Effect of pH Change upon Systemic Large and Small Vessel Resistance

By MALCOLM FLEISHMAN, M.D., JERRY SCOTT, M.S. AND FRANCIS J. HADDY, M.D., PH.D.

In the dog foreleg acute increase and decrease of hydrogen ion concentration is associated with active small vessel dilatation and constriction, respectively, through some direct effect upon vascular smooth muscle. These small vessel resistance changes do not affect total resistance in the intact leg because of directionally opposite active changes in artery resistance. The latter response appears to be related to central nervous connections and perhaps to circulating or locally released epinephrine, norepinephrine or unknown vasoactive substances.

Numerous studies indicate that blood vessel caliber is affected by variation of blood hydrogen concentration. Several studies suggest that the change in vascular smooth muscle length is the result of antagonistic local and nonlocal mechanisms. This study was undertaken in an attempt to define the importance of physiologic changes in blood pH in determining vascular resistance in the dog's foreleg, and to further elucidate the mechanisms through which resistance changes occur. In addition, special techniques were utilized to determine more precisely which blood vessels are involved in the resistance changes.

Methods

Caliber changes in various segments of the dog foreleg vascular system during standardized changes in hydrogen ion concentration were inferred from calculated resistance changes in corresponding segments. Resistance was calculated from directly measured pressures at four sites along the length of the system while blood flow rate was maintained constant with a blood pump. Observations were made with the nerves intact, following nerve block and after nerve block plus the infusion of a sympatholytic and adrenolytic agent.

With the animal pentobarbitalized, a foreleg foot vein, ventral foot artery and the brachial artery were dissected free. Following heparinization, the brachial artery was transected and the proximal and distal ends connected by a 300 cm. length of 3 mm. O.D. polyethylene tubing which coursed through an independent Sigmamotor pump. The foot artery and vein were catheterized in a distal direction with 5 cm. lengths of 0.5 mm. O.D. glass tubing according to methods previously described. The catheter tips were finally positioned in a 0.5 mm. vein and artery in the toe web and foot pad respectively. A 20 gage needle was inserted into the cephalic vein at the level of the elbow. Utilizing a multiple stopcock arrangement, pressures were rapidly and consecutively measured in the brachial artery, small artery, small vein and cephalic vein with the same 0 to 75 cm. Hg resistance wire pressure transducer. The blood pump was adjusted so as to produce a mean brachial artery pressure approximating 100 mm. Hg. At this pressure, flow ranged from 30 to 120 ml./min. in individual animals but was maintained constant throughout an experiment in any particular animal.

Following control pressure measurements with the animal spontaneously breathing air, a blood sample was withdrawn from the brachial artery just distal to the pump and its pH determined by a Beckman pH meter with the sample maintained at 37 C. The animal was hyperventilated for 7 1/2 min. and then immediately ventilated with 20 per cent CO2 in oxygen for another 7 1/2 min. The various vessel pressures were measured 3 times during each 7 1/2 min. period at 1 to 3 min. intervals. Blood pH was determined after the final pressure measurement on hyperventilation and 20 per cent CO2 respectively. Ventilation with CO2 was terminated and the animal allowed to spontaneously breathe room air. Final pressures were measured after 3 to 4 min.

The above procedure was carried out in 8 nerve intact forelegs. The nerves were then blocked by infiltrating the entire transverse diameter of the foreleg at the level of the elbow with 30 ml. 2 per cent procaine. The above experimental sequence was repeated. In 4 of the original 8 legs and in 6 additional nerve blocked legs a constant drip of a 0.005 per cent solution of phentolamine methanesulfonate (Regitine) in isotonic saline was infused into the brachial artery just distal to the pump. A total of 75 ml. was infused while repeating the above experimental sequence. Eight nerve intact, 8 nerve blocked and 10 nerve blocked phentolaminized forelegs, for a total of 14 animals, were in this way subjected to the same experimental procedure. In addition, atropine sulfate, 0.5 mg., was added to 100
ml. of 0.005 per cent phentolamine in isotonic saline and infused by constant drip into the brachial artery of 4 animals with nerve blocked legs. These animals were also subjected to the above experimental sequence.

In 6 of the above animals, 1 mg of epinephrine hydrochloride was injected into the brachial artery with blood pH at maximal and minimal values. The resulting brachial artery pressure changes were continuously monitored.

Segmental resistances were calculated by dividing segmental pressure gradients by the flow rate and expressed in mm Hg/ml./min. Detailed descriptions of the methods utilized have appeared in previous reports.1-8

**RESULTS**

The effect of various pH changes upon average vessel pressures in intact, nerve blocked, and nerve blocked phentolaminized dog forelegs with constant brachial artery blood flow rate is presented in figure 1. Figure 2 presents these data in terms of average absolute resistance for each vascular segment. The direction, magnitude and variability of change in total and segmental resistances associated with pH change 7.6 to 7.0 is presented in table 1.

Upon pH change 7.6 to 7.0, total resistance failed to change significantly in the nerve intact foreleg. Following nerve block and nerve block...
plus phentolamine, resistance decreased and the change was most regular in the latter preparation. The magnitude of change was greater on the alkaline than acid side of pH 7.3. Artery resistance increased in the nerve intact preparation but not in the other 2 preparations. Regular changes in small vessel resistance were observed in each preparation. Reduction of hydrogen ion concentration was associated with a resistance increase which occurred predominantly on the alkaline side of pH 7.3. Venous resistance did not change significantly in any preparation.

In each of 4 nerve blocked phentolaminized forelegs, the addition of atropine sulfate failed to alter changes in total and segmental vascular resistances observed with nerve block and phentolamine alone.

With blood flow rate constant, the brachial artery pressure response following brachial artery injection of 1 μl of epinephrine was the same in duration and magnitude at both extremes of pH. In 6 intact legs, average pressure increased to 165 per cent of the control values at both pH 7.6 and 7.0. In 6 nerve blocked legs, average pressure increased to 141 per cent and 156 per cent of the control values at pH 7.6 and 7.0 respectively. A pressor response was not observed following injection of epinephrine at either pH extreme in the nerve blocked phentolaminized foreleg.

**DISCUSSION**

These data appear to demonstrate that an acute increase and decrease of hydrogen ion concentration is associated with appreciable active small vessel dilatation and constriction, respectively, through some direct effect upon vascular smooth muscle. The changes occur predominantly on the alkaline side of pH 7.3. The small vessel resistance changes do not predictably affect total resistance in the intact leg because of directionally opposite active changes in artery resistance. The results also provide further evidence that the arterial and small vessel segments constitute independent resistances whose magnitudes may actively vary in opposite directions.

The small vessel resistance changes associated with pH variation probably result from some mechanism directly affecting vascular smooth muscle. They persisted in the absence of central nervous connections, circulating and locally released epinephrine and norepinephrine, and following local parasympathetic blockade.

Artery resistance changes in the intact leg were directionally opposite to those of the small vessels. The over-all results was little change in total resistance. The unusual artery response was greatly diminished following procaine block and following procaine block and phentolamine. This suggests that the artery response in the intact leg is most likely related to central nervous connections and possibly to some unknown circulating vasoactive substances.

The small vessel constriction and dilatation upon respective decrease and increase in hydrogen ion concentration appears to be active in nature. Resistance increased in the presence of rising average small vessel intraluminal pressures (average between small artery and small vein pressure) which would tend to dilate the segment passively. Resistance decreased while intraluminal pressures were decreasing. The arterial response of dilatation and constriction upon respective decrease and increase in hydrogen ion concentration in the intact leg also appears to be active in nature. Average artery segment pressure increased 13 mm. Hg and arterial resistance decreased by 40 per cent when pH was elevated from 7.3 to 7.6. Since an earlier study showed that variation of average artery segment intraluminal pressure by 30 mm. Hg was associated with passive artery resistance changes of about 20 per cent, at least part of the above artery dilatation apparently was active. The same statement is applicable to the artery constriction upon change of pH 7.6 to 7.0 since a 12 mm. Hg intraluminal pressure decrease was associated with a 40 per cent resistance increase. Similar directionally opposite active changes in artery and small vessel resistance have been observed under other experimental conditions.

Changes in venous caliber in association with pH variations, through both local and nonlocal
mechanisms, have been reported by other investigators. Predictable changes in venous resistance did not occur in any of the 4 preparations during the course of the present study. The reason for this difference is not apparent at the present time.

There appears to be no difference in the activity of epinephrine at pH 7.6 and 7.0 when assayed by vascular resistance changes in the dog foreleg. This may not be the case in other vascular beds or in the heart. Indeed Burget and Visscher showed that intravenous injections of epinephrine in the pithed cat act with progressively increasing effectiveness upon systemic arterial blood pressure, provided blood pH is rising.

The study suggests that the level of the hydrogen ion concentration may be one factor determining blood volume distribution within various segments of the systemic vascular system. Further, total resistance and hence blood flow rate in denervated limbs may be appreciably affected by changes in blood pH.

**SUMMARY**

The effect of pH change upon total and segmental foreleg vascular resistance has been studied in pentobarbital anesthetized dogs. Blood pH was varied from 7.3 to 7.6 to 7.0 by hyperventilation and ventilation with 20 per cent CO₂ over a 15 min. period. Observations were made with the nerves intact, following nerve block and after nerve block plus the infusion of a sympatholytic and adrenolytic agent.

The results appear to indicate that acute increase and decrease of hydrogen ion concentration is associated with appreciable active small vessel dilatation and constriction respectively through some direct effect upon vascular smooth muscle. The effect occurs predominantly on the alkaline side of pH 7.3. The small vessel resistance changes do not affect total resistance in the intact leg because of directionally opposite active changes in artery resistance. The latter response appears to be related to central nervous connections and perhaps unknown circulating vasoactive substances. The results also provide further evidence that the arterial and small vessel segments constitute independent resistances whose magnitudes may actively vary in opposite directions.

**Summario in Interlingua**

Le effecto de alterationes de pH super le resistentia total e segmental del vasculatura del gamba anterior esseva studiate in canes anesthesiato con pentobarbital. Le pH sanguinee esseva variato ab 7.3 a 7.6 a 7.0 per hyperventilacion e per ventilation con 20 pro cento de CO₂ durante periodos de 15 minutas. Le observationes esseva facite con nervos intacte, post bloccage de nervo, e post bloccage de nervo sequite per infusiones de un agente sympatholytic e adrenolytic.

Le resultatos pare indicar que acute ascenditas e descenditas in le concentration del iones de hydrogeno es associate con appreciabile grados de dilatation e de constriction de vasos minor per le un o le altere mechanismo que affice directemente le musculos lisie del vasculatura. Le effecto se manifesta predominantemente al latere alcalin de pH 7.3. Le alteraciones del resistentia in le vasos minor non affice le resistentia total in le gamba intacte a causa del directionalmente contrari alterationes active in le resistentia arterial. Iste ultime responsa es apparentemente relationate a eventos in le systema nervose central e forsan a non ancora cognoscite substantias vasoactive in le circulation. Le resultatos etiam supporta le conception que le segmentos arterial e le segmentos del vasos minor ha resistentias independente con magnitudes capace a variar activemente in directiones contrari.

**REFERENCES**

4 Tenney, S. M.: Sympatho-adrenal stimulation by carbon dioxide and the inhibitory effect of car-


Effect of pH Change upon Systemic Large and Small Vessel Resistance
MALCOLM FLEISHMAN, JERRY SCOTT and FRANCIS J. HADDY

Circ Res. 1957;5:602-606
doi: 10.1161/01.RES.5.6.602

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/5/6/602

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/