other efferent activity, probably from higher centers in the nervous system, and perhaps other things along with the input from the carotid sinus, that sets a level at which the system will then operate.

HEYMANS: I agree fully with what you said, Dr. Warner.

TUCKMAN: I wonder if Dr. Warner might answer this. I think there has been some work that has shown that during exercise if one decreases the pressure in the carotid sinus, not as you have done here, that there will be a great increase in systemic pressure; that is, the baroreceptors are really working and have some effect in exercise. Why they have not had an effect in your preparation I do not know. But if you did do this, for instance, by occluding the common carotid arteries during exercise I presume the systemic pressure would be greatly elevated.

WARNER: Well, you talk as though you have done this and this is what happened. Is this right?

TUCKMAN: No, but I think we have two abstracts in the program on this point and I think there has been one article on the same point recently in the *American Journal of Physiology*.

WARNER: We were surprised that the cardiac output did not increase when we lowered the carotid sinus pressure in the exercising dog. This is a reproducible experiment. This is something we had not anticipated.

PETERSON: Was the pressure lowered in the carotid sinuses on both sides?

WARNER: Yes. The cuff is around the brachiocephalic artery.

PETERSON: There is the additional factor, which I think you mentioned or if not, it is certainly going to come in the discussion, and that is the feedback, the efferent feedback to the carotid sinus itself as part of the general sympathetic response which may also play a role in this.

SCHER: Just one more point. Dr. Tuckman was talking about arterial pressure and Dr. Warner was talking about cardiac output. I think what you said agreed with Dr. Warner's slide.

WARNER: That is right. Our pressure did go up with the cardiac output.

TUCKMAN: What I actually am trying to say is that the baroreceptors are important in exercise, because if you reduce the pressure in the carotid sinus during exercise the systemic pressure will go even higher and the work that the heart has to do during the exercise will be greater.

WARNER: I want it clear that I did not say the work of the heart did not change. I said the cardiac output did not change.

TUCKMAN: But the baroreceptors are important in exercise. Am I misunderstanding that?

WARNER: I did not say anything about their importance in exercise. All I said was that they do not increase the cardiac output, and we were surprised at this.

SAGAWA: Drs. Kumada and Iriuckijima recently measured changes of cardiac output by an electromagnetic flowmeter in response to changing pressure in the carotid sinus. Raising carotid sinus pressure from 120 mm Hg to 200 mm Hg caused about 10 to 15% reduction in cardiac output, but lowering it from physiologic to subphysiologic level did not cause any significant increase in cardiac output. Their result is in agreement with Dr. Warner's finding.