Vasodilator Effects of the Sodium Acetate in Pooled Protein Fraction

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Paradoxical hypotension during rapid infusion of plasma protein fraction (PPF) has been attributed to vasodilation by bradykinin in PPF. This study employed a canine, controlled right heart bypass preparation to assess changes in systemic vascular resistance and venous capacitance during infusion of PPF and other possibly vasoactive mediators. Plasma protein fraction caused consistent vasodilation, whereas purified human albumin did not. This vasodilation could be ascribed entirely to acetate, present in PPF as a buffer. Bradykinin in PPF had no effect during venous infusion. Acetate is used widely as a buffer in intravenous and dialysate solutions. Its vasoactive properties must be recognized when such solutions are administered to patients with limited capacity to compensate for sudden vasodilation.

PARADOXICAL HYPOTENSION during rapid administration of human plasma protein fraction (PPF) was reported preliminary by Harrison et al. in Australia in 1971.[11] Torda et al.,[18] as well as Bland and co-workers[4] in this country, confirmed and expanded these observations in 1973. Some of the reported reactions occurred during cardiopulmonary bypass, when PPF was infused into the extracorporeal circuit. Other reactions, however, were documented during venous infusion in patients with intact circulation. A fall in systemic vascular resistance was documented in both circumstances. Vasoactive amines, most specifically bradykinin, were known to be present in PPF, and on the basis of both direct and indirect evidence[13] they were soon implicated as the possible vasodilator elements. Since bradykinin was known to be inactivated within the pulmonary capillary bed[6] and because sensitivity to PPF had been thought by some to be greater during arterial infusion, it was recommended by manufacturers that PPF be given only into the systemic venous system, presumably to obviate the adverse effects of bradykinin.[1]

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Despite this counsel, paradoxical hypotension during venous infusion continued to be reported.[12] During these several years, we also observed numerous incidents in which hypovolemic, hypotensive patients monitored on-line for systemic arterial, central venous and left atrial pressures not only failed to respond to rapid venous PPF infusion with increased ventricular filling pressures but often developed further hypotension that was reversible within minutes after PPF infusion was stopped. We remained convinced that either bradykinin inactivation by the lungs was inadequate or that something else in PPF was pharmacologically active as a vasodilator.

Coincidentally, at about the time that we took our clinical observations to the laboratory, attention was being focused nationally on bradykinin and on the even more severe vasodilator effects of prekallikrein activator (PKA), a substance that appeared in a PPF solution developed in 1976 that was marketed as being low in bradykinin and thus purportedly free of vasodilators.[2,7] We employed a controlled whole animal preparation to quantify the vasodilation that occurs with PPF infusion and to delineate the causative factors.

Methods

Experimental Preparation

Mongrel dogs weighing 15–20 kg were anesthetized with intravenous chloralose-urethane and ventilated via an endotracheal tube with a volume ventilator. Splenectomy was done to eliminate changes in blood volume due to splenic contraction. The heart was exposed through median sternotomy. Mean and phasic central aortic (AoP), central venous (CVP) and left atrial pressures (LAP) were monitored directly by

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semirigid catheters connected to Statham P23Db transducers. The first derivative of left ventricular pressure (dP/dt) was derived electronically from the pressure signal obtained with a short, rigid catheter inserted through the ventricular apex and connected to a Statham P-50 transducer. Pressure data and electrocardiogram were recorded continuously on a Hewlett Packard 7700 writer. Heparin (3 mg/kg) was given intravenously. Superior and inferior venae cavae and right ventricle were cannulated for venous return into a cardiotomy reservoir connected in series with a stainless steel heat exchanger (to maintain rectal temperature of 37°), a separate calibrated reservoir and a roller pump. A cannulating Micron flow probe inserted in the bypass circuit between roller pump and animal and connected to a Narcomatic RT-500 flowmeter permitted continuous assessment of the constancy of cardiac output (CO) delivered by the roller pump. The pulmonary artery was ligated, and blood was returned by flexible cannula either into the main pulmonary artery (prepulmonary) or, when bypass of the lungs was employed, into the left atrium (postpulmonary). For studies in which postpulmonary return was evaluated, a disposable oxygenator with integral heat exchanger (Bentley Q-100) replaced the cardiotomy reservoir and stainless steel heat exchanger. An infusion port for administration of test solutions was placed in the circuit between the reservoir and the roller pump so that addition of solutions did not effect CO. Changes in venous capacitance were assessed by volume changes in the calibrated reservoir as these related to baseline volume plus the volume of test solutions added to the system. The extracorporeal circuit was primed with heparinized fresh, homologous blood in which pH had been adjusted to 7.4 ± 0.1 by addition of $NaHCO_3$. Right heart bypass was established with constant CO of 80–100 cc/kg/min and with maintenance of normal baseline AoP. Arterial pH, P_{CO_2} and P_{O_2} were monitored throughout the procedure and adjusted as necessary with either the ventilator or $NaHCO_3$.

After at least 5 min of stable control hemodynamics, test solutions were administered over 2½ min with at least 10 min allowed for recovery to control values in each instance. All data were collected at 30-sec intervals. Left ventricular contractility was assessed by observation of LAP, dP/dt and $dP/dt \times P^{-1}$ at a common ventricular pressure of 40 mm Hg. Venous capacitance was assessed as noted, and total systemic resistance (TSR) was calculated from the formula

$$TSR = \frac{AoP - CVP}{CO}$$

Evaluation of Individual Solutions

Phase 1. The first series of experiments in ten dogs was designed to test whether in this preparation prepulmonary infusion of 5% PPF at rates corresponding to clinical volume replacement for hypovolemic shock caused vasodilation similar to that observed clinically. Infusion of 5% human albumin (HA_5) and 25% human albumin (HA_{25}), both known to be free of bradykinin, were also infused for comparison. To avoid vasodilation due to hemodilution, homologous red cells were added to each solution to achieve an hematocrit of 40%. pH was adjusted as necessary to 7.4 ± 0.1 with $NaHCO_3$. Twenty-five per cent human albumin was made isoncotic by dilution with a balanced crystalloid solution, Plasma-Lyte 148®.* Solutions were administered at 5 cc/kg/min (3 cc/kg/min of the colloidal component).

Phase 2. The second series of experiments expanded upon observations made in Phase 1. It was designed to elucidate the vasoactive component or components responsible for Phase 1 observations and to compare postpulmonary infusion of some of the test solutions to prepulmonary infusion. The colloidal solutions in question were prepared with red cells as before, as were several crystalloid solutions containing various concentrations of possibly vasoactive agents. Rates of administration were the same as in Phase 1 studies.

The number of dogs evaluated varied among the test solutions in Phase 2, testing being limited for some solutions by the small supply of specially prepared material available to us. Assays of the activity of bradykinin and of PKA used in test solutions were done independently by Cutter Laboratories, Inc., using techniques described previously.[1,5]

Test solutions. The constituents of all test solutions are summarized in Table 1. Solutions A and H are stock commercial PPF of different manufacturing lots, A being that marketed in January 1977 and H in June 1978. Solution B is stock HA_5, and Solution C is stock HA_{25} diluted with Plasma-Lyte 148. Solution D is stock Plasma-Lyte 148. Solution E is stock HA_{25} diluted with normal saline. Solution F is normal saline with sodium acetate added to achieve an acetate (Ac) concentration similar to that of stock PPF (A and H), 16.8 mEq/l, and G is normal saline with Ac in a concentration similar to that of experimental PPF (I), 4.7 mEq/l. Solution I is experimental PPF low in Ac and without measurable bradykinin or PKA; Solution J is Solution I to which exogenous bradykinin has been added to

*Travenol Laboratories, Inc., Deerfield, Illinois.

TABLE 1. *Constituents of Test Solutions*

Solution	Crystalloid	Protein Content (%)	Bradykinin (ng/ml)	Acetate (mEq/liter)	PKA (mUnits/ml)	No. Animals Prepulmonary Infusion
Phase 1						
A—Stock PPF (lot M6479)	None	5	17.0	16.8	<2	10
B—Stock HA_5 (lot M6420)	None	5	<2	6.6	<2	10
C—Stock HA_{25} (lot M6327)	Plasma-$Lyte_{148}$	5	<2	27.0	<2	6
Phase 2						
D—Plasma-$Lyte_{148}$	Plasma-$Lyte_{148}$	0	0	27.0	0	10
E—Stock HA_{25} (lot M6327)	Normal saline	5	<2	<2.0	<2	4
F—Acetate 16.8	Normal saline	0	0	16.8	0	8
G—Acetate 4.7	Normal saline	0	0	4.7	0	4
H—Stock PPF (lot C2068)	None	5	10.8	16.8	4	5
I—Exper. PPF (1937-57)	None	5	<4	4.7	<1	4
J—Exper. PPF (1937-57) + bradykinin	None	5	10.8	4.7	<1	4
K—Exper. PPF (PR2589)	None	5	<2	4.7	39	9

PPF = plasma protein fraction; HA_5 = human albumin 5%; HA_{25} = human albumin 25%.

achieve a concentration similar to that of stock PPF (H). Solution K is an experimental PPF without measurable bradykinin and low in Ac but containing PKA in a concentration similar to that of solutions discussed by Alving et al.[1] All colloidal solutions, except for stock PPF and HA, were designated experimental and not for use in humans. Colloidal solutions were supplied courtesy of Cutter Laboratories.†

Matched pre- and postpulmonary infusions were done for Solutions H, I and J, those combinations of bradykinin and Ac most likely to demonstrate alteration in vasoreactivity due to pulmonary inactivation of vasoactive amines. Studies were completed for H and J in three dogs and for I in two dogs.

Data analysis. All data were analyzed as per cent of control value with each animal serving as its own control. Student's t-test for paired data was used to assess significance of differences. Data are expressed as value ± standard deviation.

Results

Phase 1 (Table 2)

Prepulmonary infusion of stock PPF (A) caused a consistent decrease in TSR to 91% of control at 1 min and to 83% at end infusion, with persistence of the effect 4 min following termination of infusion. Total systemic resistance returned to control 8 min after end infusion. Stock HA_5 (B) caused no change in TSR. Stock HA_{25} diluted in Plasma-Lyte 148 (C) showed a significant fall in TSR that was analogous to that of PPF (A). None of the solutions caused alterations in the various indicators of ventricular contractility or in venous capacitance. These results have been published previously in preliminary form.[19]

Phase 2 (Table 2)

The unexpected fall in TSR during infusion of HA_{25} in Plasma-Lyte 148 (C), a solution without measurable bradykinin, and the similarity of this change to that seen with PPF (A), prompted examination of Plasma-Lyte. Infusion of Plasma-Lyte 148 (D) alone caused the same type of response seen with HA_{25}

TABLE 2. *Changes in Total Systemic Resistance (TSR) During, at Termination and 4 Minutes After Termination of Prepulmonary Infusion of Possibly Vasoactive Solutions*

	Solutions	TSR (% Control) 60 Sec	150 Sec (End Infusion)	390 Sec
Phase 1				
PPF	A	91 ± 6*	83 ± 6*	93 ± 5†
HA_5	B	99 ± 5	97 ± 5	97 ± 8
HA_{25} + P148	C	94 ± 4†	90 ± 7†	100 ± 2
Phase 2				
P148	D	89 ± 7†	76 ± 9†	88 ± 7†
HA_{25} + NS	E	102 ± 5	101 ± 6	101 ± 6
Ac 16.8	F	92 ± 3*	79 ± 6*	88 ± 4*
Ac 4.7	G	101 ± 4	95 ± 5	96 ± 8
PPF 16.8 + B	H	88 ± 6†	74 ± 9†	84 ± 8
PPF 4.7	I	99 ± 2	102 ± 5	97 ± 3
PPF 4.7 + B	J	99 ± 2	99 ± 5	101 ± 5
PPF_{PKA}	K	100 ± 4	99 ± 4	95 ± 10

PPF = plasma protein fraction; HA_5 = human albumin 5%; HA_{25} = human albumin 25%; P148 = Plasma-Lyte 148; NS = normal saline; Ac = acetate; B = bradykinin; PKA = prekallikrein activator.

* $p < 0.001$, value compared to control.

† $p < 0.02$, value compared to control.

† Cutter Laboratories, Inc., Berkeley, California.

in Plasma-Lyte (C); there was no alteration in TSR during infusion of HA_{25} diluted in normal saline (E).

Plasma-Lyte 148 is a balanced electrolyte solution containing Na, K, Mg, Cl and gluconate, with NaAc in a concentration of 27 mEq/l used as a buffer to achieve a pH in the physiological range. Of these constituents, only NaAc proved to be vasoactive in our preparation. Examination of the chemical constituents of PPF (A) revealed that it too contains NaAc. Present as 0.25 g of the trihydrate moiety per 100 ml, the calculated concentration of acetate is 18.3 mEq/l, but the actual concentration apparently varies depending on buffer needs during PPF preparation. Albumin solutions on the other hand contain very little acetate, generally around 5 mEq/l.

This finding caused us to query, first, *whether Ac and not bradykinin could be the principal vasodilator in PPF during prepulmonary infusion* and, second, whether postpulmonary infusions of solutions containing commercial concentrations of Ac and/or bradykinin would alter the responses observed with prepulmonary infusion. To pursue these questions, we requested the cooperation of Cutter Laboratories and obtained several experimental solutions along with the then current commercial lot of PPF, which itself contained 16.8 mEq/l of Ac. These are colloidal solutions H, I, J and K. Control normal saline solutions (F and G) containing the same amounts of Ac present in the experimental colloidal solutions were used as Ac controls.

Prepulmonary infusion of Ac alone in saline at 1.68 mEq/l (F) caused a decrease in TSR to 79% control. Acetate alone in saline at 4.7 mEq/l (G), the lowest concentration of Ac in PPF available to us, had no vasodilator effect. Prepulmonary infusion of the new stock of PPF (H) decreased TSR to 74% of control at end infusion. This change was similar to the decrease to 83% we had seen with the older PPF lot (A), despite lesser bradykinin concentration in the newer solution! This change correlated well with the decrease to 79% found with Ac 16.8 (F). Experimental PPF (I), low in Ac and free of measurable bradykinin, had no effect on TSR. When bradykinin (10.8 ng/ml) was added to PPF (I) to make PPF (J), prepulmonary infusion still failed to affect TSR. Thus, of the vasoactive constituents in the new colloidal solutions, H, I and J, only Ac at 16.8 mEq/l caused vasodilation during prepulmonary infusion.

Prepulmonary infusion of Solution K, high in PKA but low in Ac and free of measurable bradykinin, caused changes in TSR that were completely different in both quality and magnitude from changes observed with Ac. There were no changes in TSR during infusion, but from 4 to 9 min after end infusion, several dogs demonstrated 5–15% decreases in TSR that were progressive and sustained for up to 10 min. The group mean of TSR at 7 min from end infusion was 93 ± 9% of control ($p < 0.05$).

Matched pre- and postpulmonary infusion of Solutions H, I and J (Table 3) were inconclusive regarding the extent of vasodilation from postpulmonary infusion of bradykinin when compared to prepulmonary infusion. A trend, suggesting a propensity to further decrease of TSR beyond what might have been attributed to Ac, was apparent for solution H. Some vasodilation also seemed to occur for Solution J during postpulmonary infusion only. The small number of dogs we were able to study precluded valid statistical analysis.

None of the solutions caused alterations in the various indicators of ventricular contractility or in venous capacitance.

Discussion

This study employed a whole animal preparation designed to reveal changes in systemic vascular resistance and venous capacitance during infusion of volume expanders at rates analogous to those required clinically during rapid expansion of blood volume for hypovolemia. The data obtained strongly corroborated previous clinical observations that rapid venous

TABLE 3. *Changes in Total Systemic Resistance (TSR) During, at Termination and 4 Minutes After Termination of Prepulmonary and Postpulmonary Infusions of Possibly Vasoactive Solutions*

	TSR (% Control)					
	60 Secs		150 Secs (End Infusion)		390 Secs	
Solutions	Pre-pulmonary	Post-pulmonary	Pre-pulmonary	Post-pulmonary	Pre-pulmonary	Post-pulmonary
PPF 16.8 (H)	86 ± 7	80 ± 6	70 ± 8	68 ± 12	86 ± 10	75 ± 8
PPF 4.7 (I)	98 ± 3	96 ± 5	100 ± 5	92 ± 4	94 ± 2	97 ± 3
PPF 4.7 + B (J)	100 ± 2	93 ± 6	101 ± 2	94 ± 5	103 ± 2	101 ± 6

PPF = plasma protein fraction; B = bradykinin.

infusion of commercial PPF consistently causes arteriolar vasodilation with a decrease in TSR that is immediate, progressive during infusion and reversible when infusion is stopped. Human albumin solutions administered in the same preparation have no demonstrable vasoactive properties. As discussed below, the vasodilation observed during venous infusion of commercial PPF solutions in this study could be attributed entirely to acetate.

On the basis of these data we have stressed that PPF not be used for rapid volume expansion but that human albumin solutions be used instead.[19] This stance is consistent with that of other authors[4,7] and with the current recommendations of the major North American PPF manufacturers, whose PPF package inserts interdict arterial infusion and caution against intravenous administration at rates exceeding 10 cc/min, hardly sufficient for treatment of acute hypovolemia. Unfortunately, precedent and inertia have kept PPF solutions on emergency room and intensive care unit shelves, with usage dictated by the acute need for a volume expander without regard to the package insert. This has been true as recently as December 1978 in our own affiliated hospitals.

The larger and more interesting issue raised by this study, however, relates to the etiologic roles of acetate versus bradykinin in the vasodilation observed. Since traditional preparation of PPF solutions has preserved the presence of amines long recognized to be vasoactive and preparation of purified albumin solutions has virtually eliminated these compounds, it had seemed logical to attribute the difference in pharmacological behavior of the two solutions to the presence of such compounds as bradykinin in PPF only. To our knowledge, vasodilation by a nonprotein moiety has never been seriously suggested. A considerable amount of research effort and breast-beating has been generated by concerns about bradykinin. Indeed, PPF solutions were recently developed and marketed with bradykinin reduced to physiological amounts to prevent hypotensive reactions. Unfortunately, these solutions also caused such severe hypotensive reactions that the Food and Drug Administration was prompted to an investigation, and the manufacturers were forced to recall the products. After careful biochemical examination of this new PPF preparation, PKA was implicated as the vasoactive culprit by association.[2] It was notable that many of the reactions attributed to PKA were apparently more delayed in onset and longer in duration than those reported with previous PPF solutions. In the nine dogs we studied with prepulmonary infusion of low Ac, high PKA solution (K), hypotensive reactions were similarly delayed and prolonged but were much less severe, with overall decrease in TSR for the entire group reaching a value of 93% of control 7 min after the end of infusion. This phenomenon has been attributed to *in vivo* activation of the kallikrein system prior to generation of endogenous bradykinin. We feel, however, that the PKA story is clouded by the report to us that the PKA solutions studied by Alving et al. contained from 10 to 60 mEq/l of Ac, mostly in the range 10–20 mEq/l.[8] We do not know the correlation of Ac level with severity of clinical reaction, but it is possible that acetate in those solutions might have acted synergistically with PKA to provoke marked hypotension. The PKA problem has subsequently forced a return to PPF solutions containing higher concentration of bradykinin. Concern, therefore, over potential vasodilator properties of bradykinin in PPF has persisted.

Our study casts doubt on the concept that bradykinin was ever highly instrumental in causing hypotension during *venous* infusion of PPF. Rather, we infer from our data that Ac, which to our knowledge has been present at >15 mEq/l in every PPF solution marketed since the late 1960s (stable plasma protein solution produced in Australia may be an exception[17]) and has never been present at >6 mEq/l in purified albumin solutions, has vasoactive properties that make it likely to be a primary cause of the hypotensive reactions reported clinically. We found that Ac was the vasoactive ingredient in Plasma-Lyte 148 (used initially in our study to dilute HA_{25}). Infusion of Ac alone in the concentration present in the commercial PPF solutions (A and H), that is, 16.8 mEq/l, resulted in a decrease in TSR virtually indentical to that observed with infusion of either of the two commercial PPF solutions, each of which also contained bradykinin. When Ac in saline was reduced in concentration to 4.7 mEq/l, no significant change in TSR occurred. The availability of a small quantity of experimental PPF solution low in Ac, 4.7 mEq/l, and free of measurable bradykinin (Solution I) enabled us to examine bradykinin in PPF independent of Ac. Prepulmonary infusion of Solution I caused no change in TSR; moreover, when a commercial concentration of bradykinin was added to this low Ac PPF (to make Solution J), prepulmonary infusion still had no effect. *The vasodilation observed during venous infusion of commercial PPF solutions in this preparation could be ascribed entirely to acetate.*

Bradykinin may have had additional vasoactive effect when we infused Solutions H and J into the arterial side of the circulation. Such a finding would be consistent with the concept that pulmonary inactivation of bradykinin can be adequate only for venous infusion and would support the interdiction of PPF for arterial infusion. Unfortunately, the number of animals we were able to study successfully with matched pre- and postpulmonary infusion was too small to provide statistical

confirmation of what appeared to be a consistent trend. Further evaluation of pre- and postpulmonary administration of various doses of bradykinin is pending.

Our discovery of the vasoactive role of Ac in PPF came at a time when the attention of others was being focused on the vasoactive properties of Ac used in hemodialysate solutions. We did not know that Ac and other Krebs cycle intermediates had been evaluated as far back as 1962.[15] In 1965, Frohlich showed that in an isolated limb preparation Ac was a potent arteriolar vasodilator with what appeared to be a direct local effect on vascular smooth muscle.[9] He hypothesized that the mechanism of this effect might be local Ca^{++} binding, but further elucidation of the mechanism is still forthcoming. Nonetheless, since Ac is readily metabolized to CO_2 and H_2O and its Ca and Mg salts are highly soluble, it became an appealing alternate to bicarbonate as a buffer in hemodialysis solutions. Acetate in dialysates soon became standard, and it was well tolerated by patients despite its vasoactive potential until the utilization of large surface, high efficiency dialyzers increased the rapidity of Ac exchange. In the past 3 years, several clinical and laboratory studies have appeared in the dialysis literature showing that acetate dialysis consistently causes systemic vasodilation and that in certain patients it provokes episodes of severe hypotension.[3,10,14,16] Patients most prone to adverse effects seem to be those with preexisting cardiac insufficiency and diminished cardiovascular reserve. As suggested by Novello et al.,[16] Ac intolerance may occur by one or more of three mechanisms: 1) excessive rate of administration of exogenous Ac, 2) circulatory insufficiency with decreased delivery of Ac *in vivo* to metabolic sites such as liver and 3) decreased metabolic capability, such as in hepatic insufficiency. Any of these mechanisms in a patient unable to increase cardiac output in response to peripheral vasodilation will facilitate a hypotensive reaction.

These concurrent but independent dialysis studies substantiate our assertion that Ac is a causative factor in PPF hypotensive reactions and help to illuminate a still larger problem. Acetate is not restricted to dialysates and PPF. It is also a standard buffer in newer crystalloid solutions such as Plasma-Lyte 148 and Normosol R®‡ that are designed to provide physiological pH. Such solutions are becoming more popular for routine intravenous therapy, for crystalloid oxygenator primes during cardiopulmonary bypass and for resuscitation from hypovolemia. The potential for unsuspected adverse reactions is considerable whenever solutions containing Ac in the range of 15–20 or more mEq/l are to be administered rapidly. In this circumstance, recognition must be given to the vasoactive properties of Ac and to the ability of the patient to compensate for sudden vasodilation. We feel such solutions are contraindicated in the critically ill, hypotensive, vasoconstricted patient, particularly when there is diminished cardiac reserve. If Ac-containing solutions are being infused and hypotension occurs or fails to be corrected in the patient previously in shock, the infusion should be stopped promptly, and other volume expanders given instead. The threat of Ac "toxicity" in this context is that continued hypotension will be ascribed inappropriately to another cause and that a potentially correctable problem may remain uncorrected.

‡ Abbott Laboratories, N. Chicago, Illinois.

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