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IN POTASSIUM HOMEOSTASIS




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THE ROLE OF CATECHOLAMINES IN POTASSIUM HOMEOSTASIS

A Thesis

Submitted to the Yale University School of Medicine

in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Medicine

1979

Guthrie Birkhead

To my Family

Special thanks to Lois Mishiwiec, Louise Westover
Helen Backus, Yihfen Wu and the staff of the Clinical
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I. Introduction

Insulin and aldosterone have long been recognized to play important roles in potassium homeostasis. Both have been shown to participate in feed-back control circuits whereby rises in the plasma potassium concentration stimulates the release of each hormone (1,33). Increased levels of plasma aldosterone, in turn, stimulates both the renal excretion (33-36) and the extrarenal cellular uptake (34,38) of potassium. The primary influence of insulin on potassium balance is to augment extrarenal uptake of potassium, predominantly by liver and skeletal muscle (4,6-11). Recent studies have suggested that epinephrine and other sympathomimetic substances may also play an important role in maintaining potassium homeostasis (2, 51). More specifically, beta-adrenergic agonist agents have been shown to ameliorate the rise in serum potassium concentration following the administration of potassium chloride in cats (2,49). However, whether such a protective effect exists in man and the mechanisms underlying this effect have not been completely studied. It is the purpose of the present thesis to examine whether catecholamines exert a protective effect against hyperkalemia in man and to define the mechanism or mechanisms by which such an effect might occur. Attention will also be given to the possible interrelation-

ships between the protective effect of catecholamines on potassium tolerance and the previously described insulin and aldosterone feed-back systems.

II. Overview

A. Insulin and Potassium

Insulin infusion has long been known to lower the serum potassium concentration (3). This effect is thought to be mediated by promoting the transfer of extracellular potassium into cells, particularly liver and skeletal muscle (4,6-11). Andres and coworkers (10) employing the forearm perfusion technique in human subjects were among the first to demonstrate that insulin stimulated skeletal muscle uptake of potassium. Furthermore, the insulin mediated stimulation of potassium uptake occurred at levels of insulin that had no effect on muscle uptake of glucose. Glucose uptake, however, did move to enhance potassium uptake. In addition, Zierler (6-8) and others (9) have found that incubation of muscle tissue in vitro with insulin causes intercellular accumulation of potassium and hyperpolarization of the cell membranes even in the absence of glucose in the incubation medium. The molecular mechanism of this action of insulin has not been completely elucidated but it has been postulated that this effect of insulin on potassium is part of the chain of events which results in cellular uptake of glucose (6,8). Insulin-mediated uptake by liver cells has been less well defined. Early studies by Fenn et al. (3) suggested that the liver disposed of potassium following insulin administration. More recently,

DeFronzo and coworkers, employing hepatic venous catheterization in combination with the insulin clamp technique, have shown that over half of the potassium disappearing from the extracellular space following insulin administration can be accounted for by hepatic uptake (12). An effect of insulin on potassium uptake by the brain has also been demonstrated (13) but this is small compared to the muscle and liver uptake.

The clinical importance of insulin in maintaining potassium homeostasis is particularly evident in diabetic subjects. When these patients are given an exogenous glucose infusion creating a state of hyperglycemia, no change or a slight rise in serum potassium occurs (11). This is in contrast to normal subjects in whom hyperglycemia leads to a decline in serum potassium concentration through eliciting secretion of insulin (11). It has been postulated that hyperglycemia causes the osmotic extraction of fluid and electrolytes (predominantly potassium) from the intercellular environment (13). Glucose induced insulin release is responsible for the transport of potassium back into cells. In diabetics who lack both insulin and the second important potassium regulatory hormone aldosterone, hyperglycemia may thus result in lethal hyperkalemia (11,14,15).

While changes in the circulating insulin levels may effect serum potassium concentrations, it has also been discovered that basal insulin levels play a role in potassium

homeostasis. DeFronzo and coworkers (15,16) have shown that in normal subjects and maturity-onset diabetics who retain the ability to secrete insulin, the inhibition of basal insulin secretion with somatostatin results in a significant rise in serum potassium concentration of 0.5 to 0.6 mEq/l without a change in urinary potassium excretion. In contrast, a similar administration of somatostatin to juvenile-onset diabetics who lack endogenous insulin release has no effect on serum potassium concentration. Replacement of basal insulin levels by continuous insulin infusion in the control group reversed the somatostatin induced rise in serum potassium. Somatostatin has also been shown to markedly impair the ability of dogs to dispose of an acutely administered potassium load (16). Again, replacement of basal insulin levels restored potassium tolerance to normal. Thus, maintenance of basal insulin levels plays an important role in the defense against hyperkalemia.

In order to complete the circuit of a proposed insulin-potassium feedback loop, it is necessary to show that potassium is capable of stimulating the release of insulin. Such an effect has been demonstrated in the isolated, perfused rat (17) and dog (18) pancreas, and following potassium infusion in the dog (19) and in man (20). However, in most of these studies, the increment in plasma potassium concentration necessary to stimulate insulin release was in excess of 1.5 to 2.0 mEq/l. In studies where the plasma potassium concentration

was raised by less than 1.5 to 2.0 mEq/l, it has been difficult to demonstrate an increase in circulating insulin levels. Thus, Sterns et al. (21) found no change in plasma insulin levels during a potassium infusion which raised the plasma potassium concentration by a mean of 1.15 mEq/l, and Dluhy and coworkers (20) likewise failed to observe a rise in plasma insulin concentrations in response to an infusion of potassium which raised the serum potassium concentration by 1.5 to 2.0 mEq/l. Complicating the interpretation of these data is the fact that the portal vein insulin concentration may be four to five times the measured peripheral insulin concentration (22). It is thus possible that even small increments in plasma potassium concentration may result in significant insulin secretion which, because of the large extraction of insulin by the liver would not be reflected in the periphery. Such unmeasured insulin could still be active in effecting potassium metabolism in the liver. Support for this thesis comes from the work of Bleckard et al. who found a significant rise in the portal vein insulin concentration following potassium chloride administration without a change in peripheral insulin levels (22). Since recent studies by DeFronzo and coworkers (12) have shown the liver to be an important site of insulin mediated potassium uptake, local increases in portal vein insulin concentrations may play an important role in potassium homeostasis. However, even in the absence of a rise in plasma insulin concentration levels, the

maintenance of basal insulin levels has been shown to play an important role in potassium homeostasis.

Insulin has also been related to potassium excretion in studies by DeFronzo et al. (23) who showed that physiologic hyperinsulinemia is associated with a decline in the rate of urinary potassium excretion. However, this seemed to be secondary to a fall in plasma, and thus filtered, potassium concentration. A direct effect of insulin of renal tubular handling of potassium was not demonstrable in studies with dogs.

B. Aldosterone and Potassium

Aldosterone is an adrenal steroid hormone which mediates the exchange of sodium and potassium in the distal renal tubule. Though many factors influence aldosterone secretion, potassium is known to be a potent aldosterone secretagogue. Potassium has been found by McCaa et al. (24) to be a more potent aldosterone secretagogue than angiotensin II in dogs chronically administered either potassium or angiotensin II. This stimulatory effect has also been shown in isolated rat and human (25) adrenal cortical cells incubated in vitro with potassium, in isolated adrenal glands perfused with potassium and in intact dogs (24,26,27), and in man (28) perfused with potassium. Dluhy and coworkers have demonstrated the release of aldosterone in man without an increment in serum potassium during potassium infusion (28). This effect

was observed in nephrectomized and hypophysectomized animals thereby eliminating renin and ACTH as primary stimuli to aldosterone secretion. Infusion of potassium into adrenal arteries resulted in aldosterone release without a rise in peripheral potassium concentration indicating again that potassium is a direct aldosterone secretagogue. In the opposite direction, infusion of glucose or insulin which lowers the serum potassium concentration by as little as 0.3 mEq/l has been shown to decrease aldosterone levels by fifty per cent (28). These data indicate that physiologic decreases as well as increases in potassium concentration are important regulators of aldosterone secretion. These effects of potassium have been shown to be independent of dietary sodium intake and to occur in anephric patients (1).

In addition to its effect on aldosterone release, potassium has also been shown to exert a stimulatory effect on aldosterone synthesis. Potassium increases the activity of the 18-hydroxylase enzyme which catalyzes the penultimate step in aldosterone synthesis (29). This effect has been demonstrated in cultured zona glomerulosa adrenal cells (29). In human subjects, with the terminal part of the aldosterone synthesis pathway isolated with metyrapone (30), a requirement for potassium has been found with the initial step in aldosterone synthesis as well. This confirms earlier work by Kaplan et al. (31).

More recently, Catt (32) has shown that potassium also plays a permissive role for other aldosterone secretagogues. Using isolated zona glomerulosa cells he demonstrated that a decrease in the incubation potassium concentration markedly inhibits the activity of angiotensin and ACTH to stimulate aldosterone release.

The importance of aldosterone in maintaining normal potassium homeostasis has been recognized for years. Aldosterone deficiency is known to result in hyperkalemia (33) while aldosterone excess is associated with hypokalemia (34). In contrast to insulin, which exerts its major effect on extrarenal potassium handling, aldosterone acts primarily by augmenting renal potassium excretion (35,36). Thus, in animals the ability of the distal nephron to excrete potassium is markedly impaired, and acute and chronic potassium tolerance is diminished, in the absence of aldosterone.

Some evidence does exist, however, that aldosterone may play a small role in extrarenal potassium homeostasis as well. Alexander and Levinsky (37) found that nephrectomized rats on a high potassium diet had a better potassium tolerance following an acute potassium load than those kept on a normal potassium diet. Their results indicate that an extrarenal effect of aldosterone on potassium handling exists that is dependent on a state of chronic hyperaldosteronism secondary to a high potassium diet. A possible cellular mechanism for this effect comes from the work of Adler (38) who found that aldosterone enhances potassium uptake by skeletal muscle

cells in vitro, and that this enhancement is greater at elevated concentrations of potassium (7.5 mEq/l) in the incubation medium.

In summary, elevation of the serum potassium concentration results in increased synthesis and release of aldosterone which in turn enhances both renal and extra renal potassium disposal.

C. Epinephrine and Potassium

D'Silva was the first to suggest that epinephrine might play a role in potassium homeostasis (39). He found that an intravenous infusion of epinephrine into anesthetized cats resulted in a triphasic response in the plasma potassium concentration. Within the first two minutes following epinephrine administration, there was a small rise in the plasma potassium concentration. This was followed by a decrease in the concentration to levels 1 mEq/l below the baseline value by ten minutes following epinephrine administration. Subsequently, the plasma potassium concentration slowly returned to baseline over the next thirty minutes. This effect of epinephrine was mimicked by the sympathomimetic agent ephedrine and abolished by ergotamine, a sympatholytic agent. The triphasic response of plasma potassium concentration to epinephrine infusion has been observed many times since this first report (40).

Employing hepatic catheterization in cats, D'Silva further found that the liver was the site of the potassium

release responsible for the initial rise in the potassium concentration following epinephrine administration (41). Hepatectomy abolished the early hyperkalemic effect of epinephrine completely. D'Silva, and subsequently Brewer (42), have shown by the same technique that the second phase decline in plasma potassium concentration following epinephrine infusion is largely the result of hepatic sequestration of potassium (4,43,44).

An extrahepatic effect of epinephrine on potassium homeostasis has been suggested in the work of several investigators showing an effect of epinephrine on skeletal muscle potassium uptake (44,45). Epinephrine infusion into the femoral artery of dogs enhances the arterial-venous plasma potassium concentration difference indicating that peripheral uptake of potassium has occurred. That this increased uptake is probably accounted for by muscle tissue is suggested by studies in cats (2) and frogs (45) demonstrating increased potassium content of skeletal muscle following epinephrine induced hypokalemia.

The mechanism of the initial hyperkalemic effect of epinephrine has been shown by Vick and coworkers (46,47) to be mediated by alpha adrenergic receptors. The subsequent hypokalemia, conversely, is shown to be due to beta-adrenergic receptor stimulation. Pre-treatment with the specific alpha agonist phenoxybenzamine inhibited the initial rise and augmented the subsequent fall in plasma potassium concentration following epinephrine administration indicating that the

alpha agonistic effects of epinephrine are predominantly hyperkalemic. When phenoxybenzamine was administered alone, a decline in the potassium concentration ensued indicating a role for basal alpha sympathetic activity in potassium homeostasis (47). Infusion of the specific alpha agonist phenylephrine caused a rise in the plasma potassium concentration supporting these results. Pretreatment with the specific beta sympathetic agonist propranolol prevented the secondary fall in the potassium level following epinephrine administration, indicating that beta receptor stimulation is responsible for the hypokalemic phase of the epinephrine response. This finding is supported by the observation that isoproterenol, a pure beta stimulant, causes a fall in the plasma potassium concentration to a greater extent than with epinephrine. Interestingly, changes in the potassium concentration following the infusion of isoproterenol and phenylephrine followed closely those with epinephrine administration, confirming its mixed alpha and beta activity (48). Finally, in limited studies in man, propranolol was found to block the hypokalemic effect of a 10 ug/min epinephrine infusion (48).

In summary, the effect of epinephrine on potassium metabolism results from combined alpha and beta adrenergic stimulation with the alpha effect predominating initially and the beta effect later. The initial hyperkalemic effect is mediated via hepatic potassium release while both skeletal

muscle and liver uptake of potassium play a role in the subsequent hypokalemic effect.

The protective effect of beta stimulation on potassium tolerance has been further studied by Lum and Lockwood (2, 49). In cats infused with potassium to the point of fatal cardiac toxicity, epinephrine was found to ameliorate the rise in plasma potassium concentration and increase survival. The specific beta-2 agonists soterenol and salbutamol mimicked this protective effect but the specific beta-1 stimulant 1-isopropyl-2-(2-thiazoxy)-2 propanol did not. Similarly, the specific beta-2 antagonist butoxamine abolished the protective effect of epinephrine while the specific beta-1 antagonist practolol did not. Thus, the beta-2 adrenergic receptor appears to be the mediator of the hypokalemic effects of epinephrine. Interestingly, in Lum and Lockwood's work, the protective effect of epinephrine in acutely induced hyperkalemia persisted in pancreatectomized animals, excluding any role for insulin.

Finally, there is evidence that epinephrine infusion causes changes in renal potassium metabolism. In contrast to its effect on the systemic circulation, epinephrine causes an increase in renal vascular resistance and a concomitant reduction in renal blood flow (50). Renin secretion is also enhanced by epinephrine and would be expected to increase potassium excretion by the kidney. The changes in renal hemodynamics have been shown by Smythe et al. (51) to be associated

with a marked decrease in potassium excretion without any change in glomerular filtration rate by an as yet unclear mechanism.

D. Epinephrine and Insulin

Epinephrine has been shown to inhibit insulin secretion in a variety of experimental systems: isolated perfused pancreas (52) and in intact man and animals (53-55). Porte et al. (54,55) showed that infusion of epinephrine into human subjects resulted in hyperglycemia (180 mg/dl) yet no increase in serum immunoreactive insulin (IRI) occurred. A similar degree of hyperglycemia following glucose infusion without epinephrine resulted in an immediate and significant increase in serum insulin levels. When the epinephrine infusion was stopped in the former study, an abrupt increase in the insulin level to three-fold above basal ensued. Porte also showed that epinephrine inhibited the rise in serum insulin concentration following glucose, glucagon and tolbutamide administration. Infusion of phentolamine, an alpha adrenergic blocking agent, reversed the inhibitory effect of epinephrine and the insulin concentration rose (56). In contrast, isoproterenol, a beta adrenergic agonist, was found to stimulate insulin release. These observations indicate that the effect of alpha adrenergic stimulation is to inhibit insulin release while beta adrenergic stimulation results in insulin secretion.

The effect of epinephrine on insulin secretion has been further defined with more frequent sampling and prolongation of epinephrine infusion in human subjects (56,57). An initial fall in serum insulin levels occurred during the first fifteen minutes of epinephrine infusion and this was followed by a gradual rise to baseline by sixty minutes, and to levels two-fold above basal at one hundred and twenty minutes. The initial decline was reversed by phentolamine, and the subsequent recovery, by propranolol. A similar effect has been reported in the isolated perfused dog pancreas (52).

Finally, the effect of endogenous sympathetic activity on basal insulin secretion has been investigated by the infusion of phentolamine or propranolol alone. Phentolamine led to an increase in the serum insulin levels whereas propranolol resulted in a fall (58). Neither infusion had an effect on the serum glucose concentration.

Thus, as with epinephrine and potassium, the relationship between epinephrine and insulin seems to be dependent on a balance between alpha and beta adrenergic mechanisms. The predominant effect of epinephrine at the rate of infusion used in most studies ($6\mu\text{g}/\text{min}$) is an inhibition of insulin release which is mediated through alpha adrenergic receptors; an increase in insulin secretion is observed following beta adrenergic stimulation. A similar effect of epinephrine has also been documented with more physiologic doses of epinephrine ($20\text{-}60\mu\text{g}/\text{min}$) in human subjects (58).

E. Epinephrine and Aldosterone

Sympathetic stimulation is one of the recognized factors which stimulates renin secretion from the kidney and thus, indirectly, aldosterone release from the adrenal cortex (59). A direct effect of epinephrine on aldosterone synthesis or release has not been described.

III. Purpose

The present study seeks to define the role of epinephrine in potassium homeostasis in human beings. Previous studies have largely dealt with epinephrine induced changes in plasma potassium concentration in anesthetized laboratory animals and have employed pharmacological doses of epinephrine, resulting in serum epinephrine levels even above those found in conditions of stress. In studies involving potassium infusion in conjunction with epinephrine infusion to test epinephrine's effect on potassium tolerance, the dose of potassium chloride employed was also pharmacologic with resulting plasma potassium concentrations in the 8 to 10 mEq/l range, and cardiac toxicity and death employed as the endpoint. Whether epinephrine plays a protective role in ameliorating rises in plasma potassium concentration within the physiologic range has not been examined. In addition, no studies have been performed in which changes in renal handling of potassium were measured and correlated with changes in plasma potassium concentration during epinephrine or epinephrine and potassium chloride infusion. Similarly, the influence of epinephrine on insulin and aldosterone, hormones known to effect potassium homeostasis, was never evaluated in these previous studies. Finally, the effect of changes in plasma potassium concentration on catecholamine secretion has not previously been defined. It is to these questions that the present study is addressed.

IV. Methods

A. Subjects

Six healthy volunteers were obtained ranging in age from 18 to 22 years (mean 19.5 ± 0.7 yr).

(Table I). There were 5 males and 1 female. No subject had any significant past medical illness, none was taking any medications, and all were consuming a diet containing at least 200 grams of carbohydrate per day for three days prior to study. One patient had a family history of diabetes mellitus. Informed, written consent was obtained from each subject prior to their participation in the study.

B. Experimental Protocol

All studies were performed in the postabsorptive state at 8 a.m. following a 12 hour overnight fast. All subjects remained recumbent during the study except to void. Prior to study, polyethylene catheters were inserted under local xylocaine anesthesia into an antecubital vein for blood sampling and into a femoral vein for the infusion of all test substances. All subjects were given a distilled water load (15 ml/kg) followed by enough distilled water orally to ensure voiding every 30 minutes. Following the collection of two to three baseline urine samples, the infusion of test substances was begun. Each subject participated in three sequential studies and thereby served as his own control.

In the first study (Figure 1), potassium chloride (Potassium Chloride Injection, IVNEX Pharmaceuticals, Chagrin Falls, Ohio) was infused via a constant infusion pump (Model 975 Compact Infusion Pump, Harvard Apparatus, Millis, Mass.) at a rate of 0.75 mEq/kg over two hours. The potassium chloride was dissolved in half-normal saline solution and infused at the rate of 0.74 ml/min. The study was continued for an additional two hours after stopping the potassium infusion. In the second study, subjects received the same potassium chloride infusion as in the first study. In addition, a constant infusion of epinephrine chloride (Adrenalin Chloride Solution 1:1000, Parke-Davis and Co., Detroit, Mich.) at the rate of 0.05 μ g/kg/min was started 30 minutes prior to beginning the potassium infusion and was continued throughout the four hour study period. The epinephrine was dissolved in half-normal saline and was administered at the rate of 0.27 ml/min. In the third study, potassium chloride and epinephrine were administered as above. In addition, a constant infusion of propranolol hydrochloride (Inderal, Ayerst Laboratories, Inc., New York. N.Y.) given at the rate of 1.43 μ g/kg/min was begun concomitantly with the epinephrine. The propranolol was dissolved in half-normal saline and infused at the rate of 0.27 ml/min.

Blood pressure, heart rate and electrocardiogram were monitored at 15-30 minute intervals throughout each study.

Following at least two baseline samples, blood samples were drawn at 15-30 minute intervals throughout the study and analyzed for potassium, sodium, glucose, insulin, aldosterone, creatinine, epinephrine and norepinephrine. A total of 400 ml of blood was drawn per study. The sum of infused solutions including normal saline to flush the blood drawing catheter was also approximately 400 ml.

Urine samples were collected at 30 minute intervals during the study and were analyzed for potassium, sodium and creatinine.

C. Analytical Determinations

Potassium and sodium concentrations in plasma and urine were determined by flame spectrophotometry (Flame Photometer Model 143, Instrumentation Laboratory, Lexington, Mass.) using lithium as the internal standard. Plasma and urine creatinine concentrations were determined by the method of Jaffe adapted to the Auto Analyzer (60). Methods for the determination of plasma insulin (61) and plasma aldosterone (62) have been previously published. Plasma epinephrine and norepinephrine concentrations were determined by radioenzymatic assay (63) in the laboratory of Dr. Robert Sherwin. Plasma glucose concentration was determined by the glucose oxidase method (Glucose Analyzer, Beckman Instrument, Fullerton, C.A.).

D. Calculations

Creatinine clearance was calculated by the formula:

$$C_{Cr} = UV/P$$

where U is the urinary creatinine concentration, V is the urine volume and P is the plasma creatinine concentration.

Urinary potassium excretion rate was calculated by the formula:

$$K_{exc} = U_K V/t$$

where U_K is the urinary potassium concentration, V is the urine volume and t is the time of urine collection in minutes. K_{exc} is expressed as $\mu\text{Eq}/\text{min}$.

The net amount of potassium excreted for any given time period was calculated as the difference between the mean rate of potassium excretion during the time period and the mean baseline potassium excretion rate, times the time.

The net sodium excretion was calculated in a similar manner to that for net potassium excretion.

The amount of potassium that was translocated into cells during any given time period was calculated from the difference between the expected rise in plasma potassium concentration and the actual rise in the plasma potassium concentration multiplied by the extracellular fluid volume as follows:

$$\begin{aligned}
 \text{cellular uptake} \\
 \text{of potassium} \\
 \text{(mEq)} &= (\text{expected rise in } P_K - \\
 &\quad \text{actual rise in } P_K) \times \text{ECV} \\
 &= \frac{K_{\text{inf}} - K_{\text{exc}}}{\text{ECV}} - \Delta P_K \text{ obs} \times \text{ECV}
 \end{aligned}$$

where K_{inf} is the total amount of potassium infused (mEq), K_{exc} is the net amount of potassium excretion (mEq), $\Delta P_K \text{ obs}$ is the net observed rise in plasma potassium concentration (mEq/l) over the two hour potassium infusion and the subsequent two hour measurement period, and ECV is the extracellular fluid volume calculated as 15% of body weight (liters).

The incremental area under the plasma potassium concentration-time curves was calculated using the trapezoidal rule approximation and was carried out by the subroutine QAOLAS of the Harwell Subroutine Library of the Yale University IBM 370/158 computer. It is expressed as mEq/l x min.

E. Statistical Analysis

Values are expressed as the mean \pm SEM. Comparison of groups was performed with the paired t-test (64). Linear regression was used for curve fitting.

V. Results

A. Vital Signs

During the potassium chloride infusion alone, no change in heart rate or blood pressure was observed. When epinephrine was infused with potassium chloride, a variable increase in heart rate (15-20 beats per min) and a widening of pulse pressure (10-20 mm Hg) occurred. Subjectively, most subjects reported feelings of tremulousness and a pounding heart beat which was most marked at the beginning of the epinephrine infusion and subsided after the first sixty minutes. When propranolol was added to the potassium chloride and epinephrine infusion, no change in heart rate or pulse pressure was observed and no subjective sensations were reported by any volunteer.

B. Potassium

During the potassium chloride infusion alone baseline plasma potassium concentration (3.77 ± 0.11 mEq/l) rose by a maximum of 0.83 ± 0.09 mEq/l ($p < 0.001$) (Figure 2). This maximum rise occurred at two hours into the study when the potassium chloride infusion was stopped. Thereafter, the plasma potassium concentration progressively declined and was 0.38 ± 0.14 mEq/l above basal values at the end of the study. Urinary potassium excretion increased significantly from a mean baseline rate of 37 ± 12 μ Eq/min to a mean maximum rate of 184 ± 15 uEq/min ($p < 0.001$) (Figure 3) without a

change in creatinine clearance (Figure 4). $47 \pm 4\%$ of the infused potassium was excreted during the four hour study period (Figure 5). Of the infused potassium that was retained within the body at the end of the four hour study period, 24.8 ± 1.17 mEq was translocated into cells (Figure 6). This represented $82 \pm 5\%$ of the retained potassium (Figure 7) and $43 \pm 3\%$ of the total amount of potassium administered (Figure 8). The incremental area in plasma potassium during the 0-120 and 0-240 minute time periods was 65.3 ± 5.8 and 126.5 ± 16.2 mEq/l x min respectively (Figure 9). The incremental area in plasma potassium expressed per amount of potassium retained during the same time periods was 1.5 ± 0.2 and 4.2 ± 0.5 min/l (Figure 10).

When epinephrine was infused alone for 30 minutes preceding potassium chloride infusion, the plasma potassium concentration fell from a baseline value of 3.66 ± 0.10 mEq/l, which was similar to that in the first study, to 0.61 ± 0.06 mEq/l below baseline 30 minutes after beginning the epinephrine infusion ($p < 0.001$) (Figure 11). When potassium chloride infusion was added to the epinephrine infusion, the rise in plasma potassium concentration was significantly less than with potassium chloride infusion alone during the first 120 minutes ($p < 0.001$) (Figure 2). During the last two hours following potassium chloride administration, the elevation of the plasma potassium concentration above baseline was not

statistically significantly different from that observed with potassium chloride infusion alone. Baseline urinary excretion rate for potassium (U_KV) was $37 \pm 7 \mu\text{Eq}/\text{min}$ and was similar to that with potassium infusion alone (Figure 3). Following epinephrine infusion, however, U_KV actually fell to a mean value, $21 \pm 3 \mu\text{Eq}/\text{min}$, which was significantly below the basal excretion rate ($p < 0.001$) and was markedly less than the maximal excretion rate in the study with potassium chloride infusion alone ($p < 0.001$). Creatinine clearance did not change during this study. The total potassium excreted over the four hour study period fell below that expected to result from continued basal rates of potassium excretion ($p < 0.001$) (Figure 5). Despite the marked decline in U_KV the plasma potassium concentration actually rose less in this study because the amount of potassium translocated into cells increased by over 100% in comparison to the amount translocated with potassium chloride infusion alone ($p < 0.001$) (Figures 6 and 7). The incremental area in plasma potassium was significantly less than with potassium chloride infusion alone for all time periods ($p < 0.005$) (Figure 10).

When propranolol was infused with epinephrine for 30 minutes preceding potassium chloride infusion, the plasma potassium concentration did not change significantly from the baseline value of $3.69 \pm 0.11 \text{ mEq}/\text{l}$, which itself was similar to the baseline plasma potassium concentrations in the two previous studies. When potassium chloride infusion

was added to the epinephrine and propranolol infusions, the rise in plasma potassium concentration above baseline was significantly greater than with potassium chloride infusion alone during the first 120 minutes ($p < 0.01$) (Figure 2) and tended to remain high for the duration of the study. U_KV (Figure 3) was significantly less during the first 120 minutes of the study than in the study with potassium infusion alone ($p < 0.01$) but was not different during the remainder of the study. Creatinine clearance (Figure 4) was unaffected by the addition of propranolol. The percentage of the potassium chloride dose excreted (Figure 5) was $9 \pm 2\%$ at 120 minutes and $31 \pm 6\%$ at 240 minutes with epinephrine and propranolol infusion and was significantly less than with potassium infusion alone ($p < 0.001$ and $p < 0.02$). The absolute amount as well as the percentage of the dose of potassium that was translocated into cells tended to be increased with propranolol (Figures 6 and 8) but did not reach statistical significance. The incremental area in plasma potassium (Figures 9 and 10) also tended to be greater with the addition of propranolol to the infusate.

During the potassium chloride infusion alone the increase in the urinary potassium excretion rate correlated linearly with the increase in plasma potassium concentration over the time of the collection of each urine sample (Figure 12) ($r = 0.81$, $p < 0.001$). Following the addition of

epinephrine or epinephrine and propranolol to the infusate no correlation between the change in P_K and the change in U_KV could be demonstrated.

C. Sodium

Baseline plasma sodium concentration was similar in all three studies and was unaffected by potassium chloride, epinephrine or propranolol infusion. The baseline urinary sodium excretion rate was also similar in all three studies and rose following potassium chloride infusion (Figure 13). The rise with epinephrine and potassium chloride infusion, however, was significantly less ($p < 0.02$) than with potassium chloride infusion alone or with the addition of propranolol to epinephrine and potassium.

D. Glucose

Fasting plasma glucose concentration was similar in the potassium chloride (85.2 ± 1.8 mg/dl), the potassium and epinephrine (83.7 ± 2.8 mg/dl), and the potassium, epinephrine and propranolol (79.8 ± 2.8) studies. Plasma glucose concentration remained unchanged during the potassium chloride infusion. When epinephrine was added to the infusate, an immediate and significant rise in the plasma glucose concentration occurred and the glucose concentration remained elevated throughout the duration of the study (Figure 14). The plasma glucose concentration when propranolol was infused with potassium chloride and epinephrine also rose significantly

above the baseline value but remained significantly less than the level in the potassium chloride and epinephrine study ($p < 0.001$).

E. Insulin

Baseline plasma insulin concentration was similar in all three studies (Figure 15). No change in the insulin concentration occurred following potassium chloride infusion alone. Epinephrine infusion resulted in a 15 to 20 $\mu\text{U/ml}$ increase in the plasma insulin concentration which correlated temporally with the rise in plasma glucose concentration. This rise in the insulin level persisted throughout the four hour study period. When propranolol was administered along with epinephrine, an initial small decline in the plasma insulin concentration was observed (Figure 15) but thereafter the plasma insulin values were not significantly different from those in the potassium chloride infusion alone.

F. Epinephrine and Norepinephrine

Baseline plasma epinephrine and norepinephrine concentrations during the potassium chloride infusion study alone were 16.2 ± 8.0 pg/ml and 420.1 ± 107.2 pg/ml respectively (Figure 16). Following infusion of potassium chloride, no significant change in either catecholamine was observed.

G. Aldosterone

Results pending.

VI. Discussion

The homeostatic mechanisms which control the net balance and cellular distribution of potassium in living systems are complex and interrelated. This is necessary because potassium plays a vital role in the function of all cells, particularly in nerve and muscle tissue where electrical activity relies on the balance of intra- and extracellular potassium concentration. The contributions of insulin and aldosterone to internal and external potassium balance have been elucidated in some detail and the importance of each of these hormones in normal as well as abnormal states in controlling potassium homeostasis has been recognized. The present study indicates that epinephrine and probably other sympathomimetic agents also play an important role in both renal and extra-renal potassium metabolism.

Previous studies in animals, employing the infusion of pharmacological doses of epinephrine and potassium have demonstrated that epinephrine ameliorates the rise in plasma potassium concentration and decreases the incidence of fatal cardiac arrhythmia (2,49). The present study extends these earlier observations to man and documents that more physiologic elevations in plasma epinephrine levels, similar to those observed in stress (65), are capable of blunting the rise in plasma potassium concentration following the infusion

of small amounts of potassium. In the present study, each subject received an infusion of epinephrine at the rate of $0.05 \mu\text{g}/\text{kg}/\text{min}$ for 30 minutes prior to the administration of potassium. During this period, the plasma potassium concentration declined by $0.42 \pm 0.05 \text{ mEq}/\text{l}$ during the first 15 minutes and by $0.61 \pm 0.06 \text{ mEq}/\text{l}$ by 30 minutes. This decline could not be accounted for by an increase in plasma insulin concentration; insulin remained unchanged at 15 minutes and was only slightly elevated at 30 minutes. Three of six subjects showed no rise in plasma insulin concentration during the first 30 minutes post epinephrine infusion yet demonstrated a significant decline in plasma potassium concentration. When potassium was administered following pretreatment with epinephrine, the rise in plasma potassium concentration during the first two hours was significantly attenuated. This blunted rise in plasma potassium concentration is even more striking when changes in urinary potassium excretion are taken into account. Following potassium chloride infusion alone, 47% of the infused potassium was excreted. This value agrees well with those previously reported under similar experimental conditions (66). When epinephrine was infused along with potassium chloride urinary potassium excretion was markedly inhibited and actually fell below baseline values ($p < 0.001$). When the rise in plasma potassium concentration is viewed in the context of

the amount of infused potassium which is retained within the body, a greater than 100% increase in the amount of potassium translocated into cells was observed (Figures 6 and 10). The importance of this protective effect of epinephrine on potassium tolerance would assume particular significance during conditions of stress. Under such circumstances, protein breakdown is accelerated and a state of net catabolism exists. This would be expected to result in a net efflux of potassium from the intracellular to the extracellular compartment at a time when both insulin secretion (56,67) and insulin action (68) are significantly impaired. Since stress is known to stimulate epinephrine release, the increased circulating levels of this hormone could exert a protective effect against the development of hyperkalemia.

The sites of the stimulatory effect of epinephrine on cellular uptake of potassium are not discernible in the present study. Previous work, however, suggests that both the liver and skeletal muscle are quantitatively the most important tissues that participate in epinephrine-mediated potassium disposal. The mechanism by which epinephrine augments cellular uptake of potassium is most likely related to stimulation of beta adrenergic receptors since the augmentation can be blocked by propranolol. Recent studies have demonstrated the presence of beta receptors on both liver and skeletal muscle cells (69,70). In spite of this, an indirect

effect of epinephrine, mediated via stimulation of insulin or aldosterone secretion cannot be excluded by the present study. The latter would seem unlikely, however, since the effect of epinephrine on potassium is immediate while the increase in plasma aldosterone does not occur until 30 to 60 minutes (71) following epinephrine administration, and the onset of action of aldosterone in stimulating potassium transport in the kidney is delayed by an additional 60 to 120 minutes (72). That part of the effect of epinephrine on enhancing potassium uptake is mediated via insulin cannot be excluded. Although the initial decline in plasma potassium concentration during the first 30 minutes of epinephrine infusion prior to potassium infusion cannot be explained by stimulation of insulin secretion, the blunted rise in plasma potassium concentration during potassium chloride infusion could be explained in part by release of insulin secondary to the epinephrine-induced hyperglycemia. Previous studies, employing much higher doses of epinephrine have demonstrated a complete inhibition of insulin secretion despite the presence of hyperglycemia (53-56). In the present study, employing much lower doses of epinephrine, it is likely that the beta adrenergic inhibitory effect of epinephrine on insulin secretion was insufficient to completely block the effect of hyperkalemia on the pancreatic beta cell, and the alpha adrenergic stimulatory effect of epinephrine on insulin

secretion predominated. In any event, it is clear that in terms of potassium metabolism, an intermediary role for insulin cannot be ruled out in this study. Infusion of insulin to levels similar to those observed in response to epinephrine infusion in the present study have been shown to result in increased cellular uptake of potassium and a fall in plasma potassium concentration (12). However, the magnitude of this fall was significantly less than that observed in the present study with epinephrine infusion leaving open the possibility of a direct role for epinephrine in ameliorating the rise in plasma potassium following potassium infusion. Studies are presently in progress to evaluate what role, if any, insulin plays in the epinephrine-mediated hypokalemic effect. In these studies, somatostatin is infused to inhibit insulin secretion and basal insulin levels are replaced with an exogenous infusion of insulin. The same infusion of potassium chloride and epinephrine will then be administered while plasma insulin levels are maintained at basal. Any observed hypokalemic effect would then be attributable to epinephrine alone.

The effect of epinephrine on potassium tolerance cannot be explained by enhanced renal excretion of potassium since this excretion is decreased markedly following epinephrine infusion. This anti-kaluretic effect cannot be explained by a fall in the peritubular capillary potassium concentration perfusing the distal nephron or by a fall in

the filtered load of potassium since the plasma potassium concentration increased following potassium chloride infusion and the glomerular filtration rate was unchanged. Epinephrine is known to decrease renal plasma flow (50,51), however, and it is possible that the total amount of potassium presented to the distal potassium secretory sites actually diminished, leading to a decrease in the potassium excretion rate, even though the plasma potassium concentration rose. Alternatively, a direct inhibitory effect of epinephrine on peritubular potassium uptake is possible. This seems unlikely, though, since one would have to postulate that the renal tubular cell is different from other cells where epinephrine stimulates potassium uptake (7-10).

Following epinephrine infusion, the rise in urinary sodium excretion was not as great as with potassium infusion alone (Figure 13). Although this relative decrease (compared with potassium chloride alone) in sodium excretion could explain a blunted rise in renal potassium excretion, it cannot explain the absolute decrease in potassium excretion that was actually observed.

Since epinephrine is known to increase aldosterone secretion (57) (results from present study pending) over a prolonged time course and insulin has no known effect on renal potassium handling (23), it is unlikely that changes in the circulating levels of these hormones would effect renal potassium excretion in the present study.

The infusion of propranolol in conjunction with epinephrine and potassium chloride reverse almost completely the renal and extra-renal effects of epinephrine indicating that the effect of epinephrine on potassium metabolism is mediated by stimulation of beta adrenergic receptors. The addition of propranolol effectively blocked the initial fall in plasma potassium concentration observed with epinephrine infusion alone, and prevented the protective effect of epinephrine on potassium tolerance. In fact, the rise in plasma potassium concentration when propranolol was infused with epinephrine and potassium chloride was actually greater than with potassium chloride alone. Renal excretion was returned almost to normal by propranolol but the rate was still less than with potassium infusion alone indicating that the propranolol was not completely blocking the effects of epinephrine on potassium excretion at the doses of the two drugs used. Propranolol also markedly decreased cellular uptake of potassium that would have proceeded under the influence of epinephrine alone (Figures 6 and 7).

The deleterious effects of propranolol on potassium tolerance could be explained in several ways. First, it is possible that during the potassium chloride infusion alone the rise in plasma potassium concentration stimulates epinephrine release from the adrenal medulla or leads to local

release of epinephrine at sympathetic nerve terminals innervating liver and skeletal muscle cells (73). Propranolol, by blocking this stimulatory effect of potassium, could have a detrimental effect on potassium tolerance. Preliminary measurements of circulating catecholamines during the potassium chloride infusion, however, fail to demonstrate a consistent increase in circulating plasma epinephrine levels (Figure 16). However, this could not exclude the possibility that a rising plasma potassium concentration could activate sympathetic nerve fibers innervating muscle and liver cells with local uptake and degradation of epinephrine. Such local epinephrine metabolism has been shown to occur by Axelrod (73). It is also possible that basal levels of epinephrine or sympathetic nervous activity are necessary to dispose of an exogenous potassium load normally and that propranolol, by inhibiting basal epinephrine release or sympathetic nervous system activity, leads to impaired potassium tolerance. This would be similar to the situation with insulin where inhibition of basal insulin secretion by as little as 50% results in a marked impairment in potassium tolerance. Further studies are now in progress with potassium chloride and propranolol infusion alone to investigate this question.

The results in the present study also exclude a direct effect of propranolol mediated by mechanisms other than inhibition of beta adrenergic receptors stimulation. When propranolol was infused with epinephrine, insulin levels

fell slightly (2 to 5 μ U/ml). This decrease was not significantly different from control after the first 15 minutes of potassium chloride infusion and in 3 of 6 subjects no decrease at all in plasma insulin concentration was observed. These results make it unlikely that the decrement in potassium tolerance can be explained by inhibition of insulin release. Likewise, the time course of the inhibitory effect of propranolol on aldosterone secretion would be too long to explain the present results. Measurement of plasma aldosterone concentrations are pending and will directly answer this question. If it indeed becomes clear that basal sympathetic activity is important in potassium tolerance and homeostasis in general it would raise the question of whether potassium tolerance is compromised in states of functional sympathectomy such as diabetic neuropathy or propranolol use for ischemic heart disease.

VII. Summary

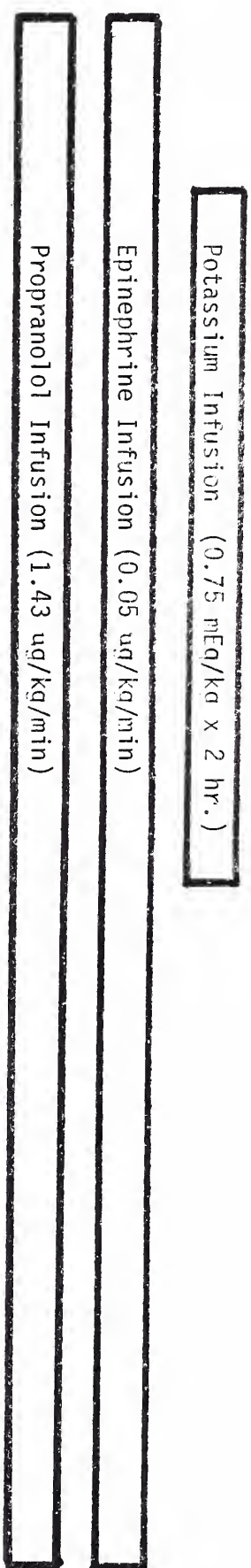
In summary, the present study documents that physiologic elevations of circulating plasma epinephrine concentrations ameliorate the rise in plasma potassium concentration following a potassium chloride infusion. This effect is the result of enhanced cellular uptake of potassium and can be completely reversed by propranolol, indicating that epinephrine's protective effect on potassium tolerance is mediated via stimulation of beta adrenergic receptors.

Table I. Subject Profile

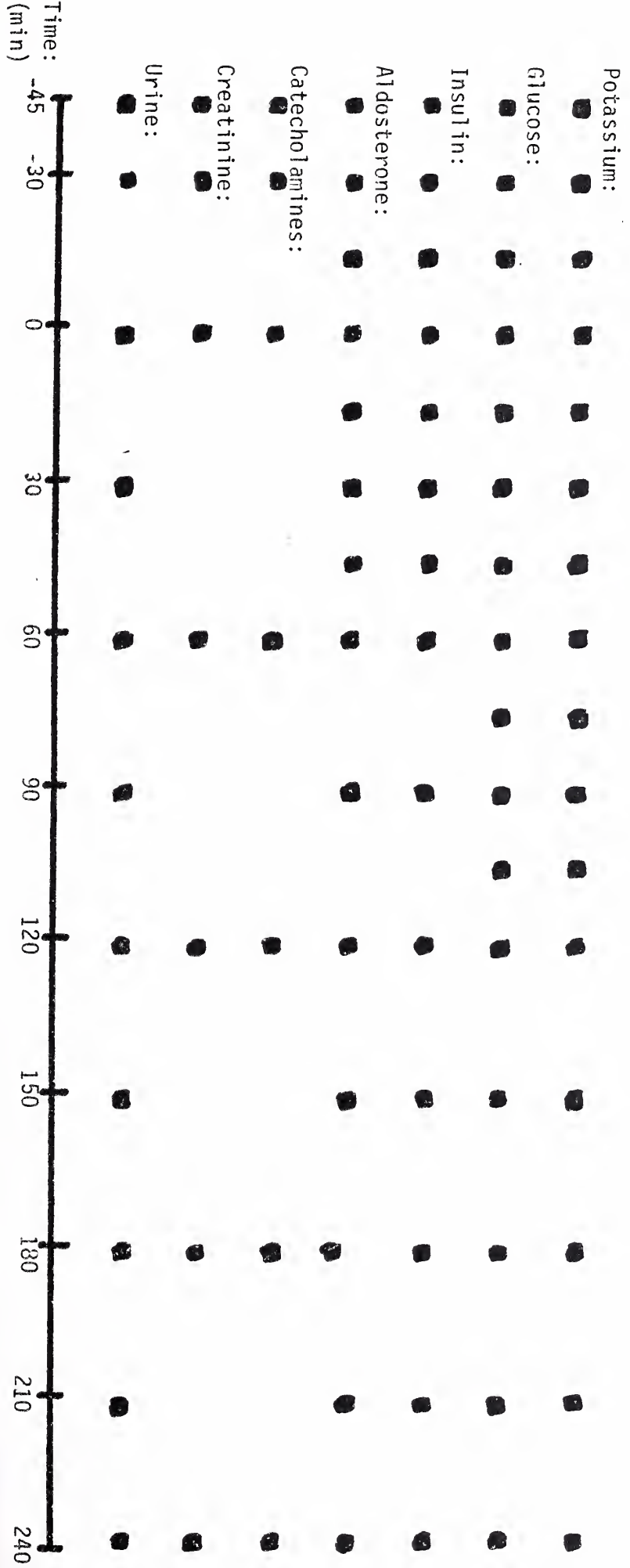
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1	22	M	188	76
2	21	M	186	82
3	18	M	192	96
4	20	F	160	65
5	18	M	172	71
6	18	M	186	76

EXPERIMENTAL PROTOCOL

FIGURE 1.

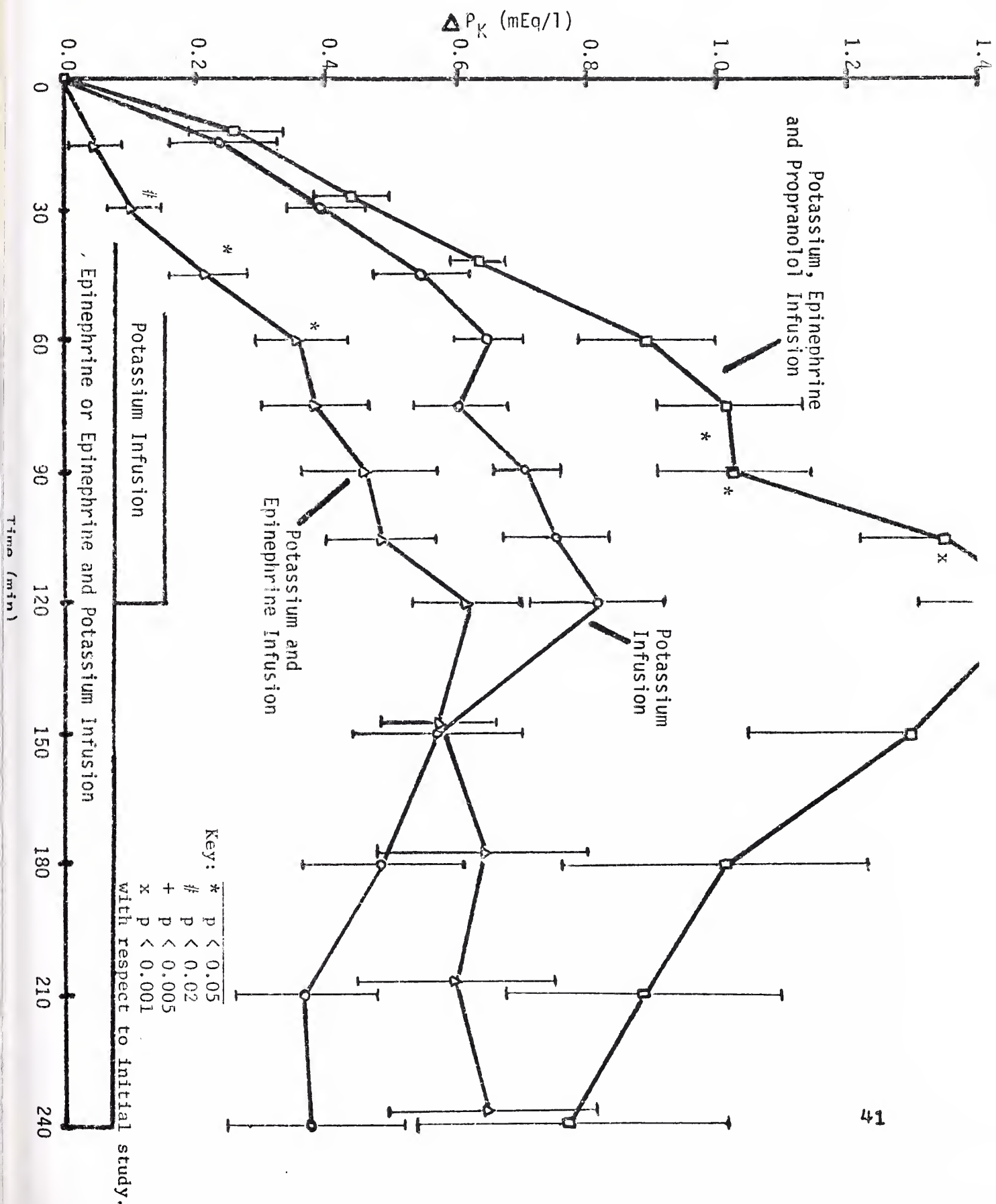


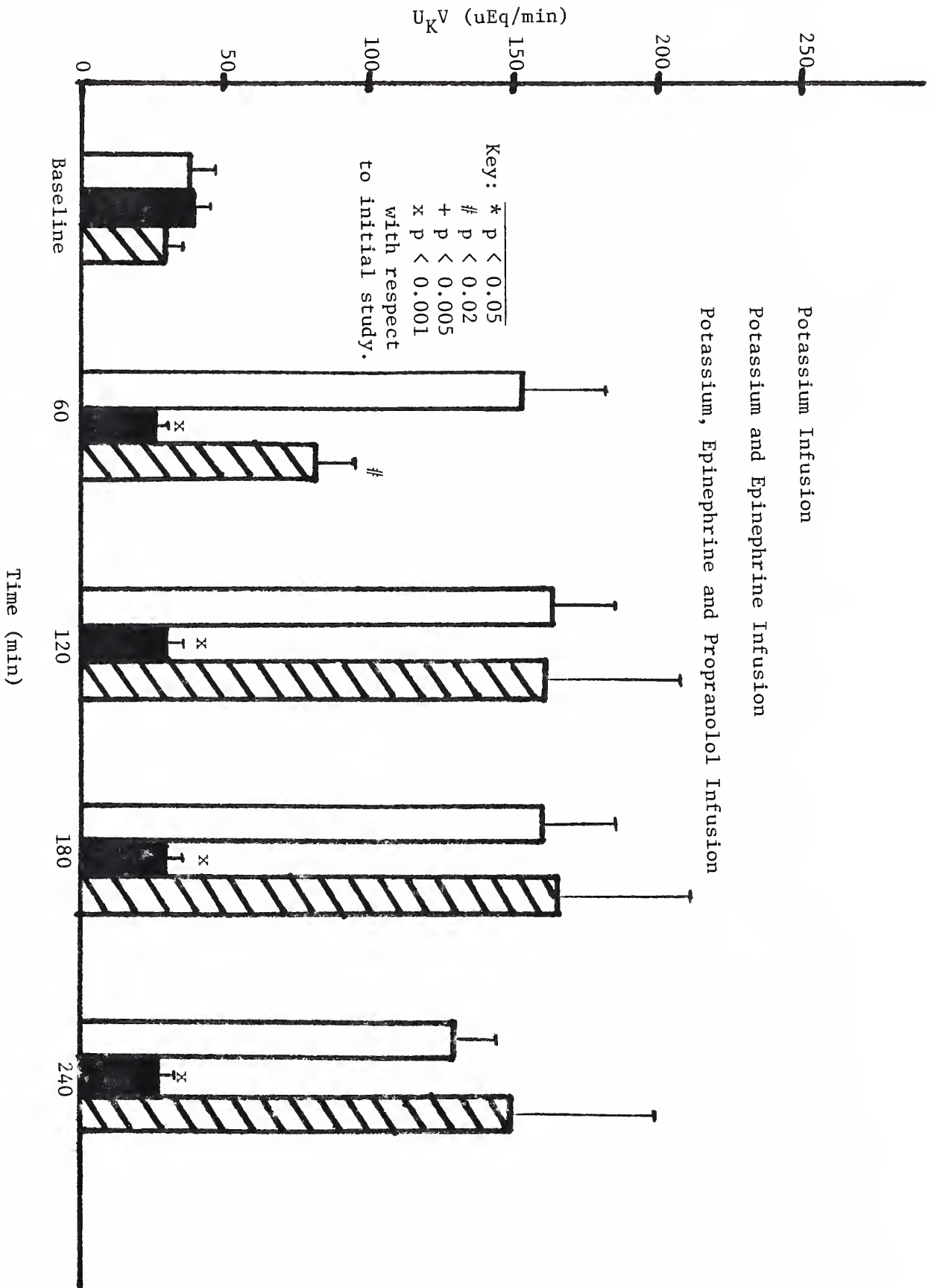
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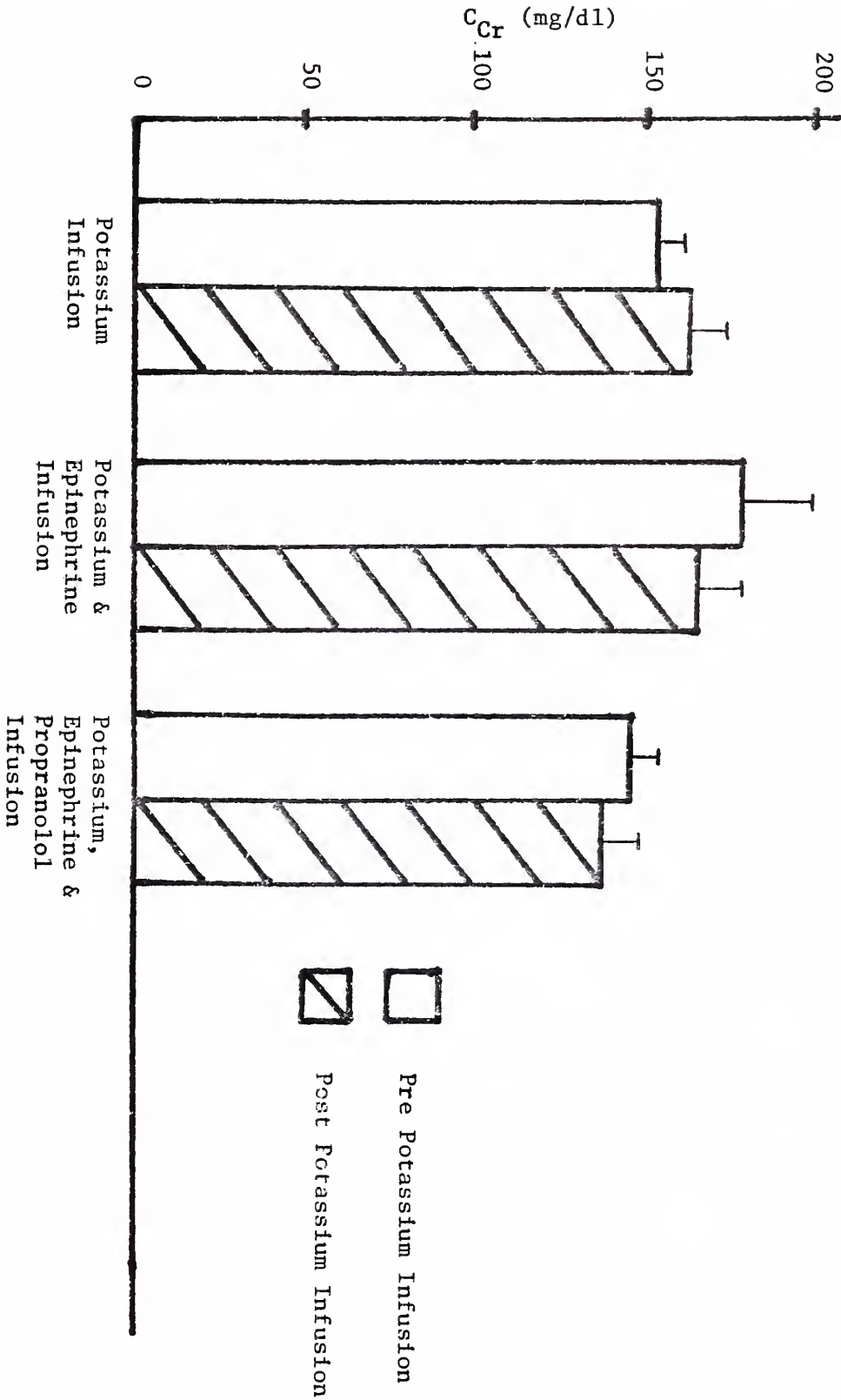


PLASMA POTASSIUM CONCENTRATION
VS. TIME

FIGURE 2.

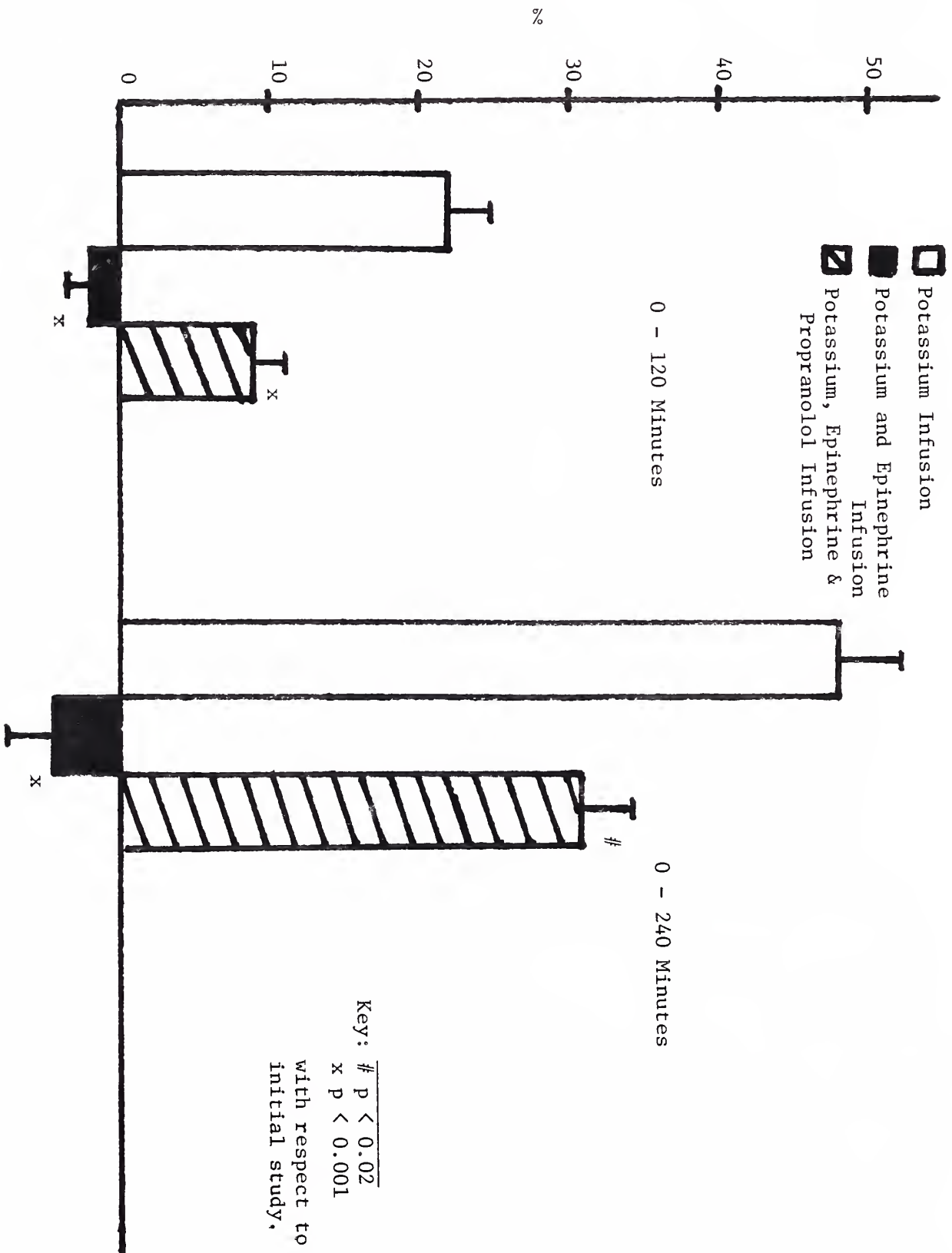


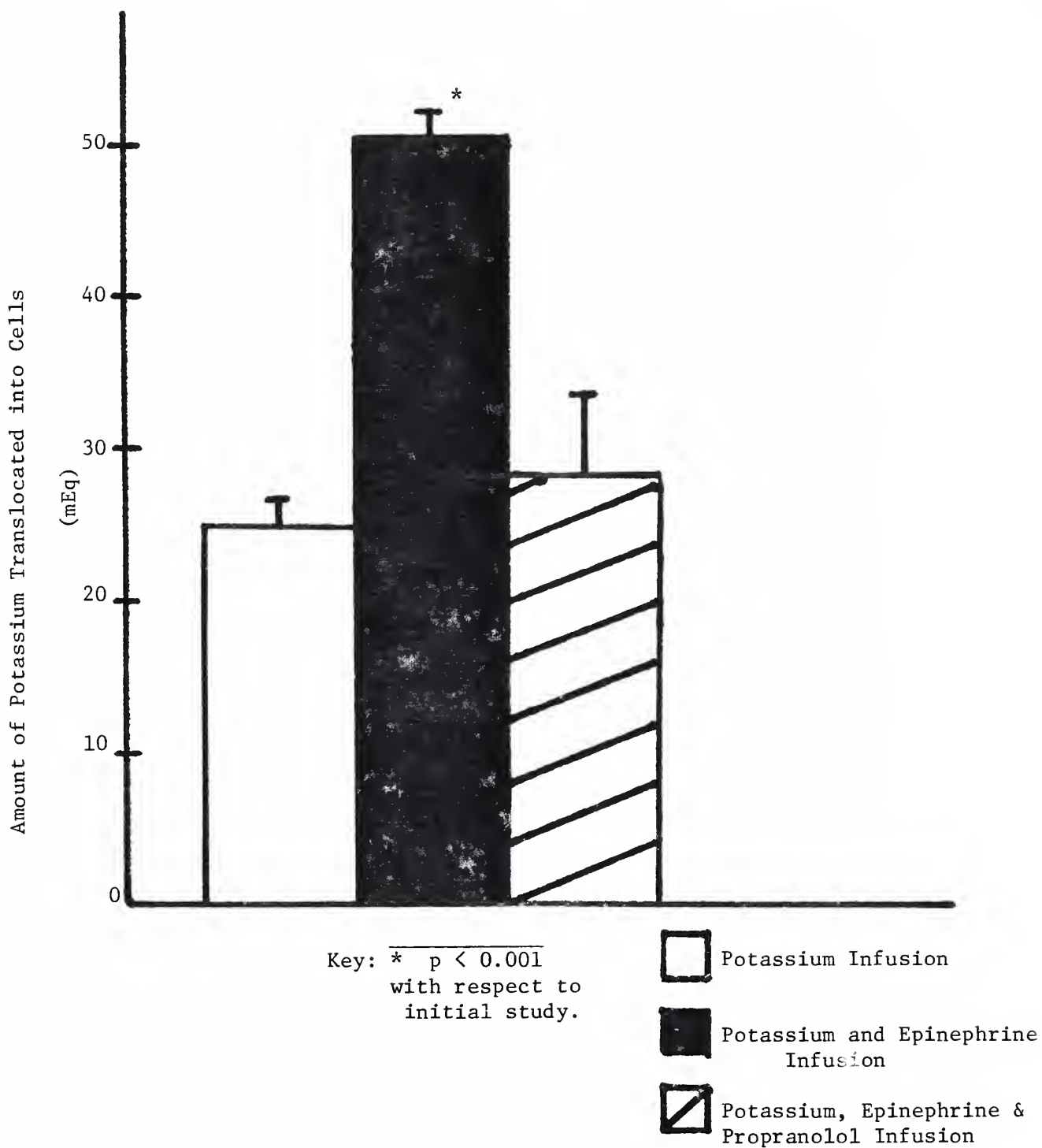


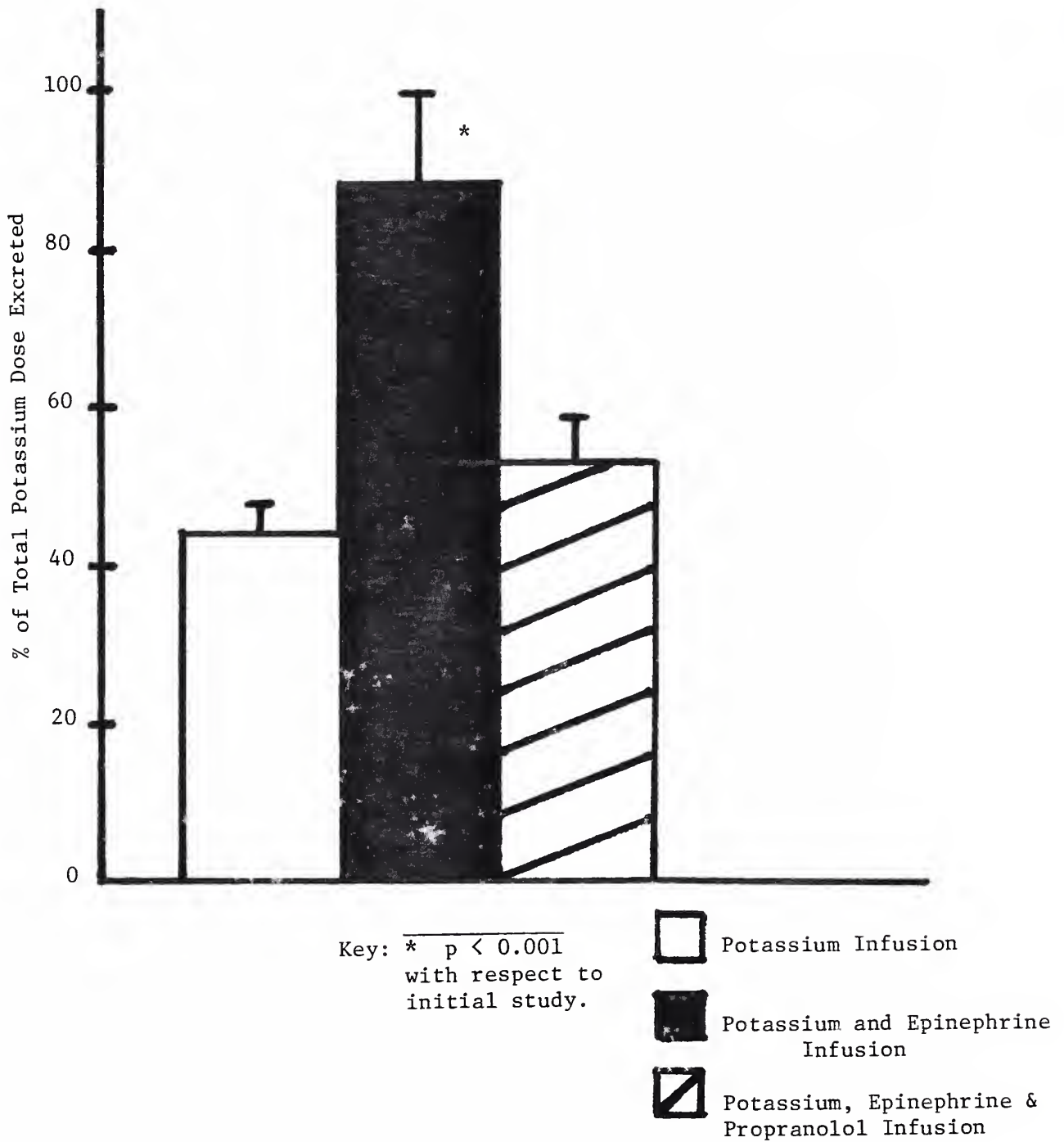


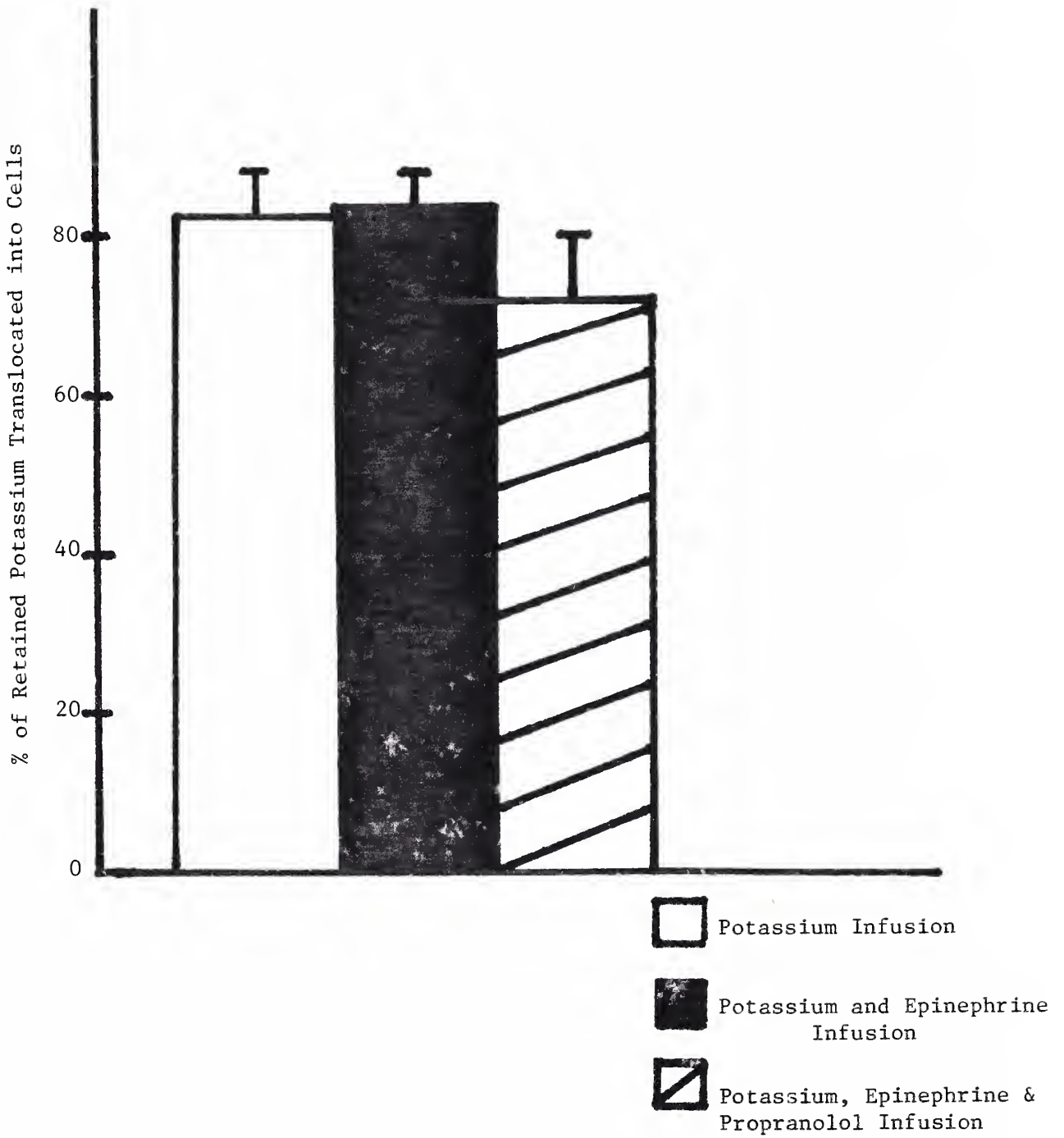
PERCENT OF POTASSIUM DOSE EXCRETED

FIGURE 5.



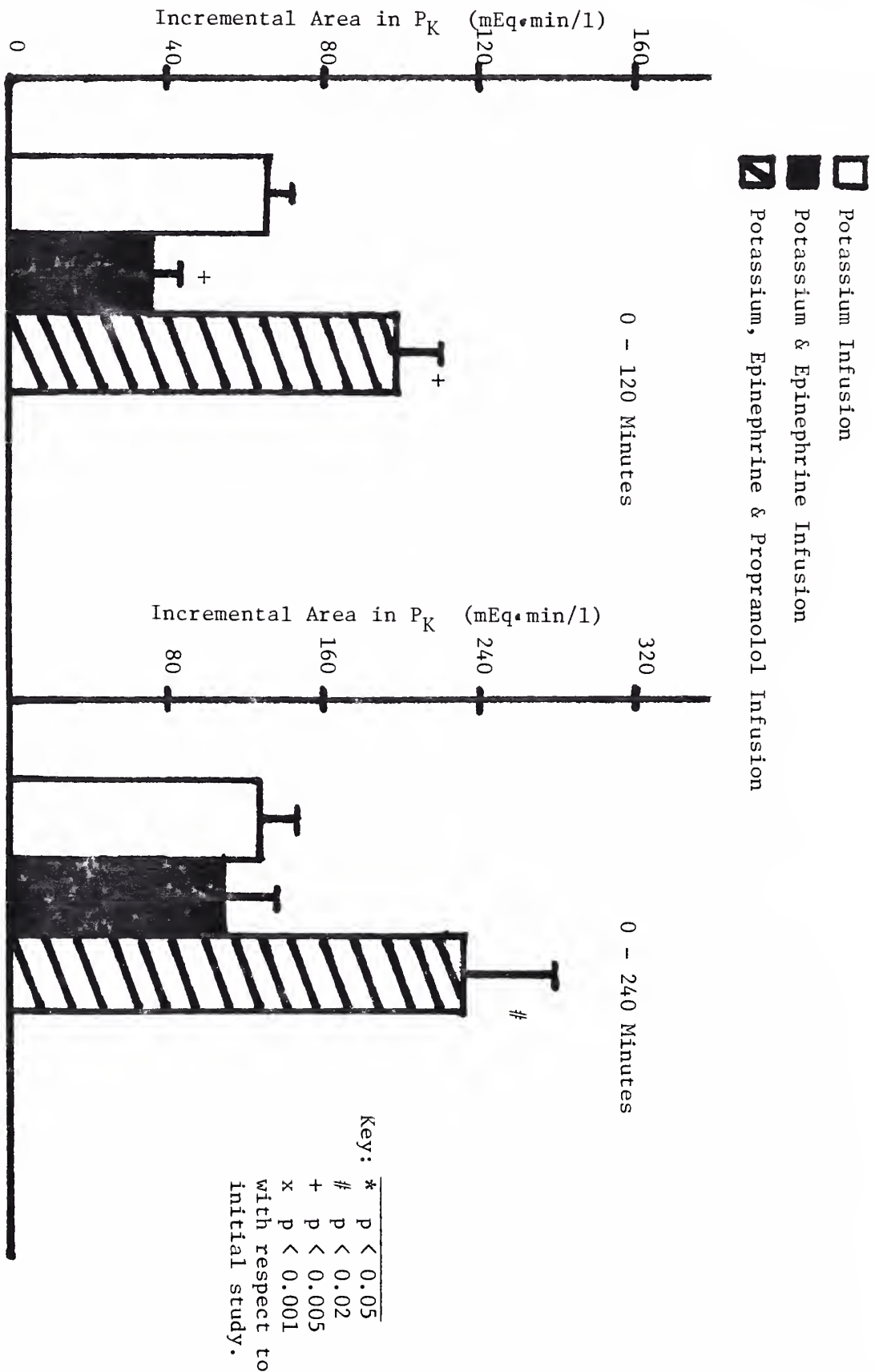


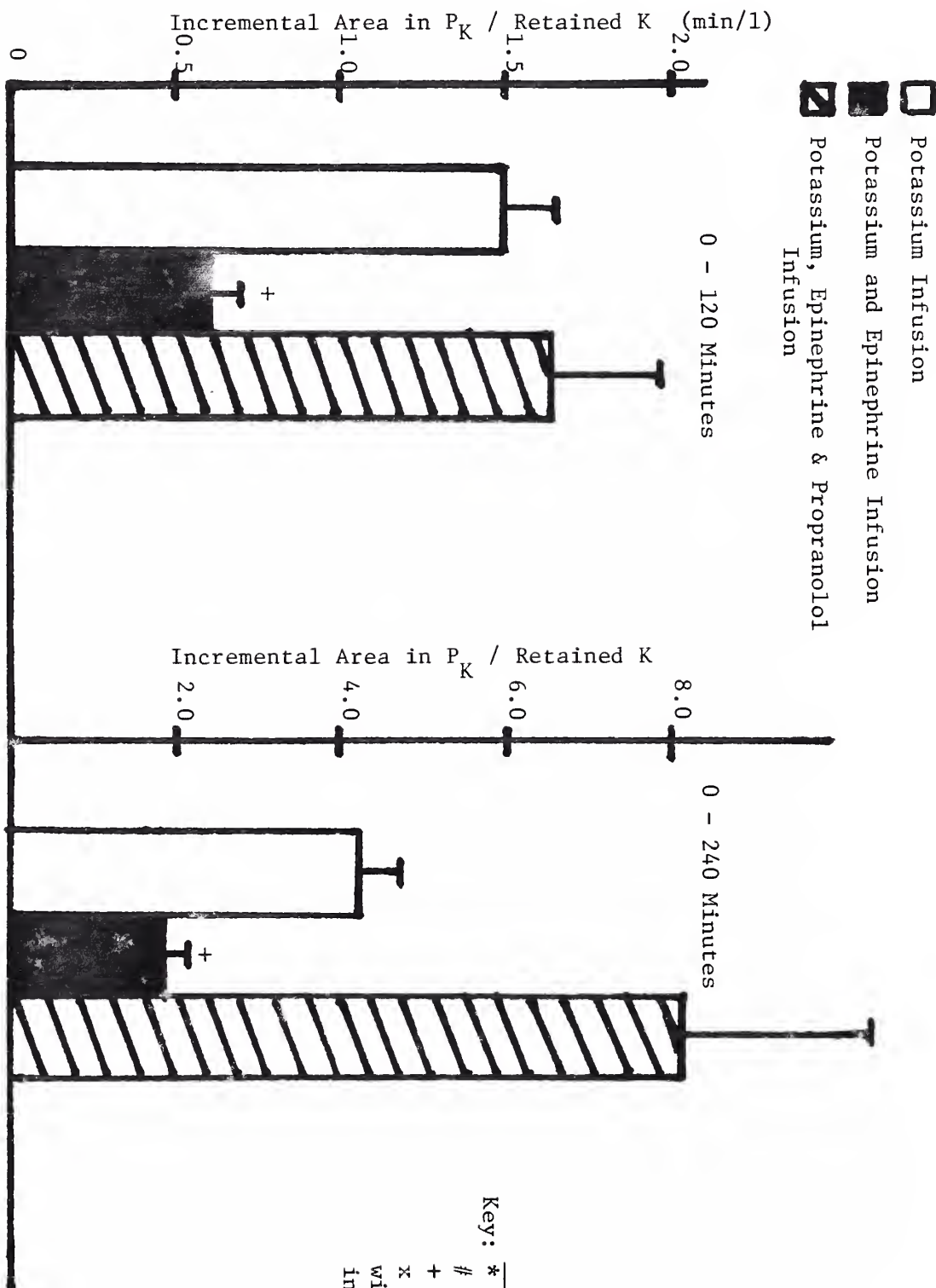


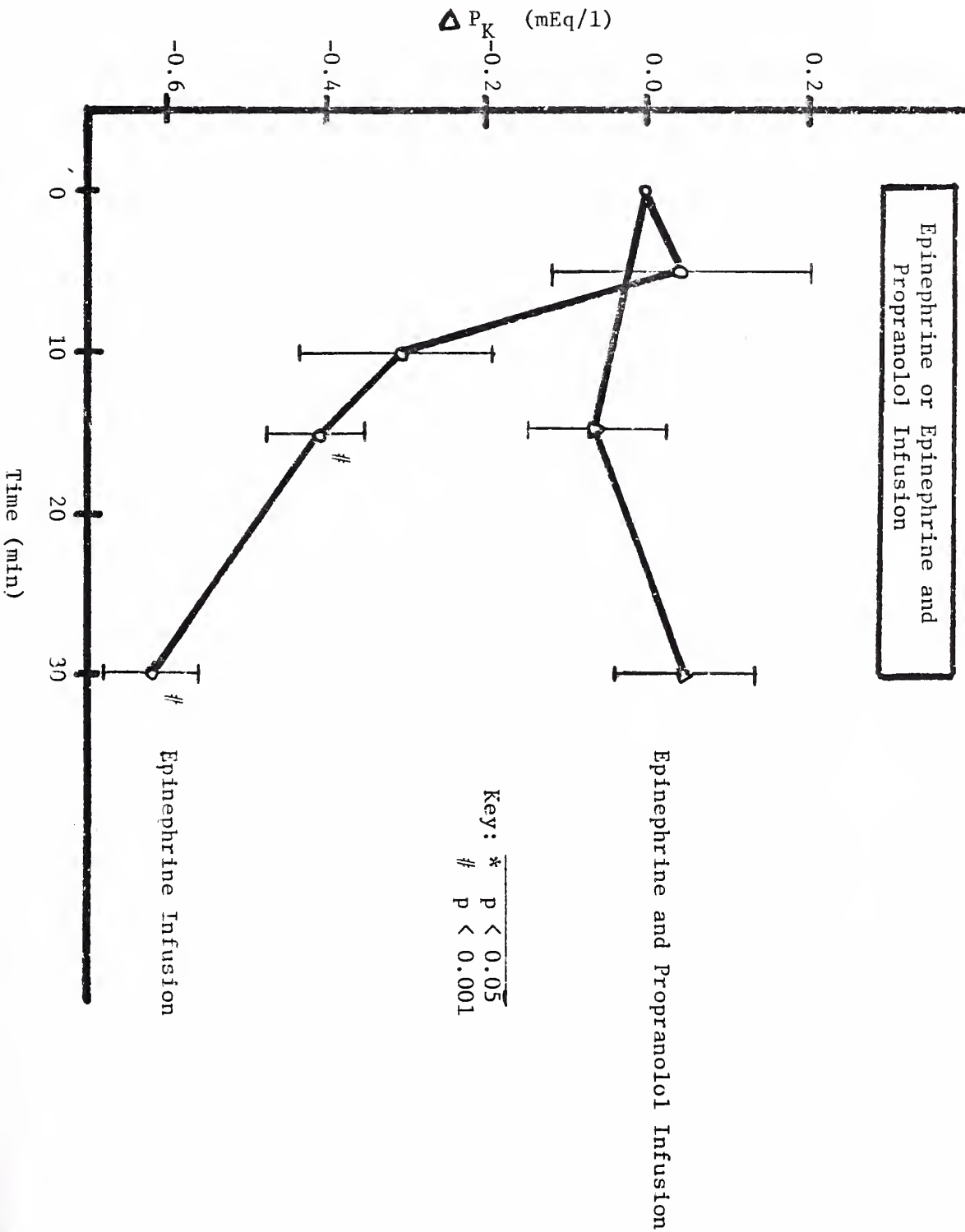


INCREMENTAL AREA IN PLASMA POTASSIUM

FIGURE 9.







ΔU_{K^+V} (uEq/min)

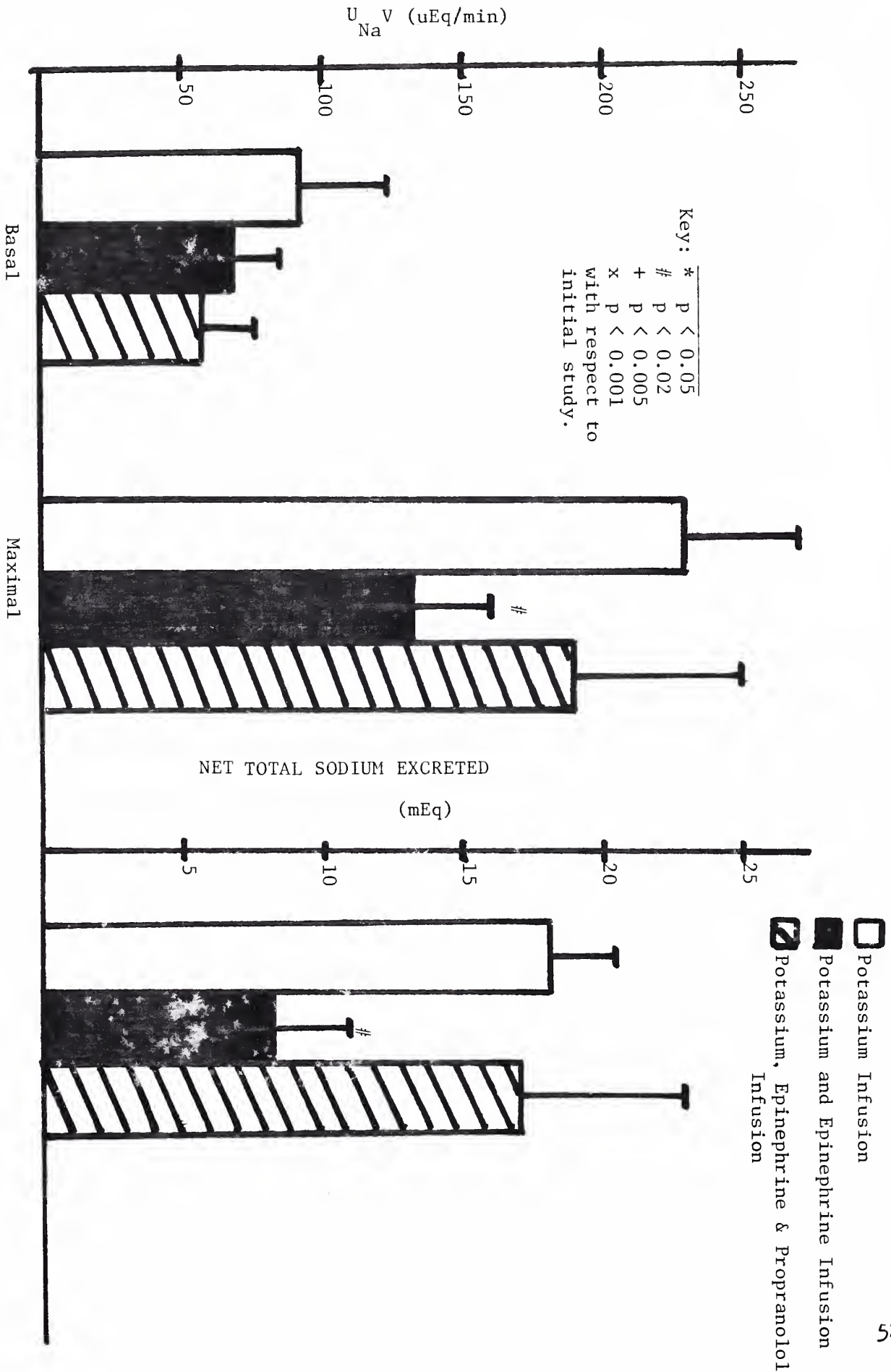
THE CHANGE IN URINARY POTASSIUM EXCRETION VERSUS THE CHANGE IN PLASMA POTASSIUM CONCENTRATION WITH POTASSIUM INFUSION

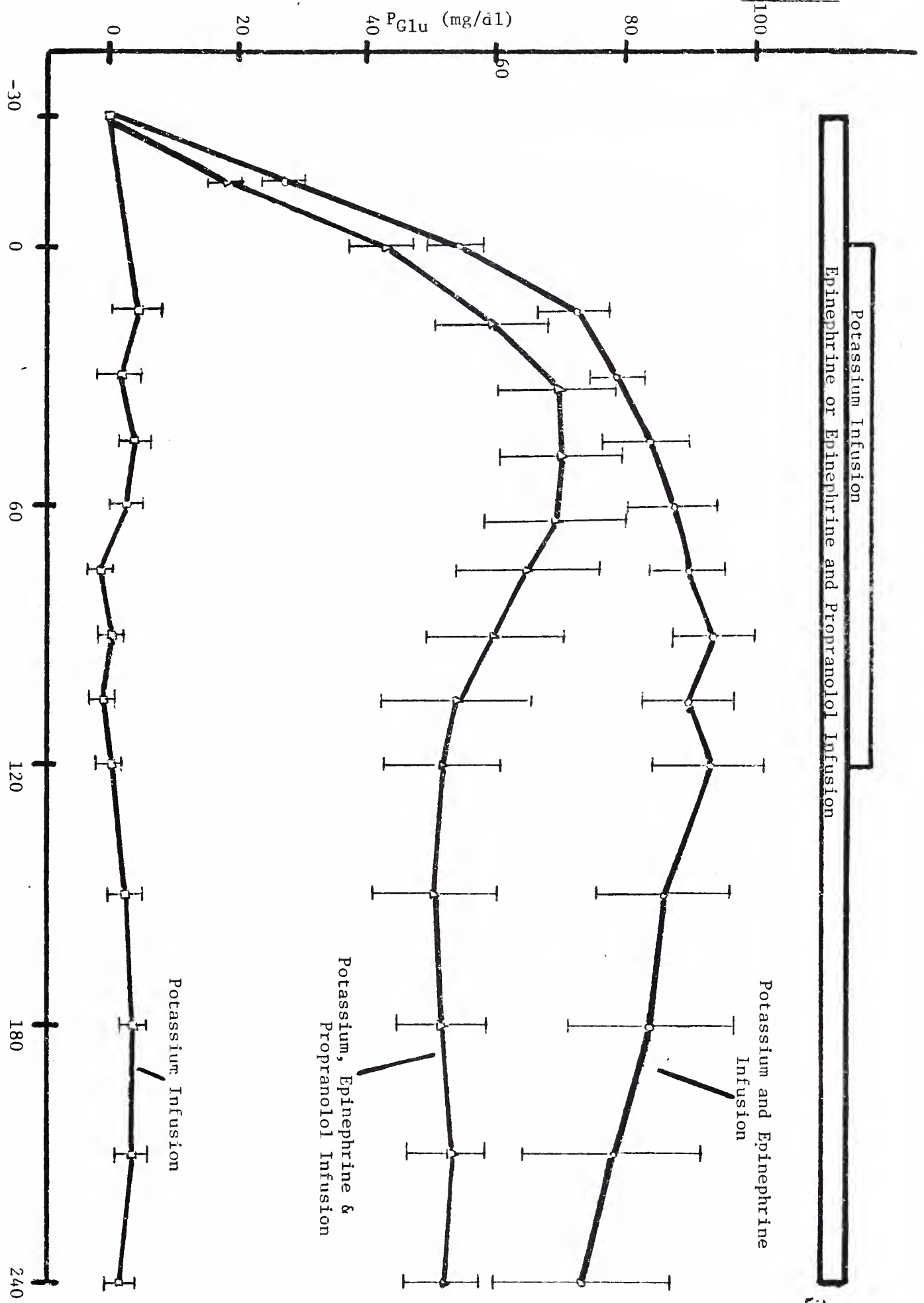
FIGURE 12.

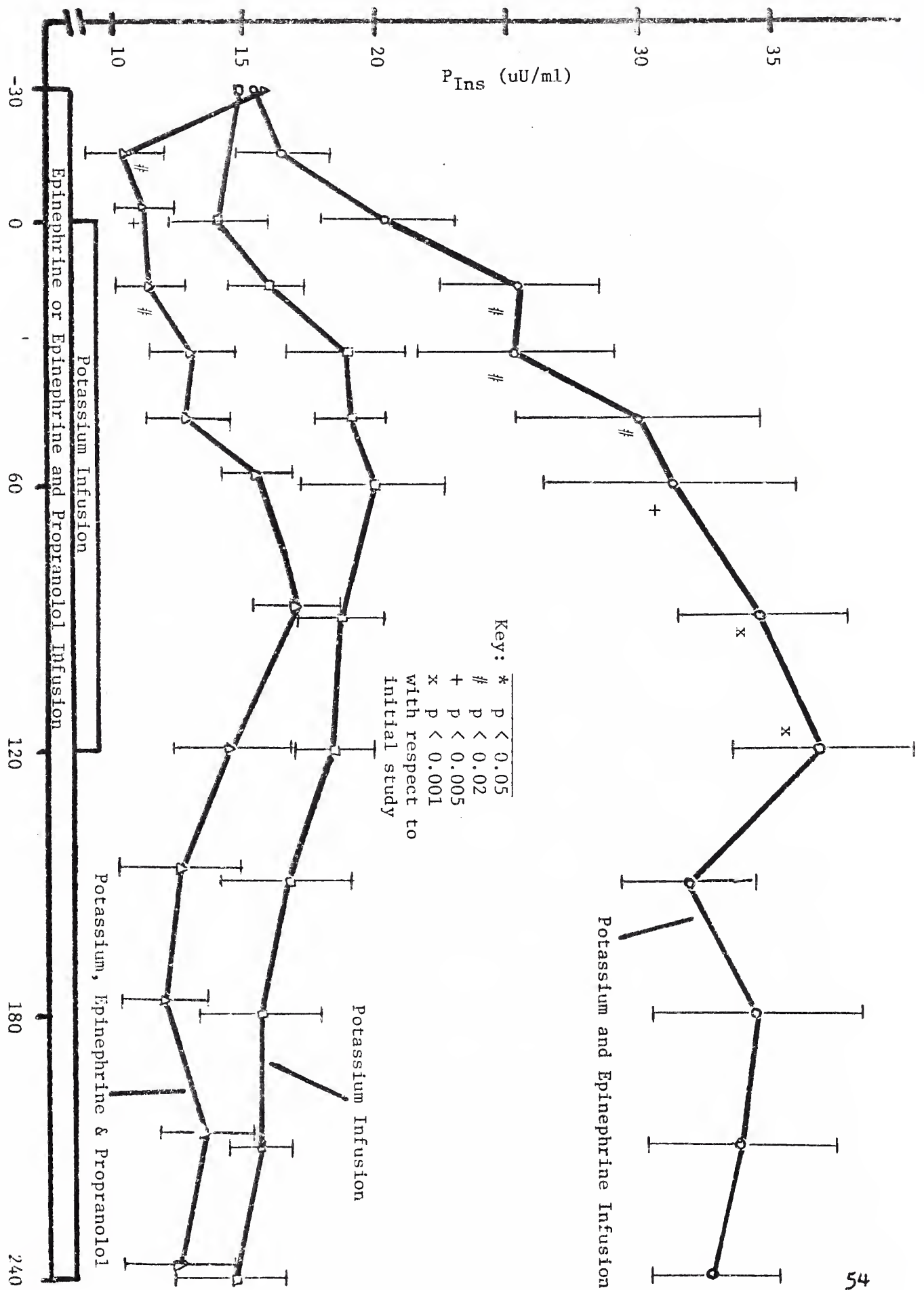
ΔP_K (mEq/l)

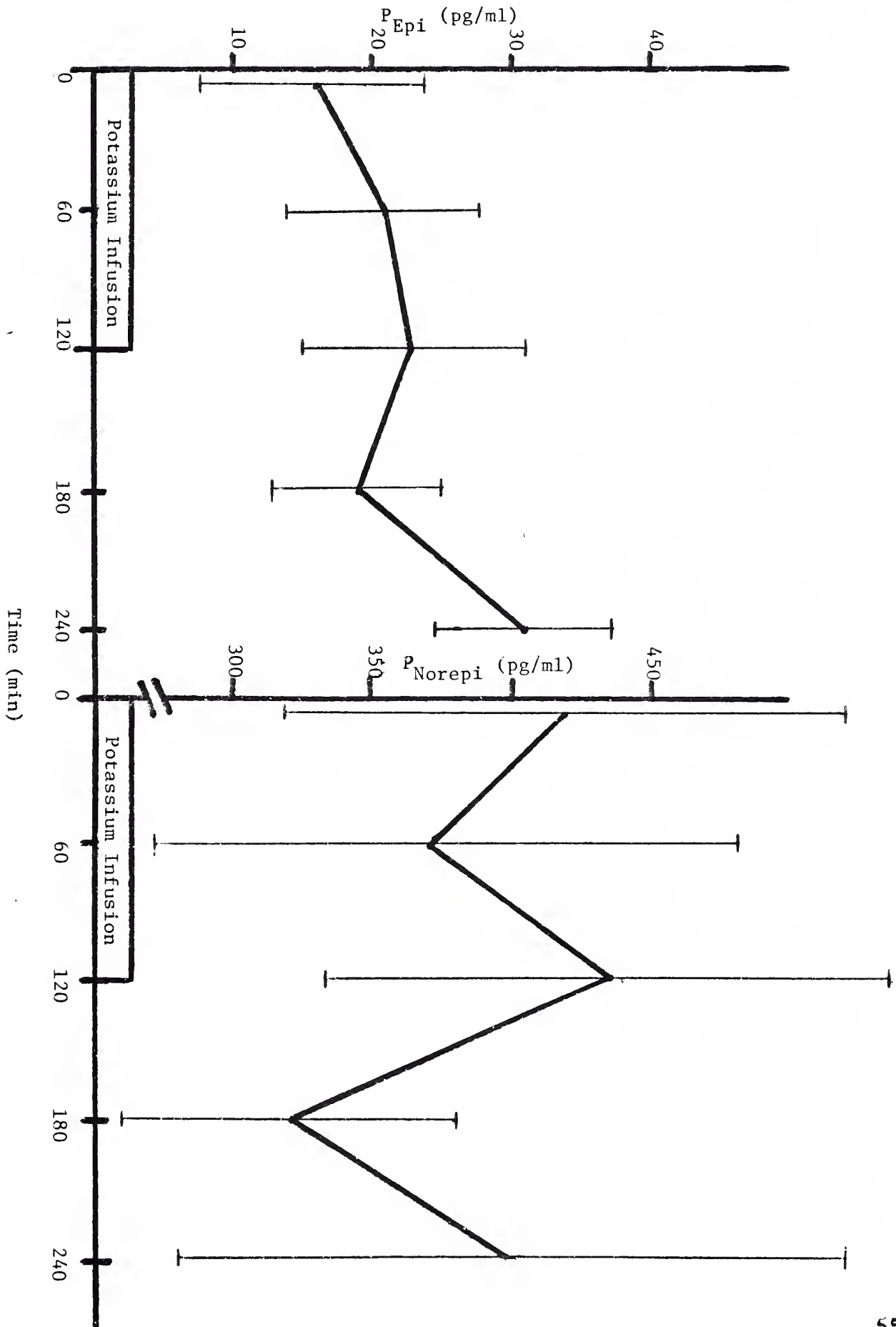
Potassium Infusion

$r = 0.81$
 $p < 0.001$









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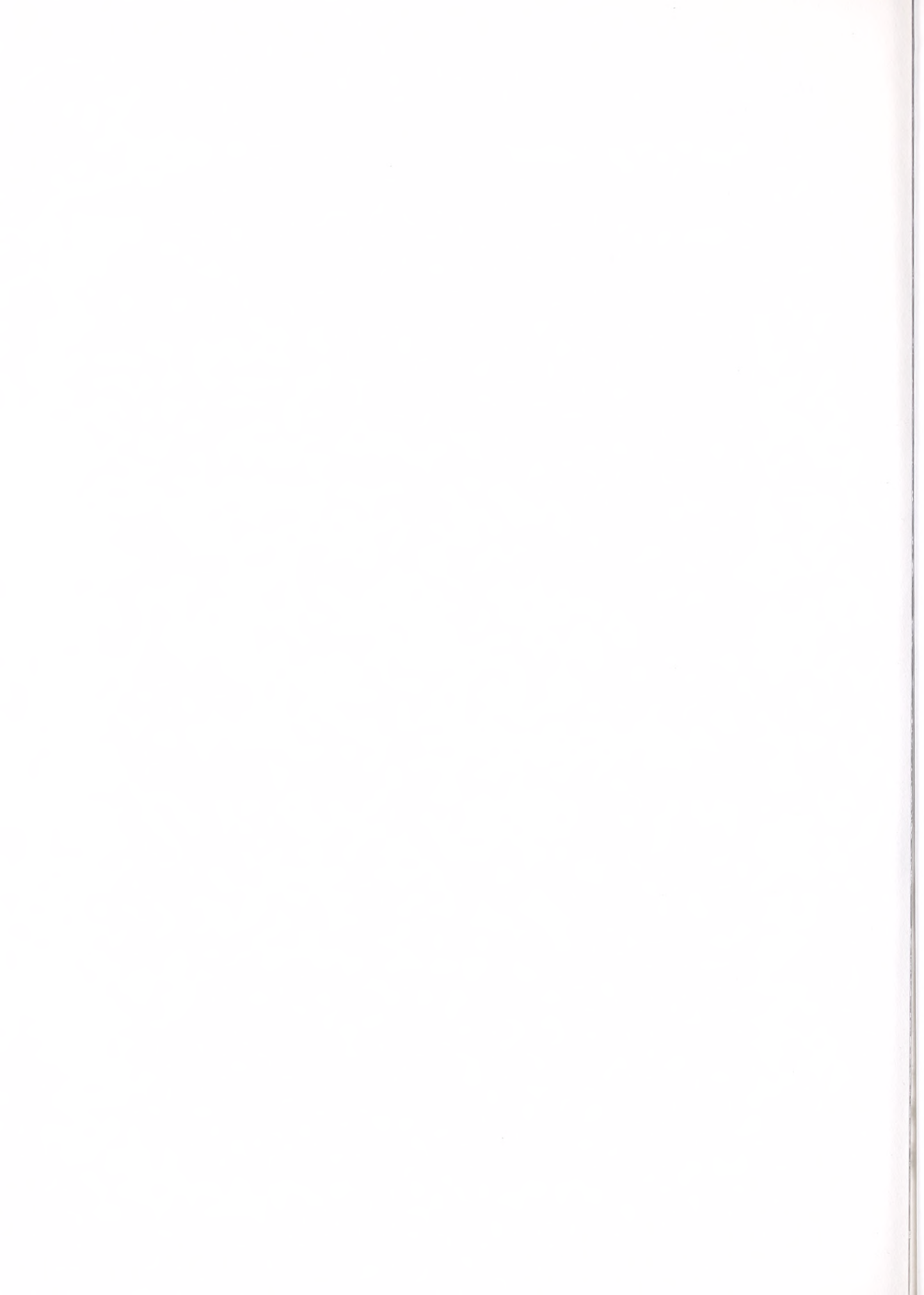
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