Effect of Change in Air Temperature Upon Systemic Small and Large Vessel Resistance

By F. J. HADDY, M.D., PH.D., MALCOLM FLEISHMAN, M.D. AND JERRY B. SCOTT, JR., M.S.

Direct resistance measurements in the foreleg of the anesthetized dog show that the rise in total resistance following reduction of air temperature is due predominately to small vessel constriction and is based upon at least three different mechanisms. The large arteries and veins also constrict and evidence is presented which suggests that the venous and possibly the arterial resistance responses are predominately due to changing levels of circulating epinephrine, norepinephrine or both.

Numerous studies indicate that blood vessels in the extremities constrict when air temperature is lowered. However, no studies precisely define the sites of constriction or quantitatively the degree of constriction at various sites. Further, no studies indicate the relative contributions of nervous, humoral and local factors to resistance changes induced by temperature variation. For these reasons total, arterial, small vessel and venous resistances were measured directly in extremities of dogs during standardized changes of air temperature. Observations were made with nerves intact, following nerve block and after nerve block plus the injection of a sympatholytic and adrenolytic agent.

Methods

Mongrel dogs, approximating 35 lbs. in weight, were anesthetized with sodium pentobarbital and placed on their sides. The brachial artery was exposed high in the lowermost foreleg. A dorsal foot vein and a ventral foot artery, each about 1 mm. in diameter, were dissected free. The animal was completely heparinized. The brachial artery was partially transected and the proximal end connected to the distal end with a length of polyethylene tubing which coursed through a pump.* Retrograde catherization of a subcutaneous small paw vein and a foot pad small artery (both 0.2 to 0.5 mm. in diameter) was carried out with glass capillary tubes according to methods previously described.1 A 20 gage needle was inserted in the cephalic vein at the level of the elbow. Pressures were measured in the brachial artery just distal to the pump, in the cephalic vein and in the small vessels utilizing a 0-75 cm. Hg resistance wire pressure transducer. Foreleg blood flow rate was regulated to a value which produced a mean brachial artery pressure of approximately 100 mm. Hg with the room temperature at 20 C. This value varied from 45 to 120 ml./min. (average 75 ml./min.) in different animals but was maintained constant throughout an experiment in any particular animal. Blood flow was maintained constant in order to minimize possible resistance changes due to anomalous viscosity and changing metabolite (CO₂, O₂, H⁺) concentrations, obviate practical difficulties encountered in measuring flow with a flowmeter, increase accuracy of flow and, thereby, resistance estimations, and simplify recognition of resistance changes during experiments since change in pressure gradient could be directly interpreted as change in resistance.

In a first group of 7 animals, vessel pressures were recorded at 2 to 3 min. intervals during successive 10, 15 and 10 min. periods of exposure to 20, 0 and 20 C. air temperatures respectively. The entire transverse diameter of the leg at the level of the elbow was infiltrated with 30 ml. 2 per cent procaine. The sequence was repeated.

In a second group of 7 animals, the nerves were blocked immediately. The above observations were made. While repeating the experiment, 0.02 Gm. of phentolamine were dissolved in 100 ml. physiologic saline and infused into the brachial artery. Rectal temperatures were recorded at 2 to 3 min. intervals. The average initial temperature was 37.3 C. Following the first and second 0 C. exposures, it averaged 35.3 and 33.3 C. respectively.

The pressure gradients from brachial artery to cephalic vein, brachial artery to small artery, small artery to small vein and small vessel to cephalic vein were calculated at each 2–3 min. interval. Resistance values were calculated for each vascular segment. Resistance was taken to be the ratio of pressure gradient to flow and expressed as mm. Hg/ml./min. Total resistance refers to the resistance to flow between the points of measurement of pressure in the brachial artery and cephalic vein. Arterial resistance refers to the resistance between brachial artery and foot pad small artery, small vessel resistance to that between small artery and small vein and venous resistance to that between small vein and cephalic vein.

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In 3 additional nerve blocked legs, total resistance was observed as all nerves were surgically sectioned just above the level of the elbow. A further resistance decrease did not occur, attesting to the completeness of the procaine nerve block. In 6 additional foreleg preparations 1 γ of epinephrine was injected into the brachial artery before and during phentolamine infusion. Before phentolamine infusion, total resistance rose on the average to 157 per cent of the control value. During phentolamine infusion, resistance decreased by 4 per cent. Intra-arterial injection of physiologic saline does not produce resistance changes in the preparation used.

RESULTS

Figures 1 and 2 present the average pressure and resistance changes respectively. Total vascular resistance of the intact leg began rising immediately upon 0 C exposure in 7 of 7 experiments. The rise was gradual and progressive, reaching after 15 min. a level which was, on the average, 143 per cent of the 20 C. value (table 1). In 6 of 7 animals, a fall in resistance began promptly upon return to 20 C. temperatures. In the seventh animal, total resistance continued to increase for 11 min. This post-cold total resistance rise was associated with a large rise in venous resistance (fig. 3, experiment 2), a small rise in arterial resistance and an unchanging small vessel resistance.

On the average, 83 per cent of the total resistance rise occurred at the small vessel level (table 1). A progressive small vessel resistance rise began in 6 of 6 experiments within 3 min. of the onset of 0 C. exposure. In 5 of 6 instances, a resistance decrease was observed promptly following return to 20 C. temperatures. The sixth animal is mentioned above.

The response of the arteries to 0 C. exposure was variable in pattern and degree. Arterial resistance increased in 5 of 6 instances immediately upon exposure. Subsequently, as arterial intraluminal pressure continued to rise
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(Fig. 1), resistance decreased from the initial 0 C. value in 4 of the 5, but increased further in the fifth. In the sixth leg, the arterial resistance did not change significantly throughout the experiment.

The venous responses to 0 C. exposure are of particular interest. Resistance changes varied in degree, pattern and time of onset. With nerves intact, venous resistance increased to approximately 200 per cent of the 20 C. values in 4 of 7 experiments (Fig. 3). The responses, however, occurred at variable time intervals following onset of 0 C. exposure and, indeed, constriction sometimes proceeded following return to 20 C. temperature (Fig. 3, experiments 2 and 5) at a time when small vessels were dilating. In the remaining 3 experiments, a significant resistance rise did not occur.

Nerve block decreased the absolute level of total resistance in each experiment. The resistance decrease was almost entirely due to a fall in small vessel resistance (Fig. 2, Table 1). Cold exposure increased total resistance in each experiment. In 3 of 4 experiments with complete data, the total resistance rise was less than with nerves intact due to a decreased responsiveness of the small vessels. The arterial and venous resistance levels and degree of change upon 0 C. exposure were not different from those observed with nerves intact. However, the arterial response pattern differed. Though the arteries again immediately constricted in 6 of 7 instances, they continued to constrict as cold exposure progressed in 5 of the series of experiments (Fig. 1), resistance decreased from the initial 0 C. value in 4 of the 5, but increased further in the fifth. In the sixth leg, the arterial resistance did not change significantly throughout the experiment.

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**Table 1.** Effect of Change in Air Temperature Upon Vascular Resistance (mm. Hg/cm./min. + S.E.), Same Number of Cases as in Figure 3.

<table>
<thead>
<tr>
<th>Vessel Segment</th>
<th>Nerves intact</th>
<th>Nerves blocked</th>
<th>Nerves blocked plus phentolamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 C. Value*</td>
<td>Average final 0 C. value</td>
<td>Per cent change</td>
</tr>
<tr>
<td>Total</td>
<td>1.34±.20</td>
<td>1.92±.26</td>
<td>143</td>
</tr>
<tr>
<td>Arteries</td>
<td>.46±.04</td>
<td>.56±.06</td>
<td>122</td>
</tr>
<tr>
<td>Small vessels</td>
<td>.75±.23</td>
<td>1.25±.28</td>
<td>160</td>
</tr>
<tr>
<td>Veins</td>
<td>.075±.013</td>
<td>.114±.023</td>
<td>152</td>
</tr>
</tbody>
</table>

* Average of mean value for each dog during first 20 C. exposure period.
† First 0 C. value was used.
§ Fifteen minute 0 C. value.
¶ First value during second 20 C. exposure period.
†† First 0 C. value.
§§ Six minute 0 C. value.
6 legs. This difference from the intact leg may be related to the lesser rise in arterial intraluminal pressure with nerves blocked than with nerves intact (fig. 1). In one instance, evidence was obtained which suggests that the arterial resistance response also may be dissociated directionally from that of the small vessels.

Nerve block plus local phentolamine infusion further decreased the absolute level of total resistance in all experiments. Total resistance increased on 0 C. exposure in 5 of 6 instances. Both in terms of absolute change and as per cent of the 20 C value, the resistance increase was less than in the nerve blocked extremity in 5 of 6 experiments. The latter difference from the nerve blocked leg appeared to result from a decreased responsiveness of all 3 vascular segments (table 1). The limitation of arterial constriction occurred despite a limited rise in arterial intraluminal pressures during 0 C. exposure. In no instance was a distinct venous constriction observed.

**DISCUSSION**

These studies show that the changes in total limb vascular resistance following 0 C. and 20 C. temperature exposures are due, predominately, to regular prompt progressive small vessel constriction and dilatation respectively. In most instances, the large arteries and veins also actively change caliber but the resistance changes in these segments may be entirely dissociated in terms of time, direction and pattern from that in the small vessel segment. At least three mechanisms contribute to the small vessel and, therefore, total resistance responses. The changes in venous and possibly arterial resistances may be predominately due to changing concentrations of epinephrine, norepinephrine, or both.

The results indicate that changing activity in nonlocally distributed nerves and changing levels of circulating or locally released epinephrine or norepinephrine constitute important mechanisms contributing to the observed changes in total and small vessel resistance. The resistance responses following nerve block phentolamine infusion likely are predominately the result of a direct local effect of temperature change upon blood vessel musculature. However, variations in blood viscosity, metabolite concentrations and levels of vasoactive substances other than adrenalin may have contributed to the latter response.

The absence of a difference in venous and arterial resistance responses with nerves blocked and unblocked and the greatly limited response following phentolamine suggest that the veins and possibly the arteries were predominately responsive to circulating epinephrine and norepinephrine. The irregularity of the venous response and its dissociation in terms of time from the 0 C. exposure period and small vessel constriction support such a contention. Further, a previous study has shown that in the dog foreleg, intra-arterial injection of epinephrine and norepinephrine bring about large rises in small vein pressure in addition to the expected elevation of small artery pressure and decreased flow rate. This response was tentatively interpreted as indicating a vein or venule constrictor action, proportionately greater than the arteriolar action. The present study tends to support such an interpretation. The changes in venous resistance, though irregular in occurrence and small in terms of absolute change relative to the change in the small vessel segment, are of special interest and importance. The irregular occurrence may be related to the brevity of the exposure periods employed in these experiments. When resistance elevations did occur, however, they were marked relative to 20 C. resistance values. In those instances, small vein pressure rose to high levels (maximal value 23.3 mm. Hg). By inference, capillary pressures were likely also elevated. Venous or venule constriction, therefore, may account for the hemoconcentration, reduction in blood volume and edema which occurs during prolonged cold exposure. Filtration of fluid out of the capillary is especially likely to occur should veins constrict while arterioles dilate. These experiments show that such a combination may occur with temperature change, especially during the rewarming period. Kelly and Visscher have recently shown that this combination of events also occurs following the release from electric stimulation of sympathetic nerves.
The finding that veins may be highly sensitive to changing concentrations of epinephrine may explain several previously reported but unexplained observations. These include the large elevations of small to large vein gradient sometimes observed in resting wakened dogs, regularly observed in normal exercising dogs and sometimes observed in resting wakened dogs with compensated and decompensated heart disease due to artificially produced lesions of the pulmonic and tricuspid valves. Implication of epinephrine induced venous constriction as the cause of these changes becomes more plausible in light of the fact that large flow rate changes produce only small changes in the absolute small and large vein pressure levels or the pressure gradient between these vessels.

The large artery constrictor activity may have been more pronounced than the resistance figures indicate. With blood flow rate constant, the absolute brachial and small artery pressures rose greatly (fig. 1) during 0 C. exposure. Therefore, a portion of the active constriction may have been masked by passive dilatation subsequent to elevated transmural pressures. A greater rise in arterial resistance undoubtedly would have been observed in a system designed for constant arterial pressure but variable flow. The effect of transmural pressure on resistance may also be seen in the initial 20 C. arterial resistance values for each preparation. The general absence of a decrease following nerve block and following nerve block plus phentolamine may be related, in part, to the decrease in arterial intraluminal (fig. 1) and, therefore, transmural pressures subsequent to these procedures.

**Summary**

Observations were made upon small and large vessel resistance in the foreleg of the pentobarbital anesthetized dog in relation to 10 and 15 min. exposures to air temperatures of 20 and 0 C. respectively. Studies were made with nerves intact, blocked and blocked plus local phentolamine infusion.

Upon 0 C. exposure, total resistance of the intact leg increased to 143 per cent of the 20 C. value. Eighty-three per cent of the rise was due to small vessel constriction. Arterial and venous resistance elevations were not necessarily related in terms of time, direction or pattern to that observed in the small vessel segment. Venous resistance sometimes continued to rise during the rewarming period at a time when small vessels were dilating.

At least three mechanisms contributed to changes in total and small vessel resistance. These include changing activity in nonlocally distributed nerves, changing levels of circulating or locally released epinephrine and a direct effect of temperature change on blood vessel musculature. The changes in venous and possibly arterial resistance are interpreted as due predominately to changing levels of epinephrine, norepinephrine, or both.

**Summary in Interlingua**

Esseva executate observationes del resistentia de minor e major vasos in le gamba anterior de canes anesthesiate per pentobarbitol, in relation a expositiones durante 10 e 15 manutes a temperaturas aeree de 20 e 0 C, respectivemente. Le studios esseva facite con nervos intacte, con nervos blocate, e con nervos blocate insimul con infusion de phentolamina.

Post exposition a 0 C, le resistentia total del gamba intacte montava a 143 pro cento de su valor post exposition a 20 C. Octanta-tres pro cento del augmento esseva debite a constriction de vasos minor. Le elevation del resistencias arterial e venose in lor characteristicas temporal, directional e configurational non eseva necesserimente relate al elevationes observe in le segmento de vaso minor. Le resistentia venose continuava montar a vices durante le periodo de recalfeccion a un tempore quando le vasos minor se dilatava.

Al minus tres mecanismos contribueva a alteraciones in le resistentia total e le resistentia de vasos minor. Istos es (1) un alterate activitate in nervos de distribution non-local, (2) alterate nivellos de epinephrina circulante o de epinephrina de liberation local, e (3) un efecto directe de alteraciones del temperatura super le musculature del vasos sanguine. Le alteraciones del resistentia venose e possiblemente
arterial es interpretate como resultante primariamente ab alterate nivellos de epinephrinas.

REFERENCES


Myocardial Efficiency and Cardiac Competence

It is one of the tenets of muscle physiology that the efficiency of contraction (ratio of thermodynamic equivalent of external work to O₂ consumption) is related to its biologic competence. Since the advent of arterial puncture and coronary catheterization this concept has been extended to the human heart operating under different conditions in health and disease.

Recent studies on a dog's heart-preparation in which coronary flow and cardiac metabolism could be studied with an intact circulation, has led to the conclusion that this may not be permissible. The oxygen utilization of the heart in the body is susceptible to many variables that do not exist in simple excised muscle preparations studied in laboratories. For instance, the oxygen required for basal metabolism and for different modes of contraction induced by changes in diastolic stretch, aortic pressure and heart rate are not taken into account. The varying effects of nervous and humoral factors on metabolism are not known. For these reasons a low, calculated myocardial efficiency does not necessarily signify an incompetent heart, nor one that is beating ineffectively.

The importance of these premises in future experimental and clinical studies would seem to warrant confirmation of the experimental evidence, for, at present, they are based on mean values of data from comparatively few experiments which show considerable variations in directional trends and magnitude of efficiency changes when aortic pressures and cardiac output are caused to increase.

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