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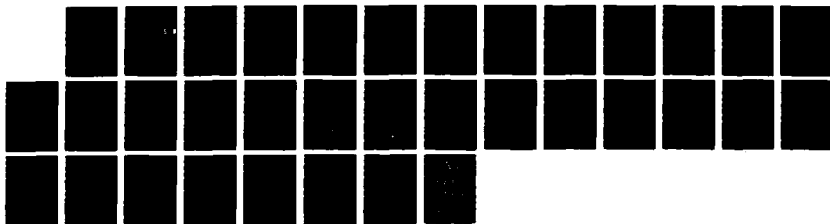
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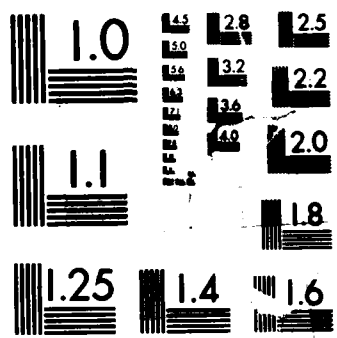
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THE USE OF ATP-MgCl₂ IN THE TREATMENT
OF INJURY AND SHOCK

Annual Report

Arthur E. Baue, M.D.
Irshad H. Chaudry, Ph.D.

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earpiece densitometry. Measurements were made prior to infusion, at 5 minute intervals during infusion and following termination of the infusion. Blood samples were obtained for determination of hemoglobin, sodium, potassium and glucose. Stroke volume index (SVI) and total systemic resistance (TSR) were derived from standard formulae. The results indicated that cardiac output increased by 76% from control values ($p < 0.0001$) with ATP-MgCl₂ infusion. This increase in cardiac output correlated positively with ATP-MgCl₂ infusion rate ($r = 0.75$, $p < 0.001$). This was paralleled by a 45% increase in heart rate ($p < 0.0001$). SVI increased by 14% ($p < 0.005$), however, the mean blood pressure did not change significantly over the entire range of infusion rates. TSR decreased 56% at the highest rate of ATP-MgCl₂ infusion. A mean infusion rate of 0.32 ± 0.02 mg/kg/min was associated with maximal increases in heart rate (52%) and cardiac output (119%) without affecting mean blood pressure. Hemodynamic effects were poorly correlated with total dose of ATP-MgCl₂ ($r = 0.20$).

All hemodynamic changes returned to normal within 2 minutes after the ATP-MgCl₂ infusion was discontinued ($p = NS$). Sodium, potassium, hemoglobin and glucose levels did not change during or after ATP-MgCl₂ administration. All subjects experienced transient mild nausea at infusion rates greater than 0.3 mg/kg/min. There were no delayed side effects.

ATP-MgCl₂ is a potent vasodilator. As demonstrated in this study, the increase in cardiac output offset the decrease in total systemic resistance. Thus, blood pressure (MBP) was maintained. Furthermore, the increase in SVI demonstrated a mild inotropic effect. These findings suggest that the increase in heart rate and cardiac output may depend upon an intact sympathetic nervous system. In addition, the pharmacologic profile of vasodilatation, augmentation of cardiac output, maintenance of blood pressure and mild positive inotropy coupled with beneficial effects on cell function and survival in animal studies suggest potential clinical applications of ATP-MgCl₂ in patients with low flow states or organ ischemia. In conclusion, data from our studies suggest a potentially beneficial role of ATP-MgCl₂ in the treatment of low flow states and confirms the safety of ATP-MgCl₂ in humans.

We also submitted the protocol of our Phase II studies of ATP-MgCl₂ to our Human Investigation Committee and they have approved the protocol. In addition, the protocol was submitted to the Army's Human Investigation Committee and we have only recently received the approval of our protocol for the Phase II studies of ATP-MgCl₂ from the U.S. Army. We are now in the process of recruiting the patients for such studies and hope to initiate the Phase II studies of ATP-MgCl₂ in the near future.



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SUMMARY

The purpose of our studies was to determine the hemodynamic responses to ATP-MgCl₂ in conscious dogs and primates. ATP-MgCl₂ infusion into normovolemic and hypovolemic dogs at rates < 5mg/kg/min and in primates at rates < 1mg/kg/min produced a decrease in systemic vascular resistance, an increase in cardiac output and a decrease in heart rate. This combination of effects would be particularly beneficial to the hypovolemic patient. Our objectives were to also determine the safety and hemodynamic response of ATP-MgCl₂ infusion in normal awake human volunteers. In accordance with a protocol approved by the Human Investigation Committee, five healthy adult male volunteers received an intravenous infusion of ATP-MgCl₂ (0.1-0.4mg/kg/min) on four separate occasions. The total dose infused was 3, 6, 10 and 30mg/kg (n=20 studies). Hemodynamic measurements were made at end exhalation in the supine position and included heart rate and systolic, diastolic and mean blood pressure. Continuous electrocardiographic monitoring of lead II was performed. Cardiac output was determined by injection of indocyanine green and measured by the principle of earpiece densitometry. Measurements were made prior to infusion, at 5 minute intervals during infusion and following termination of the infusion. Blood samples were obtained for determination of hemoglobin, sodium, potassium and glucose. Stroke volume index (SVI) and total systemic resistance (TSR) were derived from standard formulae. The results indicated that cardiac output increased by 76% from control values ($p < 0.0001$) with ATP-MgCl₂ infusion. This increase in cardiac output correlated positively with ATP-MgCl₂ infusion rate ($r = 0.75$, $p < 0.001$). This was paralleled by a 45% increase in heart rate ($p < 0.0001$). SVI increased by 14% ($p < 0.005$), however, the mean blood pressure did not change significantly over the entire range of infusion rates. TSR decreased 56% at the highest rate of ATP-MgCl₂ infusion. A mean infusion rate of 0.32 ± 0.02 mg/kg/min was associated with maximal increases in heart rate (52%) and cardiac output (119%) without affecting mean blood pressure. Hemodynamic effects were poorly correlated with total dose of ATP-MgCl₂ ($r = 0.20$).

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ATP-MgCl₂ is a potent vasodilator. As demonstrated in this study, the increase in cardiac output offset the decrease in total systemic resistance. Thus, blood pressure (MBP) was maintained. Furthermore, the increase in SVI demonstrated a mild inotropic effect. These findings suggest that the increase in heart rate and cardiac output may depend upon an intact sympathetic nervous system. In addition, the pharmacologic profile of vasodilatation, augmentation of cardiac output, maintenance of blood pressure and mild positive inotropy coupled with beneficial effects on cell function and survival in animal studies suggest potential clinical applications of ATP-MgCl₂ in patients with low flow states or organ ischemia. In conclusion, data from our studies suggest a potentially beneficial role of ATP-MgCl₂ in the treatment of low flow states and confirms the safety of ATP-MgCl₂ in humans.

We also submitted the protocol of our Phase II studies of ATP-MgCl₂ to our Human Investigation Committee and they have approved the protocol. In addition, the protocol was submitted to the Army's Human Investigation Committee and we have only recently received the approval of our protocol for the Phase II studies of ATP-MgCl₂ from the U.S. Army. We are now in the process of recruiting the patients for such studies and hope to initiate the Phase II studies of ATP-MgCl₂ in the near future.

FOREWORD

The studies described in this report were conducted after we obtained the IND for ATP-MgCl₂ from the Food and Drug Administration and following the approval of our protocol from the Army's Human Investigation Committee, our local Human Investigation Committee and from the Food and Drug Administration.

For the protection of human subjects the investigator(s) have adhered to policies of applicable Federal Law 45CFR46.

In conducting the research described in this report, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals", prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

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Body of Report

Publications

The following papers and abstract have been accepted for publication:

1. Chaudry IH, Keefer R, Barash P, Clemens MG, Kopf G, Baue AE: ATP-MgCl₂ (ATP) infusion in man: Increased cardiac output without adverse systemic hemodynamic effects. Surg.Forum.35:14-16, 1984.
2. Keefer JR, Chaudry IH, Barash PG, Clemens MG, Baue AE: ATP-MgCl₂: Safety and hemodynamic responses in humans. Anesthesiology 61:A119, 1984.
3. Chaudry IH: Cellular energetics and ATP-MgCl₂ therapy in sepsis. Am.J. Emerg Med.2:38-44, 1984.

The following paper has been submitted for publication:

1. Clemens MG, Chaudry IH, Hull M, Baue AE: Hemodynamic responses to ATP-MgCl₂ infusion in conscious dogs and primates. J.Surg.Res.

We have participated in a number of programs in which the work supported by this contract has been presented. These include presentation of our work at various national, regional and local programs on shock and circulatory failure. In addition, we presented our work supported by this contract at the American College of Surgeons' meeting and at the Annual American Society of Anesthesiology meeting in October, 1984.

The principle findings for the period of Sept. 1, 1984 - Jan 30, 1985 will now be summarized.

1. Hemodynamic responses to ATP-MgCl₂ infusion in conscious normovolemic and hypovolemic dogs and primates

In order to determine the hemodynamic responses to infusion of ATP-MgCl₂, experiments were performed on conscious dogs and primates under both normovolemic and hypovolemic conditions. Hypovolemia was produced by bleeding to a mean arterial pressure of 80mmHg. ATP-MgCl₂ was infused into the pulmonary artery at rates of 0.1 to 10mg/min/kg body weight and cardiac output was monitored. ATP-MgCl₂ infusion into both dogs and primates resulted in a dose-dependent decrease in mean arterial pressure. During hypovolemia, the infusion of high doses of ATP-MgCl₂ resulted in mean arterial pressures of as low as 20mmHg. In spite of this severe hypotension, however, arterial pressure was rapidly restored upon cessation of the infusion and returned to preinfusion values within 5 minutes.

The effect of ATP-MgCl₂ infusion on heart rate was slightly more complicated. In normovolemic dogs, infusion of ATP-MgCl₂ at rates of < 1.0mg/kg/min produced a mild tachycardia. At higher infusion rates, however, bradycardia was observed. Moreover, at all doses tested in hypovolemic dogs and in both normovolemic and hypovolemic primates, only bradycardia was observed. This is particularly relevant to application of ATP-MgCl₂

treatment of hypovolemic patients since bradycardia would tend to decrease the oxygen demands of the heart.

The cardiac output response to ATP-MgCl₂ infusion in conscious dogs and primates was found to have a biphasic dependence on infusion rates. At lower infusion rates (< 5.0mg/kg/min for dogs and < 1.0mg/kg/min for primates), cardiac output was increased by as much as 60%. Such increases in cardiac output were observed even when the heart rate was decreased. At very high doses of ATP-MgCl₂, however, cardiac output was decreased but was rapidly restored when infusion was terminated.

In summary, ATP-MgCl₂ infusion into dogs and primates at optimal doses produced a decrease in systemic resistance, an increase in cardiac output and a decrease in heart rate. This combination of effects would be particularly beneficial to the hypovolemic patient.

2. Phase I Studies of ATP-MgCl₂.

Since the approval of the Phase I studies by our Human Investigation Committee and the U.S. Army Medical Research and Development Command, we completed the four components of the Phase I studies. All five volunteers who had signed the consent form and participated in that study received ATP-MgCl₂ on four separate occasions with a total dose of 3, 6, 10 and 30mg/kg (20 studies).

The volunteers underwent a physical examination by a primary care physician prior to receiving ATP-MgCl₂ and they were all found to be free of any renal or cardiovascular problems. All Phase I studies were carried out in the operating room at Yale-New Haven Hospital solely for the benefit of having the facilities available in the unlikely event that ventilatory and cardiac support would be required during the study.

On the day of each study, two intravenous catheters were placed in the forearm veins, under sterile conditions, and ATP-MgCl₂ was infused through one of the catheters. Blood sampling and injection of dye (indocyanine green) for cardiac output determinations were carried out through the second catheter. Each volunteer had his baseline values of sodium, potassium, glucose, hemoglobin, blood pressure, heart rate and cardiac output recorded just prior to receiving ATP-MgCl₂. ATP-MgCl₂ was infused intravenously at rates of 0.1, 0.2, 0.25, 0.28, 0.32, 0.38, 0.40 and 0.56mg/kg/min. Vital signs were recorded every 3 minutes except at the high-dose ATP-MgCl₂ infusion during which they were obtained every minute. Each infusion rate was carried out, usually for ten minutes. In the final study (full dose of ATP-MgCl₂), however, each infusion rate was carried out for 20 or 30 minutes. Infusions were stopped for 5 minutes prior to switching to higher infusion rates. Blood samples were taken during each ATP-MgCl₂ infusion and cardiac output was measured using the Nihon-Kohden cardiac output computer at various ATP-MgCl₂ infusion rates. Five minutes after the last ATP-MgCl₂ infusion, blood samples were obtained and cardiac output determined in addition to recording vital signs. In addition, blood samples were obtained from volunteers one week after the administration of the full dose of ATP-MgCl₂ and SGOT and SGPT levels were determined. Statistical analysis was performed with ANOVA and

coefficients of correlation. Statistical significance was attributed to values of $p < 0.05$.

General Observations

With the infusion of 0.1mg/kg/min ATP-MgCl₂ and higher, most subjects experienced a feeling of slight chest congestion, flushing in the face, overall warmth and light-headedness. The intensity of the symptoms, however, decreased with the continuation of ATP-MgCl₂ infusion and all of the above symptoms disappeared within a minute or two after the ATP-MgCl₂ infusion was stopped or completed. The mean arterial blood pressure, electrolytes, hemoglobin and serum glucose levels did not change significantly even with the continuous infusion of ATP-MgCl₂. The heart rate and cardiac output, however, increased with the increase in ATP-MgCl₂ infusion rates.

In the final study (i.e. the full dose of ATP-MgCl₂), most subjects experienced a feeling of chest congestion, flushing of the face, and light-headedness. The intensity of these symptoms, however, decreased during the ATP-MgCl₂ infusion. Most subjects also had a feeling of transient nausea if the ATP-MgCl₂ infusion rates were above 0.30mg/kg/min. In one subject, when the ATP-MgCl₂ infusion rates were increased to 0.56mg/kg/min, the subject vomited during the infusion. The rate of ATP-MgCl₂ infusion in the subsequent volunteers was therefore kept below 0.5mg/kg/min and none of the other volunteers had any vomiting as a result of ATP-MgCl₂ infusion. In addition to the above mentioned symptoms, most subjects experienced increased intestinal motility. This was probably due to the effects of ATP-MgCl₂ on the intestinal smooth muscle. Nonetheless, despite the small discomfort, all five subjects tolerated the ATP-MgCl₂ infusion and the slight discomfort they experienced during the high dose ATP-MgCl₂ infusions disappeared shortly after completion of the infusion. Our studies have thus indicated that ATP-MgCl₂ infusion is well tolerated by normal subjects, provided that the rate of infusion is not above 0.5mg/kg/min. No ventilatory or cardiac support was required in any subject during any of the ATP-MgCl₂ infusion studies.

Measurement of serum GOT and GPT levels before, during, at the end of ATP-MgCl₂ infusion and one week after the last ATP-MgCl₂ infusion indicated that the level of these enzymes were not affected by the administration of ATP-MgCl₂. In addition, there was no adverse effects of ATP-MgCl₂ on renal function and there were no delayed side effects of ATP-MgCl₂ infusion.

Effects of ATP-MgCl₂ infusion on heart rate

The percent increase in heart rate (HRPCT) versus ATP-MgCl₂ infusion rates (INFUSRT) is presented in Figure 1. The numbers 1, 2, 3, 4, and 5 represent the code for each volunteer. The results indicated that the heart rate increased with the increase in ATP-MgCl₂ infusion rates. There was a good correlation between ATP-MgCl₂ infusion rates and the increase in heart rate with an r value of 0.72 ($p < 0.001$).

Plotting the percent increase in heart rate (HRPCT) versus percent change in cardiac output (COPCT) indicated that the correlation between these two parameters was not very good (Fig. 2). The r value was found to be 0.55.

From these results, it is clear that maximal increase in heart rate was observed when ATP-MgCl₂ was infused at a rate of approximately 0.3mg/kg/min and with the infusion of 0.1mg/kg/min ATP-MgCl₂, the increase in heart rate was marginal.

The absolute heart rate versus ATP-MgCl₂ infusion rate is presented in Fig. 3. It is clear from this figure that only in two subjects the heart rate exceeded 130 with the infusion of 0.38mg/kg/min ATP-MgCl₂. With the infusion of 0.1mg/kg/min ATP-MgCl₂, the heart rate in any of the subjects did not increase over 100 beats/min. There was a poor correlation between the absolute heart rate and the total dose of ATP-MgCl₂ infused (Fig. 4). The r value in this case was found to be 0.22.

Effects of ATP-MgCl₂ infusion on mean blood pressure

In Figure 5 the percent change in mean blood pressure versus ATP-MgCl₂ infusion rates is plotted. The results indicated that there was no correlation between ATP-MgCl₂ infusion rates and the mean blood pressure. The r value was found to be -0.05.

There was also no correlation between the percent change in mean blood pressure and the total amount of ATP-MgCl₂ infused (Fig. 6). The r value was found to be 0.03.

Plotting the percent change in mean blood pressure versus percent change in cardiac output (COPCT) indicated that there was no correlation between the changes in mean blood pressure and cardiac output. The r value was found to be -0.09 (Fig. 7).

From these results, it is clear that the mean blood pressure did not change significantly with the infusion of ATP-MgCl₂.

Since the heart rate increased with ATP-MgCl₂ infusion, it could be suggested that the observed increase in cardiac output may be due to the increase in heart rate. Since there was no significant change in mean blood pressure with ATP-MgCl₂ infusion but cardiac output increased significantly, it indicates that ATP-MgCl₂ must be producing peripheral vasodilatation and the increase in the heart rate may be due to sympathetic system stimulation.

Effect on Systemic Vascular Resistance (SVR)

SVR decreased significantly with the increase in ATP-MgCl₂ infusion rates. The plot of SVR versus cardiac output (CO) indicates that there is a good correlation between those parameters (Fig. 8). The r value was found to be 0.89. The decreased SVR during ATP-MgCl₂ infusion may also be contributing to the increase of CO. Thus, the increased CO appears to be compensating for the decrease of SVR and hence maintaining the mean blood pressure during ATP-MgCl₂ infusion.

Effect of ATP-MgCl₂ on Stroke Volume Index and Other Parameters

The results presented in Table I indicate that cardiac output increased by 77% ($p < 0.0001$) at maximum infusion rate. This was paralleled by an increase in heart rate (45%, $p < 0.0001$). Stroke volume index increased by 14% ($p < 0.05$). However, the mean blood pressure did not change significantly over the entire range of infusion rates. Systemic vascular resistance decreased 56% at the highest rate of ATP-MgCl₂ infusion. A mean infusion rate of 0.32 ± 0.02 mg/kg/min was associated with maximum increases in heart rate (52%) and cardiac output (119%) without affecting mean blood pressure.

The results of this study demonstrate that the increase in cardiac output offset the decrease in systemic vascular resistance. Thus, blood pressure (MBP) was maintained. Furthermore, the increase in stroke volume index demonstrated a mild inotropic effect. Thus, the pharmacologic profile of vasodilatation, augmentation of cardiac output, maintenance of blood pressure and mild positive inotropy coupled with beneficial metabolic effects in animals suggests an important therapeutic role of ATP-MgCl₂ in the treatment of conditions characterized by regional or global ischemia.

Effects of ATP-MgCl₂ infusion on cardiac output

The results presented in Figure 9 are expressed as percent increase in cardiac output versus ATP-MgCl₂ infusion rates in mg/kg/min. As can be seen from this figure, cardiac output increased progressively with the increase in ATP-MgCl₂ infusion rates and there was a good correlation between the increase in cardiac output and ATP-MgCl₂ infusion rates. The r value was found to be 0.75 ($p < 0.001$). The correlation between percent increase in cardiac output and the total dose of ATP-MgCl₂ infused was not good ($r = 0.20$) (Fig. 10). Thus, the increase in cardiac output was dependent upon the rate of ATP-MgCl₂ infusion but not on the total dose of ATP-MgCl₂ infused. From the results presented in Fig. 9, it appears that maximal increase in cardiac output in normal volunteers was obtained with the infusion of approximately 0.3mg/kg/min ATP-MgCl₂ and that approximately 10% increase in cardiac output was observed when ATP-MgCl₂ was infused at a rate of 0.1mg/kg/min.

Effects of ATP-MgCl₂ on sodium, potassium, blood glucose and hemoglobin concentration

The percent changes in sodium (NAPPCT) versus ATP-MgCl₂ infusion rates (INFUSRT) is plotted in Fig. 11 and, as can be seen, there was no correlation between the percent change in sodium and ATP-MgCl₂ infusion rates. The r value in this case was found to be 0.04. There was also no correlation between NAPPCT and total dose of ATP-MgCl₂ infused (Fig. 12). The r value in this case was -0.12. Likewise, there was no correlation between the percent change in potassium (KPPCT) and ATP-MgCl₂ infusion rates (Fig. 13) and total dose (Fig. 14). The r values in these cases was found to be 0.02 and -0.12, respectively.

The percent change in glucose (GLUCPCT) versus ATP-MgCl₂ infusion rates is plotted in Fig. 15 and, as can be seen, there was no correlation between these two parameters. The r value in this case was found to be 0.28.

Similarly, there was no correlation between GLUCPCT and total dose of ATP-MgCl₂ infused ($r=0.16$)(Fig. 16).

The percent change in hemoglobin (HBPCT) versus ATP-MgCl₂ infusion rate (INFUSRT) is plotted in Fig. 17 and, as can be seen, there was no correlation between these two parameters. The r value in this case was found to be 0.35. Likewise, the correlation between HBPCT and total dose of ATP-MgCl₂ infused was not good ($r=0.26$)(Fig. 18). These results therefore indicate that there were no significant changes in blood levels, sodium, potassium or hemoglobin contents with ATP-MgCl₂ infusion.

Effect of ATP-MgCl₂ infusion on serum GOT and GPT levels

Measurement of serum GOT and GPT during different rates of ATP-MgCl₂ infusion and at 7 days after ATP-MgCl₂ administration revealed that there were no changes in the levels of the above enzymes during or after ATP-MgCl₂ administration (Table II).

Summary of the Phase I studies

Our studies have indicated that, depending on the dose of ATP-MgCl₂ infusion, most subjects experienced a feeling of slight chest congestion, increased intestinal motility, flushing of the face, light-headedness and occasionally a feeling of transient nausea. The intensity of these symptoms, however, decreased with the continuation of the same dose of ATP-MgCl₂ infusion. All the above symptoms disappeared within a minute or two after the ATP-MgCl₂ was discontinued or completed. There was no significant change in mean arterial blood pressure, sodium, potassium, hemoglobin and blood glucose levels. However, the heart rate and the cardiac output increased progressively with the increase in ATP-MgCl₂ infusion rates. Our studies have also indicated that infusion of greater than 0.5mg/kg/min ATP-MgCl₂ may cause vomiting and severe discomfort and, thus, ATP-MgCl₂ infusions in man should be carried out below the rate of 0.5mg/kg/min. None of the volunteers required any ventilatory or cardiac support during any of the studies and all volunteers tolerated the ATP-MgCl₂ infusion. There were no delayed side effects of ATP-MgCl₂ infusion in any of the volunteers. In addition, none of the subjects requested that the study be terminated. These results have therefore demonstrated that it is safe to administer ATP-MgCl₂ in normal volunteers.

The results also suggest that while it is possible to administer ATP-MgCl₂ in normal volunteers to a rate of up to 0.4mg/kg/min without any significant adverse effects, such higher rates of ATP-MgCl₂ administration may not be advisable in certain subsets of patients. In patients in whom large increases in heart rate may have adverse hemodynamic effects, the rate of ATP-MgCl₂ infusion should be 0.1-0.2mg/kg/min. Thus, infusion of ATP-MgCl₂ in such patients should be carried out with monitoring of the heart rate.

In conclusion, data from this study suggest a potentially beneficial role for ATP-MgCl₂ in the treatment of low flow states and confirm the safety of ATP-MgCl₂ in humans.

3. Approval of Phase II Studies of ATP-MgCl₂ by our Human Investigation Committee.

We submitted the protocol to our Human Investigation Committee for their approval of ATP-MgCl₂ for Phase II studies. The application was reviewed by the full committee and approved.

4. Submission of our protocol for Phase II studies of ATP-MgCl₂ to the Army's Human Investigation Committee.

We also submitted our protocol for Phase II studies of ATP-MgCl₂ to the U.S. Army's Human Investigation Committee for their approval. We received the approval of our protocol only recently and we are now beginning to recruit patients for our Phase II studies of ATP-MgCl₂. We hope to initiate such studies in the near future.

5. Preparation of ATP-MgCl₂:

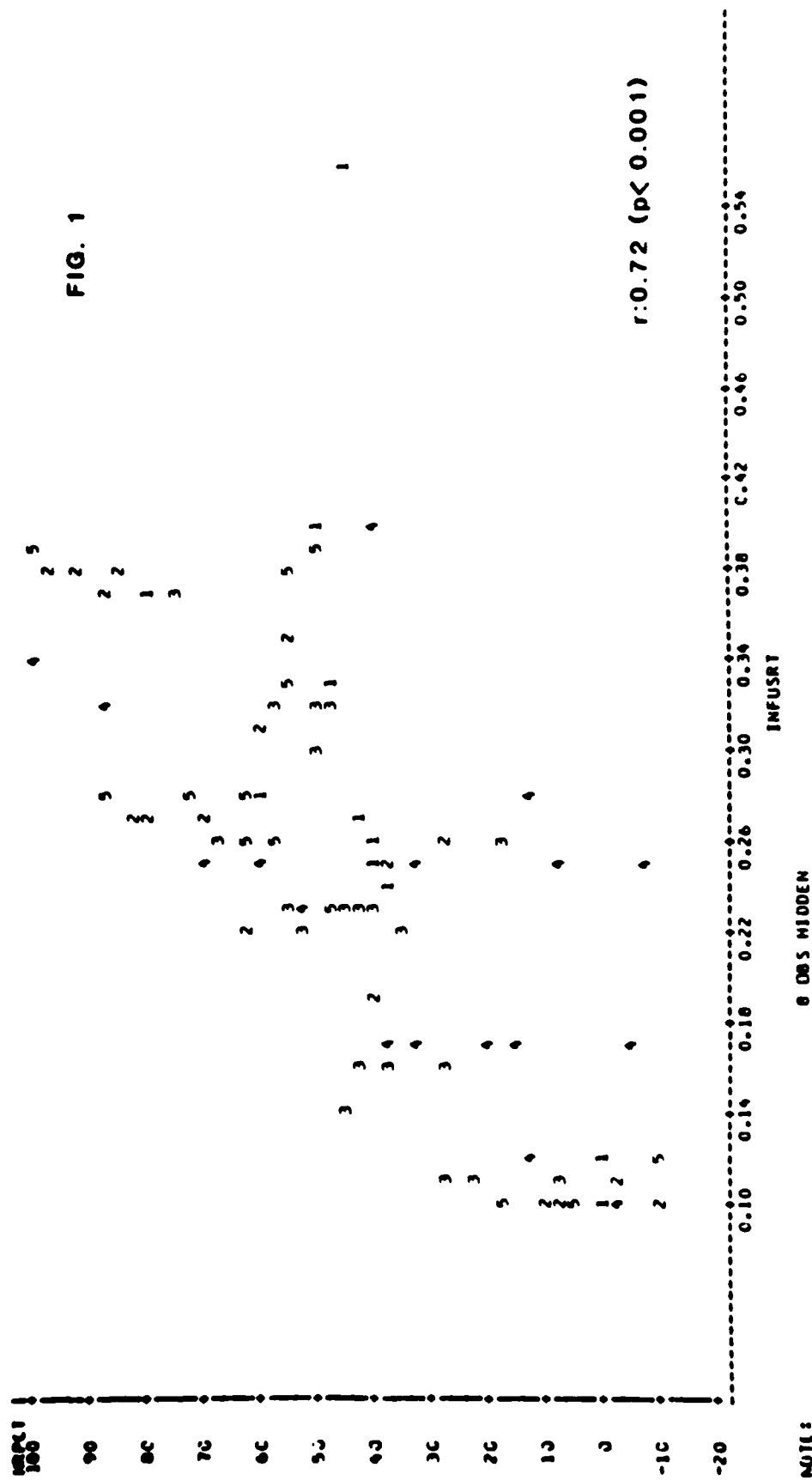
We have already prepared all the ATP-MgCl₂ solutions for the Phase II studies. Such solutions were found to be sterile and pyrogen-free.

6. Food and Drug Administration.

We have requested the FDA to permit us to use yeast ATP instead of muscle ATP in our Phase II studies of ATP-MgCl₂. The reason for this is as follows:

In most of our previous experimental studies with ATP-MgCl₂ we have used the disodium ATP obtained from equine muscle. This source of ATP was used since it was considered to be the highest purity ATP available at the time we initiated our studies. Recently, Sigma Chemical Co. has been able to obtain ATP from yeast which is also 99-100% pure. Since ATP obtained from yeast is far less expensive than ATP from equine muscle, we conducted additional studies in which we compared the effects of yeast versus muscle ATP on hepatic mitochondrial function and blood flow following hepatic ischemia. The results indicated that the improvement in mitochondrial function as well as in hepatic blood flow following ischemia and treatment with yeast or muscle ATP was the same. Thus, it is clear that the beneficial effects of ATP-MgCl₂ following adverse circulatory conditions are not dependent on the source of ATP. The efficacy of yeast ATP is of potentially far-reaching practical importance since we are in the process of initiating a large number of clinical studies with ATP-MgCl₂. Although the isolation of ATP from equine muscle has been adequate to meet the needs imposed by research demands, there may be limitations for large-scale production for clinical use. Yeast ATP, on the other hand, can be produced in large quantities by phosphorylation of adenosine by yeast and has the added advantage of being far less expensive than ATP isolated from equine muscle. Thus, the use of this source of ATP would make potential ATP-MgCl₂ treatment far more cost-effective.

$r:0.72$ ($p<0.001$)



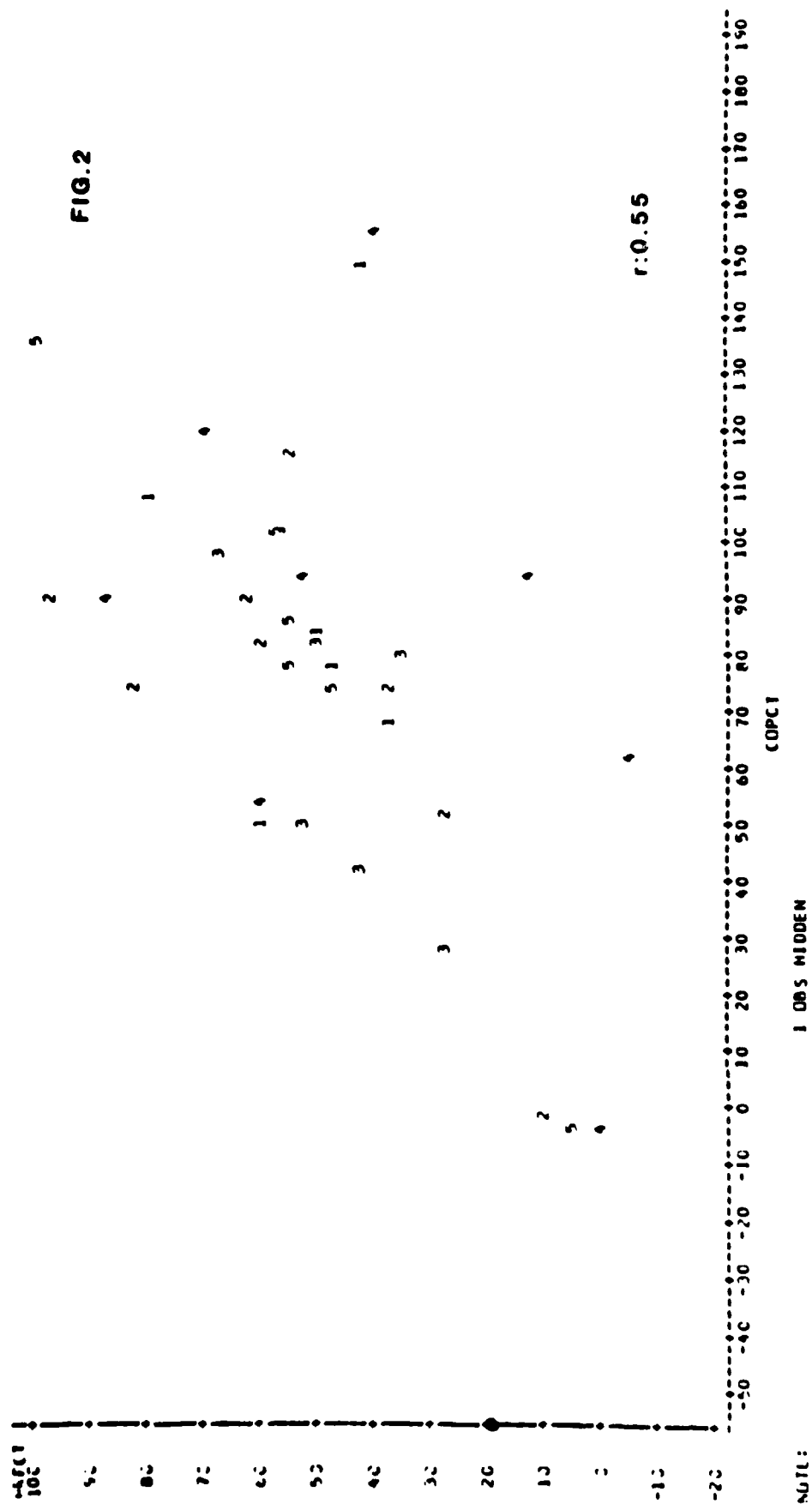
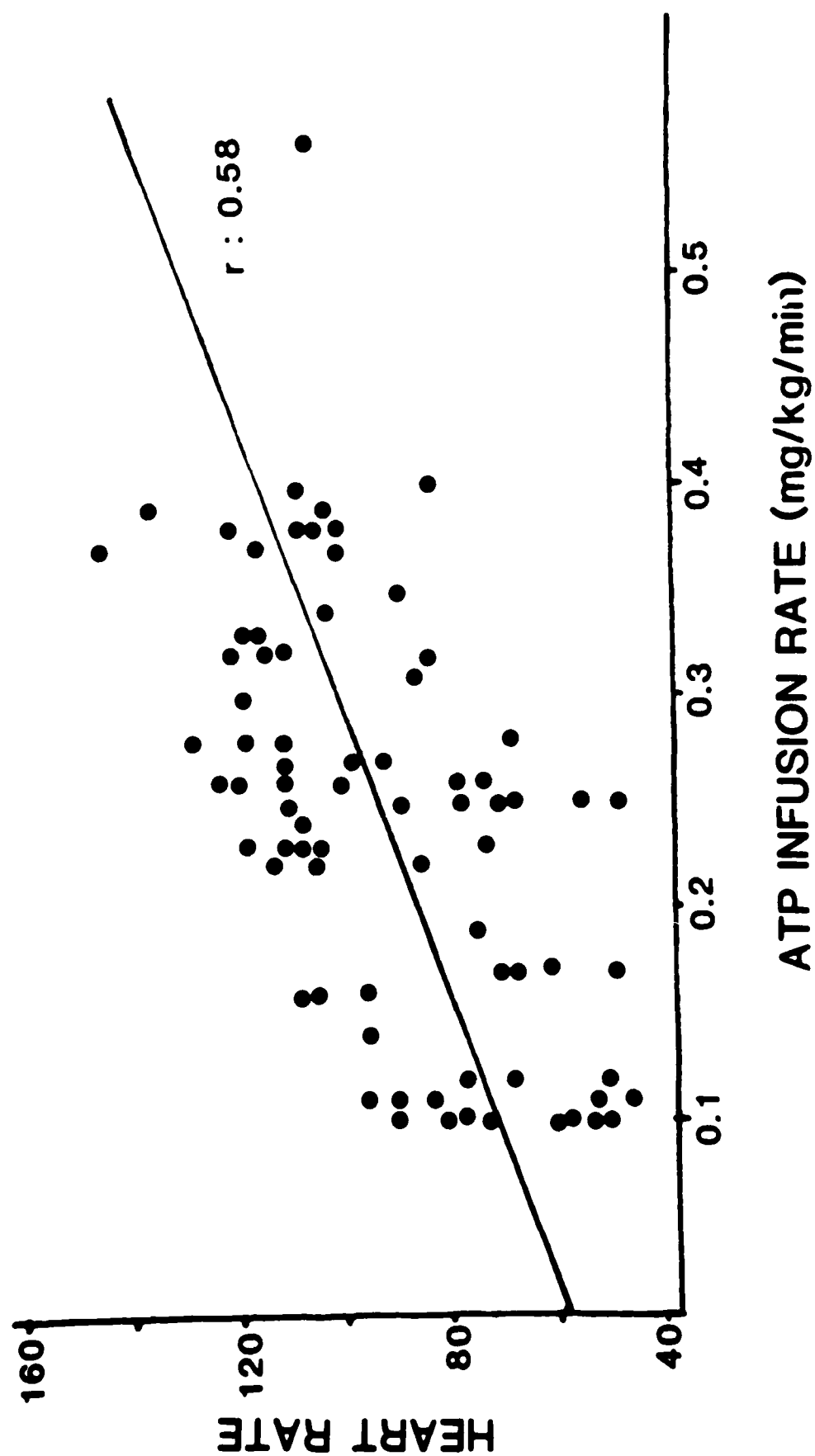


FIG.3



r:0.22

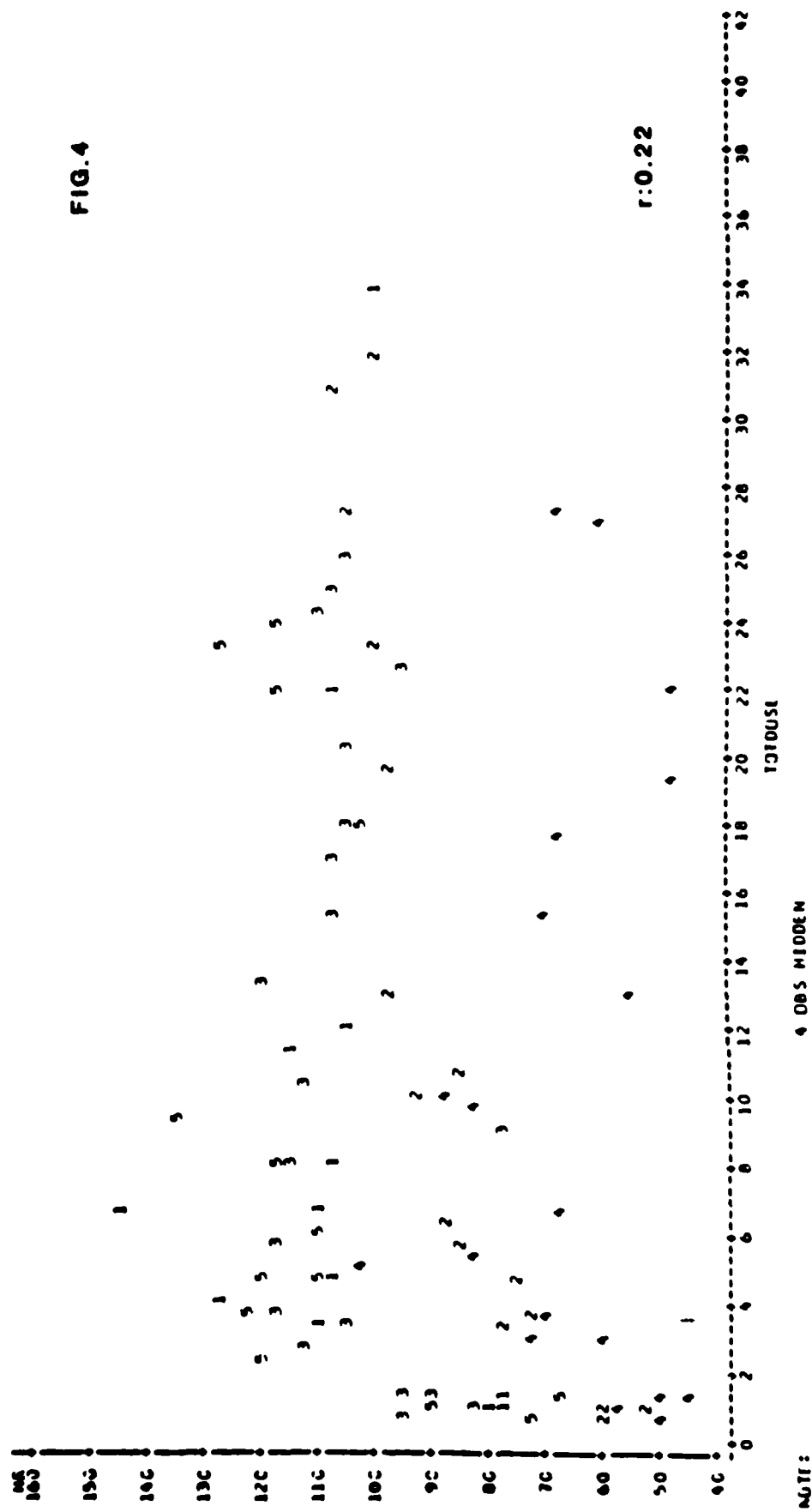


FIG. 5

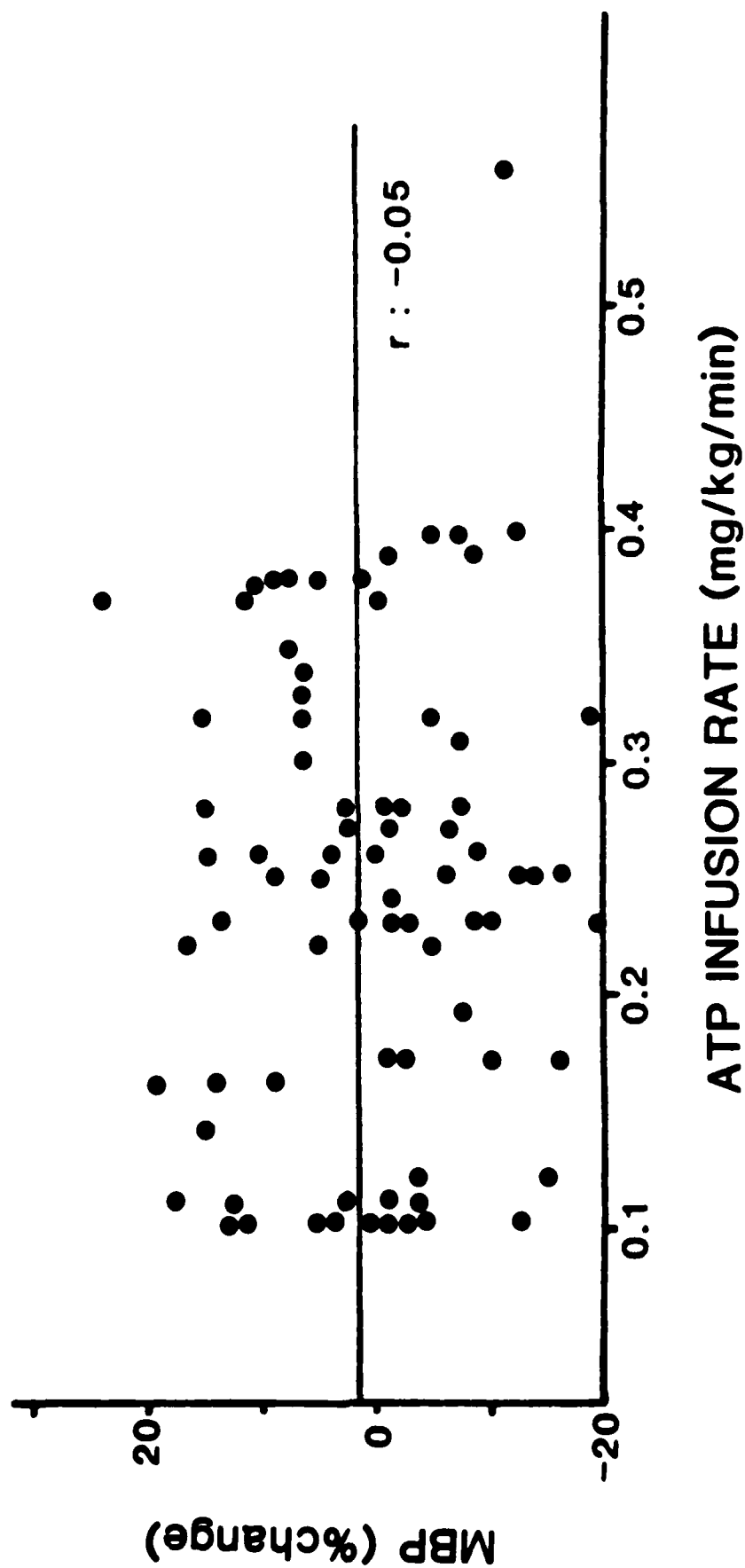
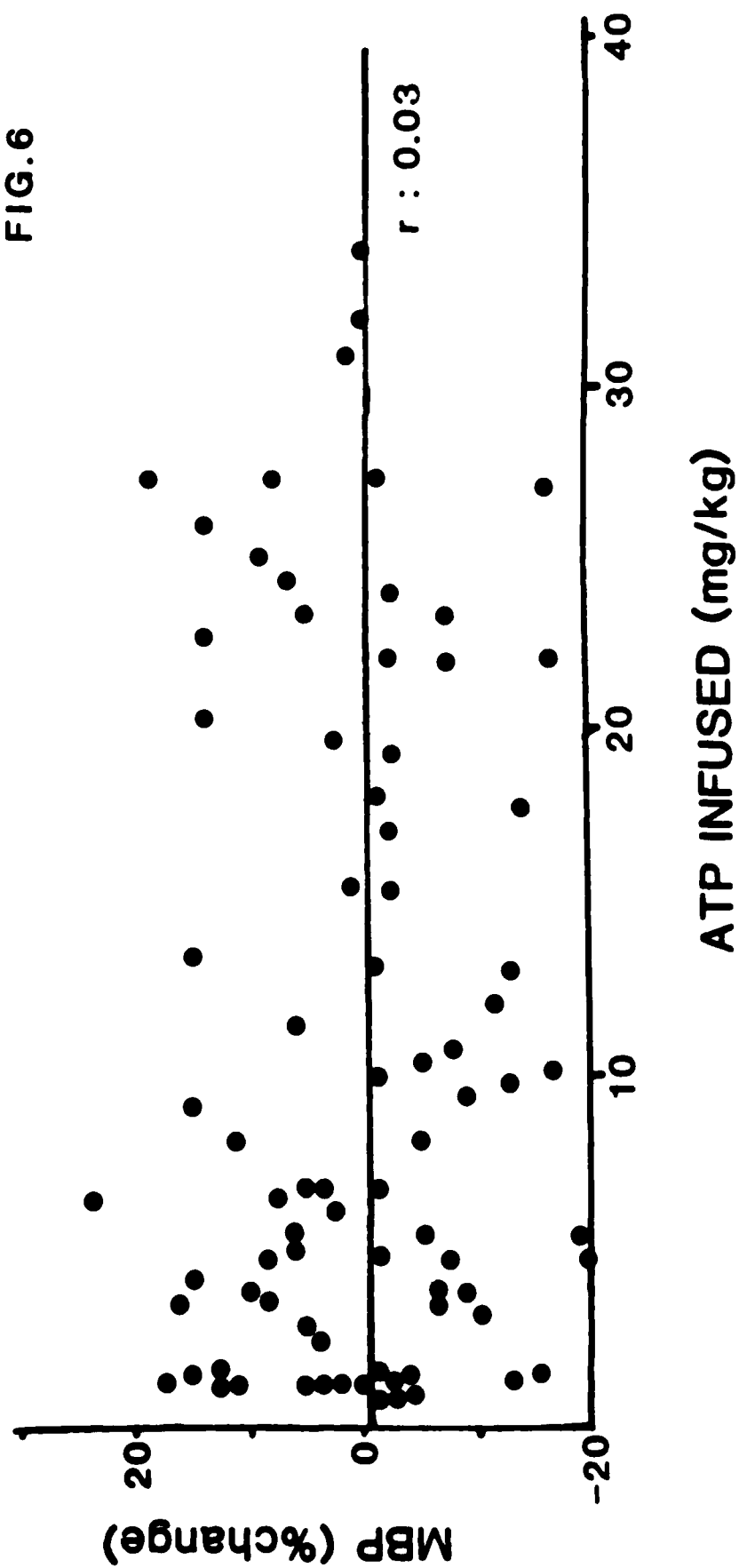
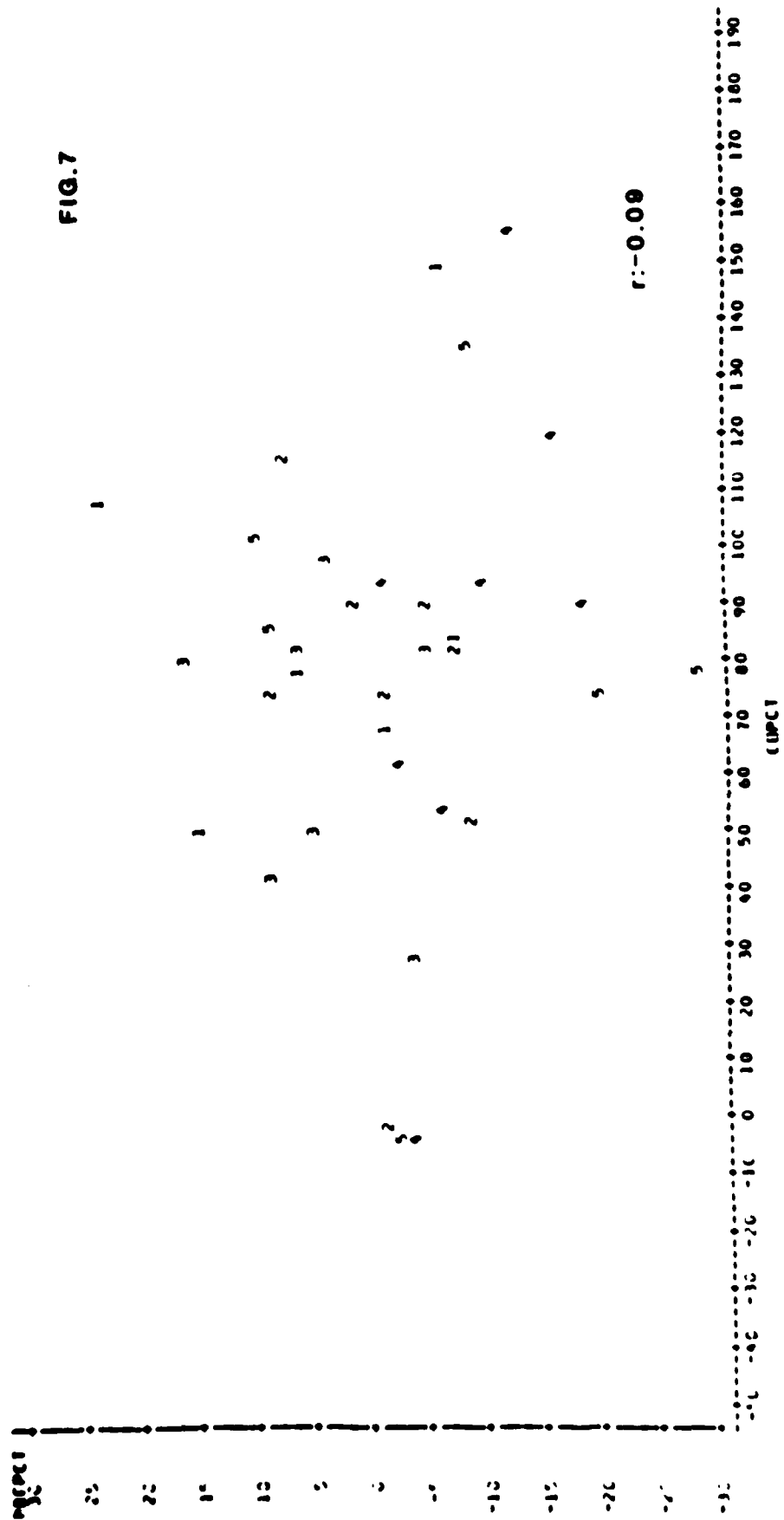


FIG. 6





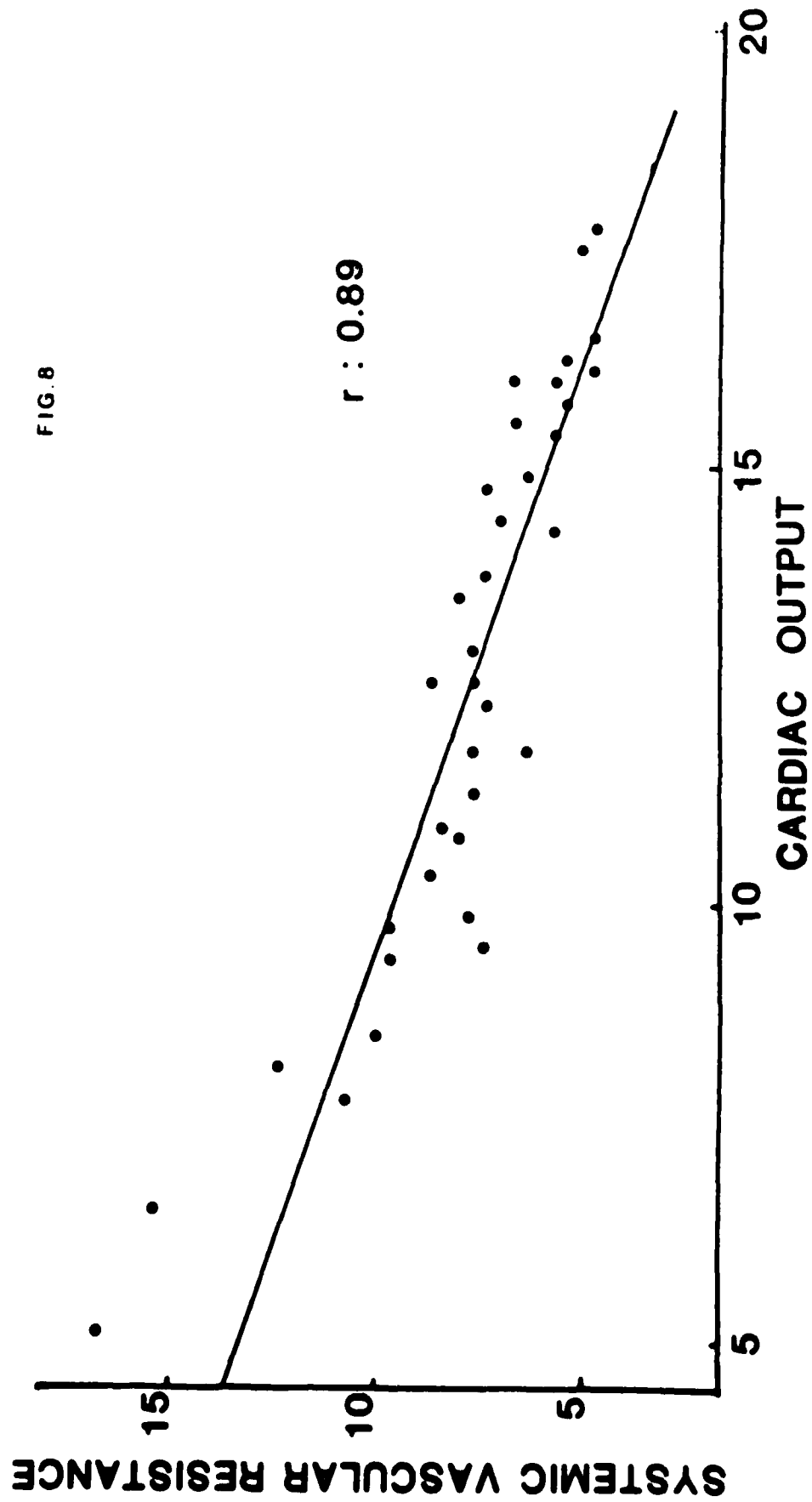
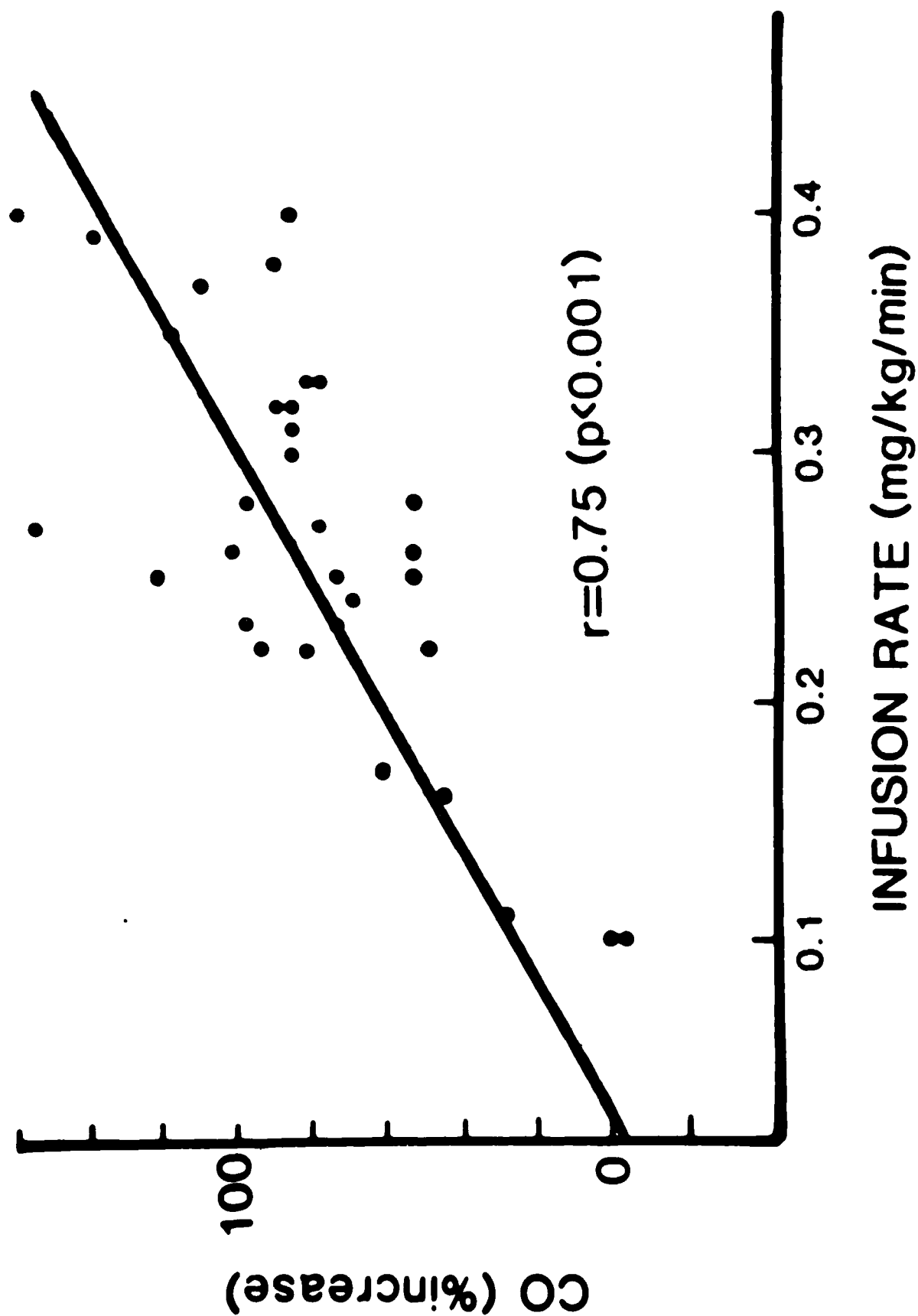
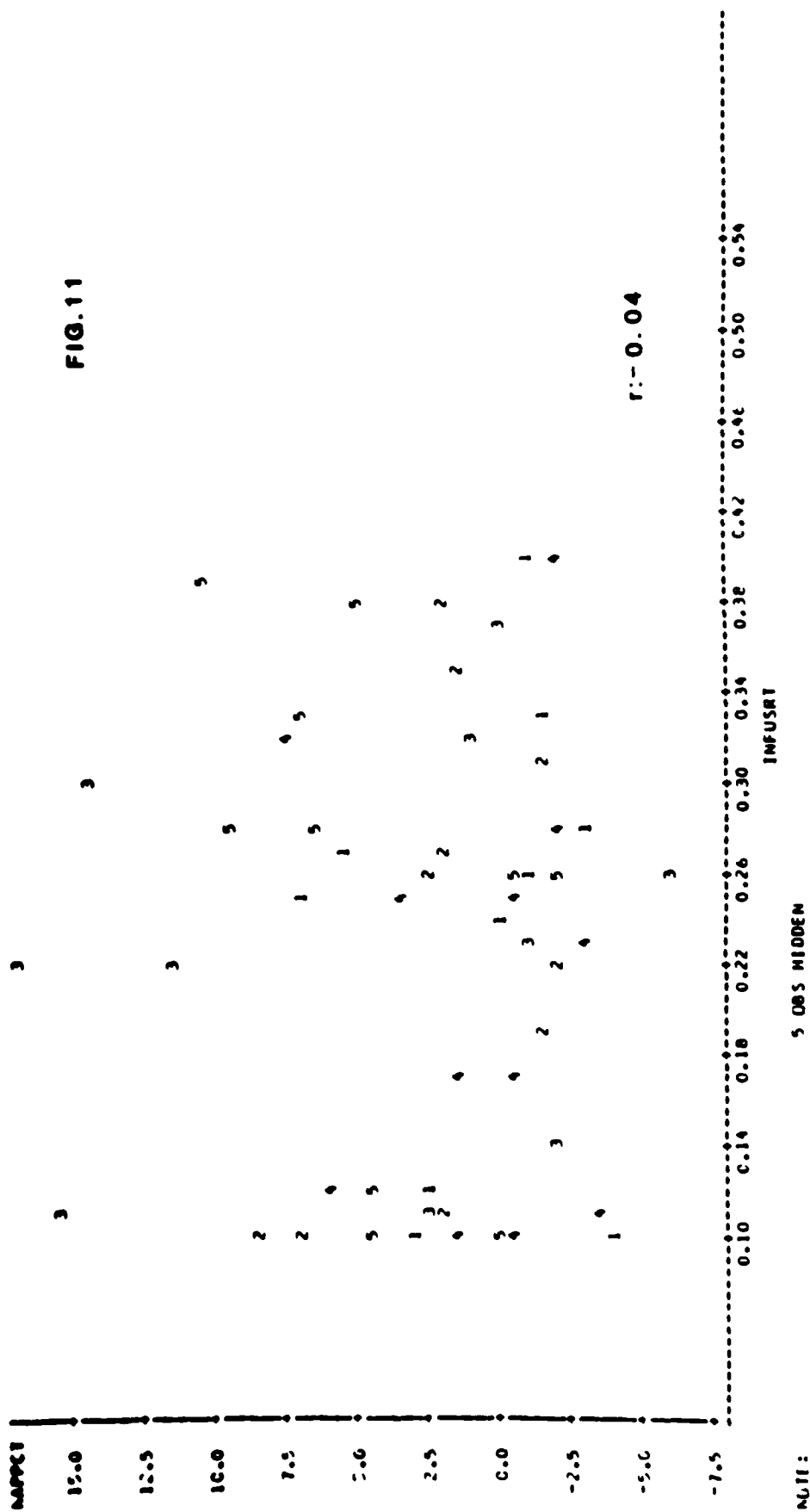


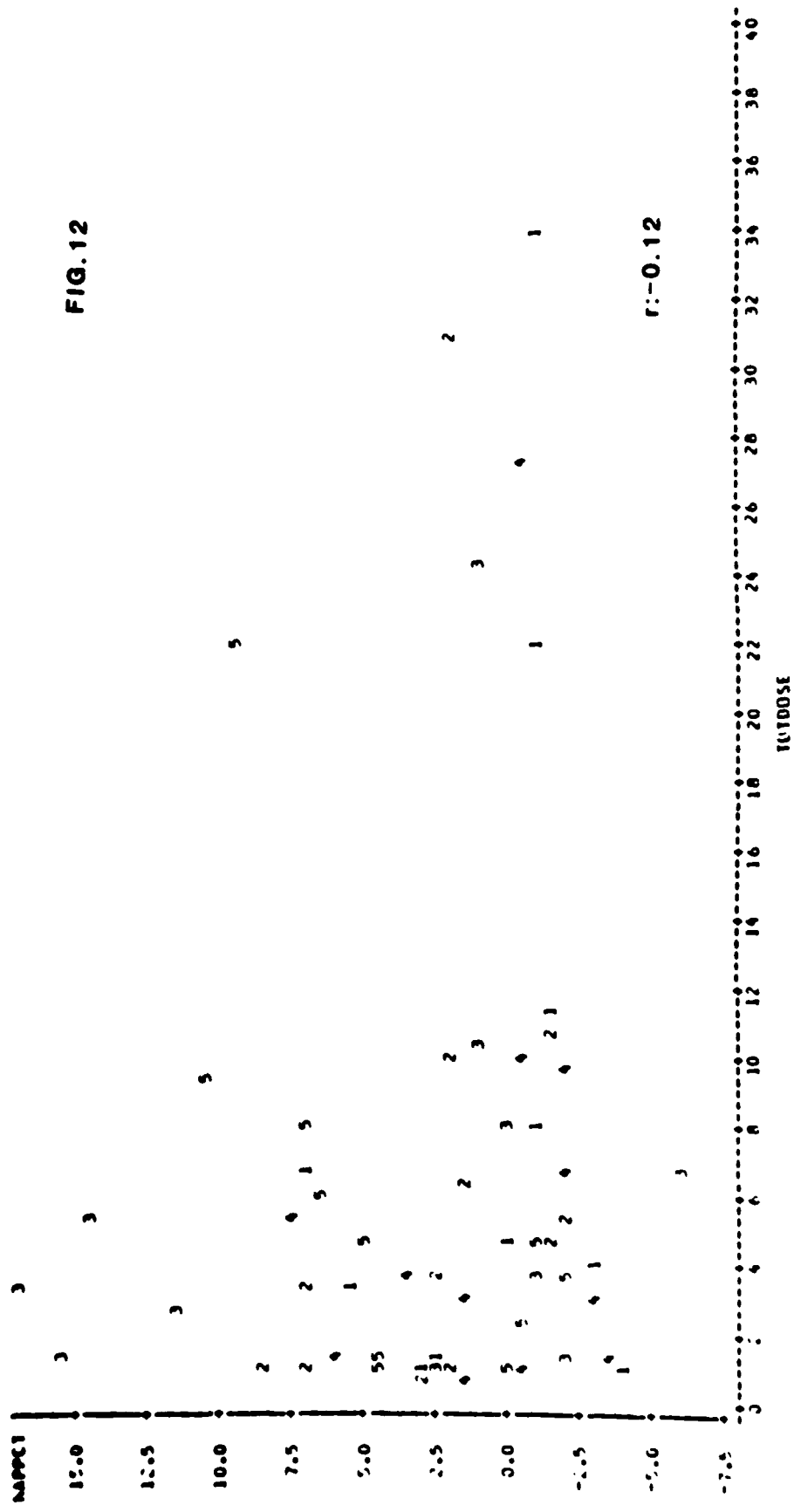
FIG. 9

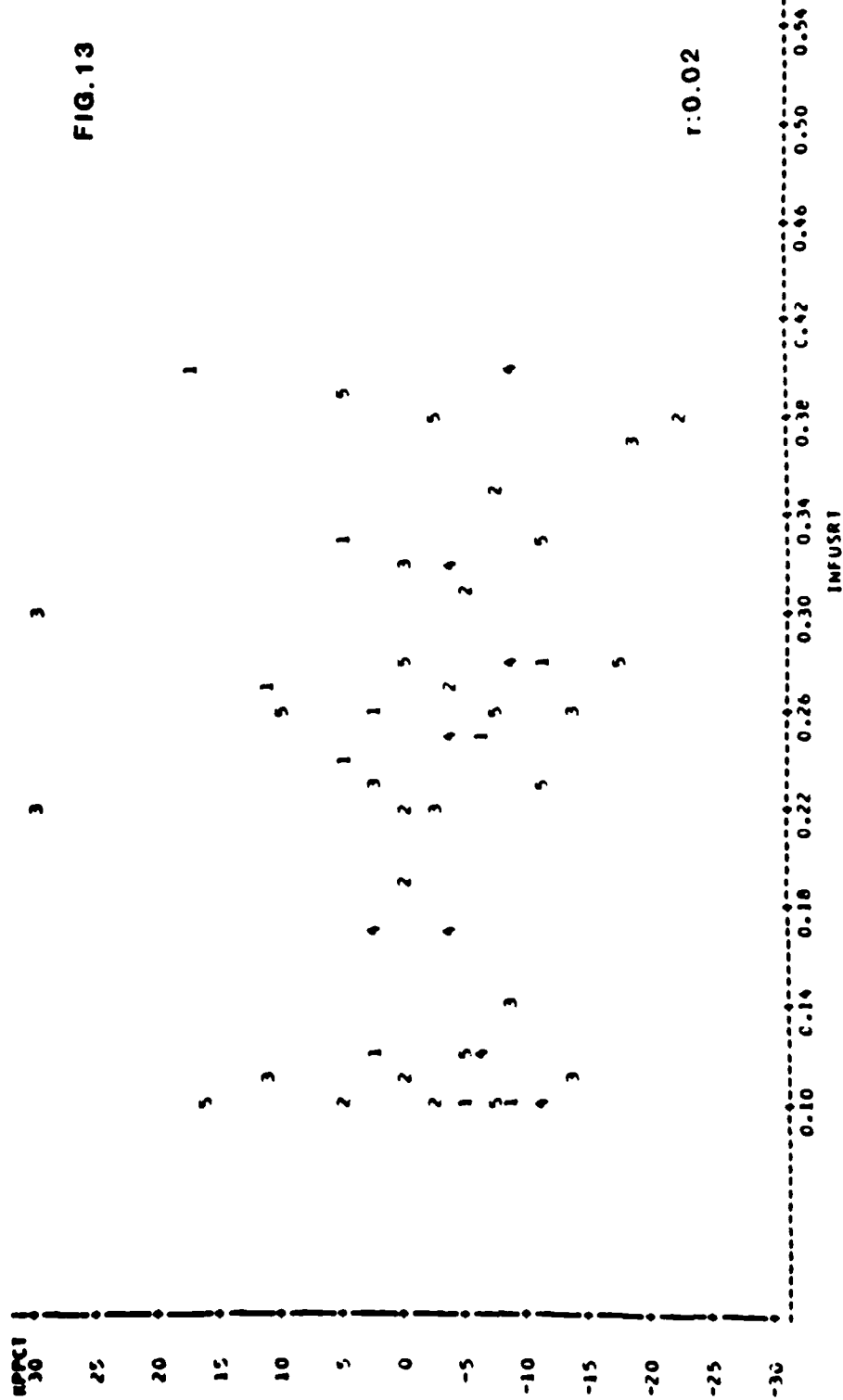


A scatter plot showing the relationship between CO (%increased) on the y-axis and ATP INFUSED (mg/kg) on the x-axis. The y-axis has major tick marks at 0, 60, and 120. The x-axis has major tick marks at 0, 10, 20, 30, and 40. There are 25 data points plotted as solid black circles. A correlation coefficient $r:0.2$ is indicated in the upper right quadrant of the plot area.

ATP INFUSED (mg/kg)	CO (%increased)
0.5	10
1.0	10
1.5	10
2.0	10
2.5	10
3.0	10
3.5	10
4.0	10
4.5	10
5.0	10
5.5	10
6.0	10
6.5	10
7.0	10
7.5	10
8.0	10
8.5	10
9.0	10
9.5	10
10.0	10
10.5	10
11.0	10
11.5	10
12.0	10
12.5	10
13.0	10
13.5	10
14.0	10
14.5	10
15.0	10
15.5	10
16.0	10
16.5	10
17.0	10
17.5	10
18.0	10
18.5	10
19.0	10
19.5	10
20.0	10
20.5	10
21.0	10
21.5	10
22.0	10
22.5	10
23.0	10
23.5	10
24.0	10
24.5	10
25.0	10
25.5	10
26.0	10
26.5	10
27.0	10
27.5	10
28.0	10
28.5	10
29.0	10
29.5	10
30.0	10
30.5	10
31.0	10
31.5	10
32.0	10
32.5	10
33.0	10
33.5	10
34.0	10
34.5	10
35.0	10
35.5	10
36.0	10
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38.0	10
38.5	10
39.0	10
39.5	10
40.0	10



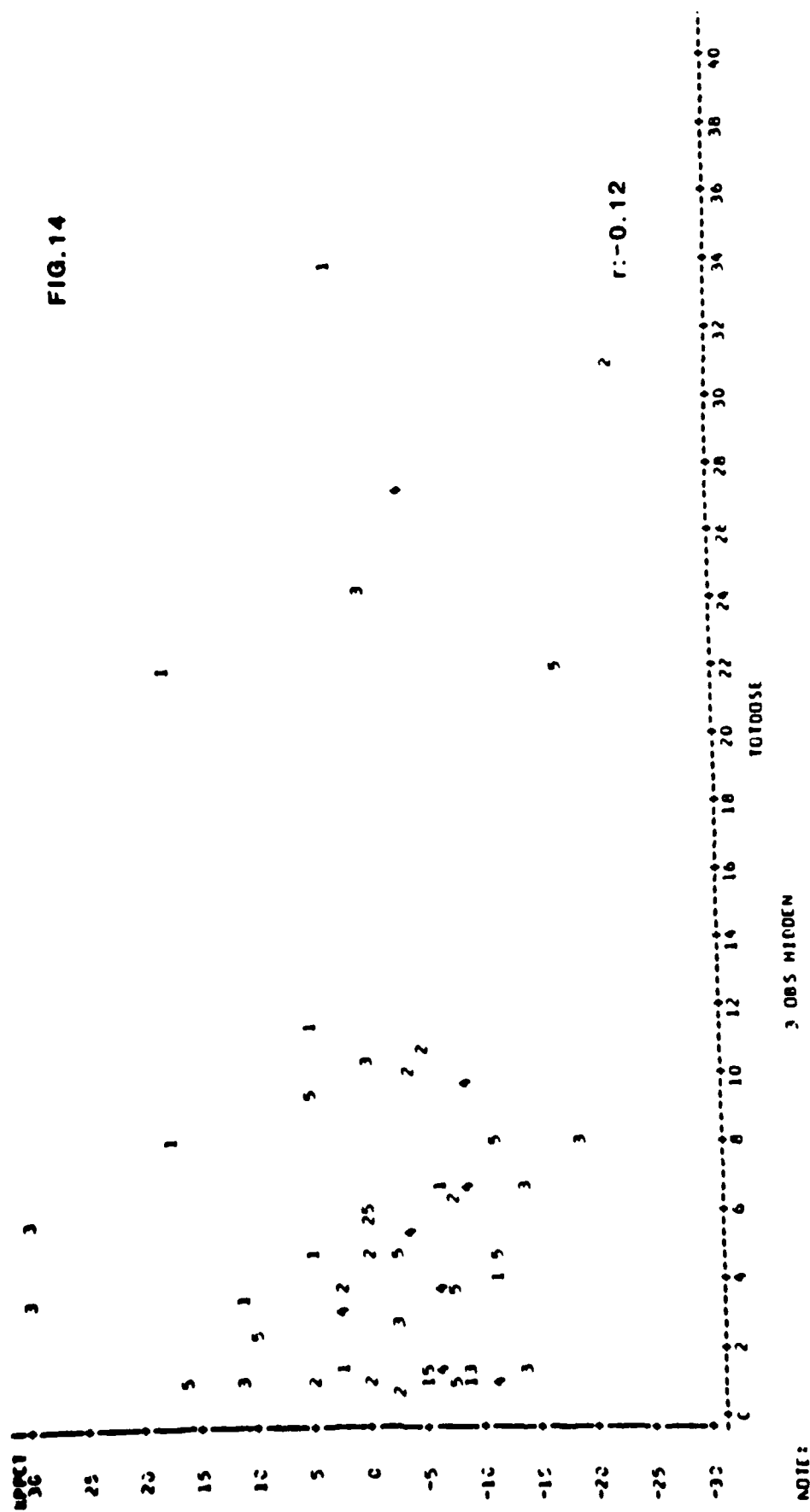


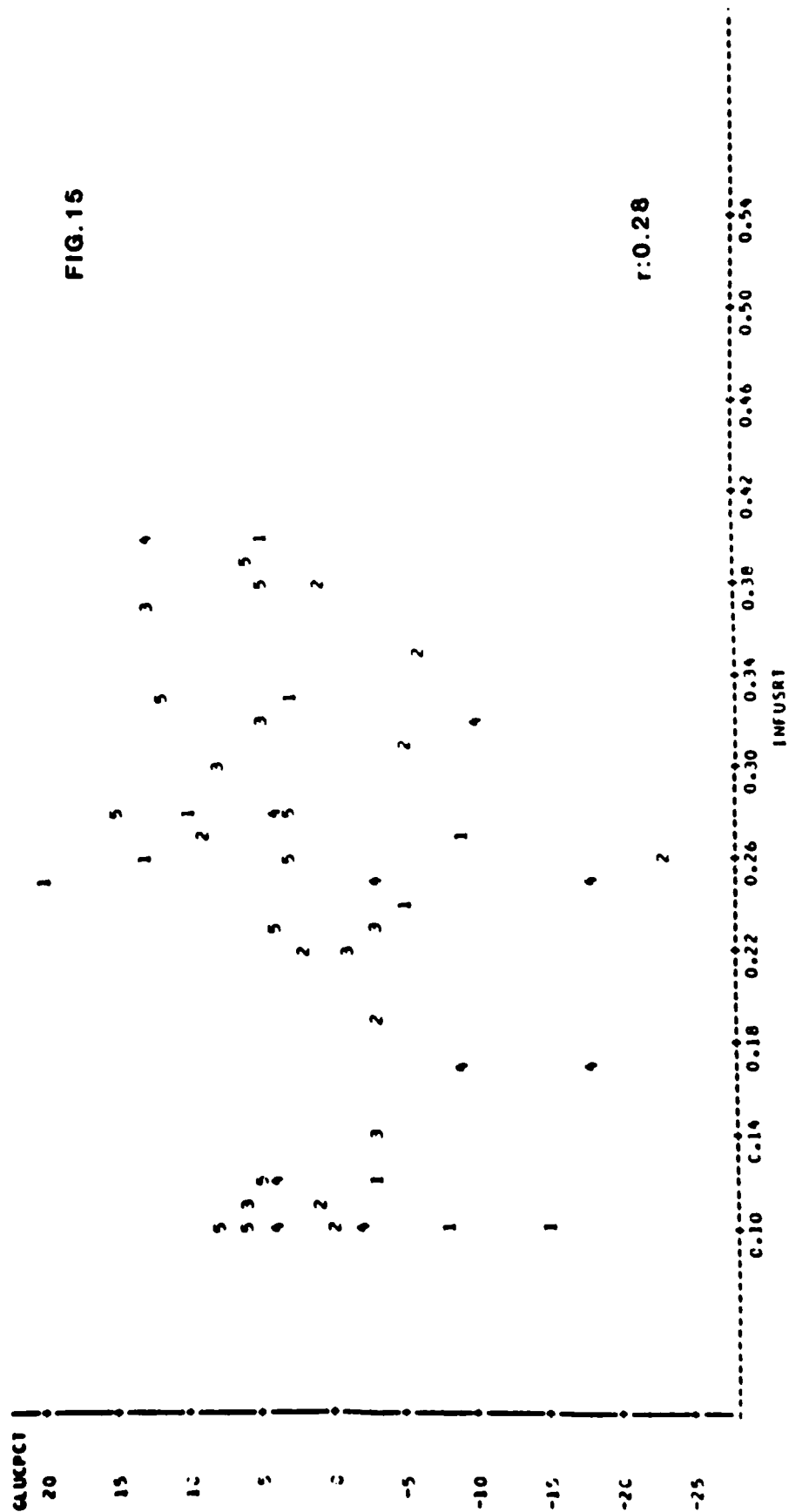


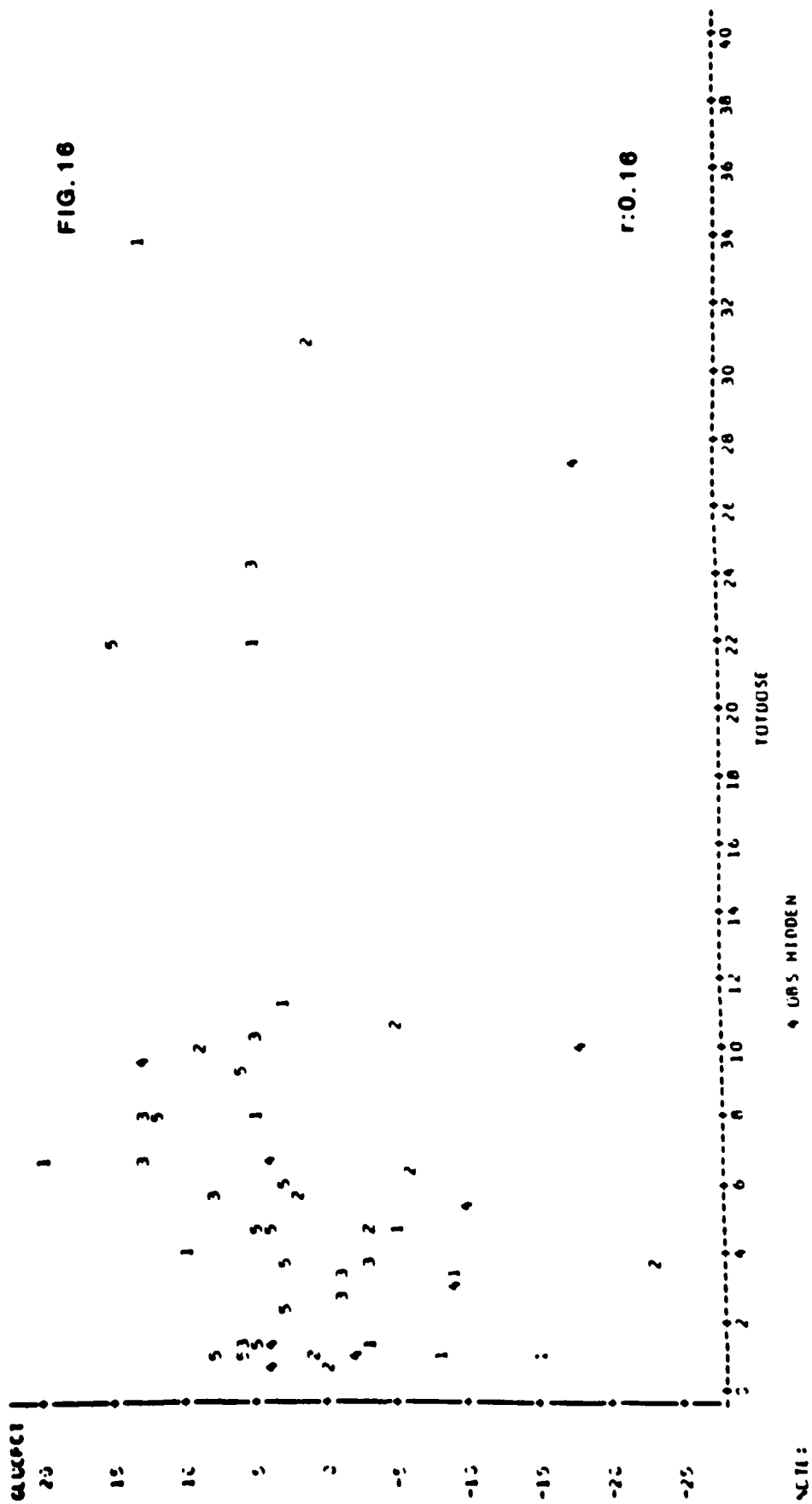
NOTE:

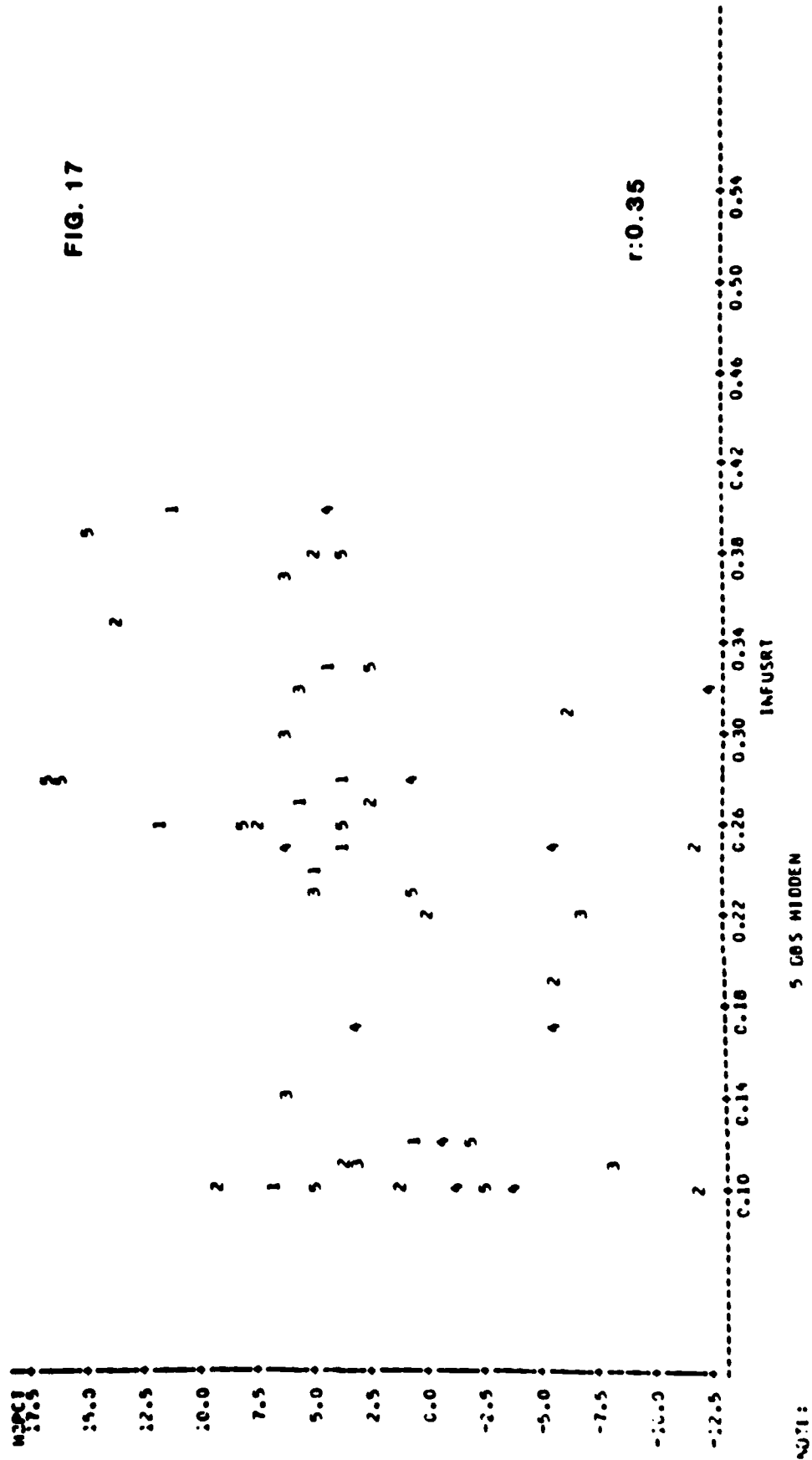
5 DOTS HIDDEN

FIG. 14









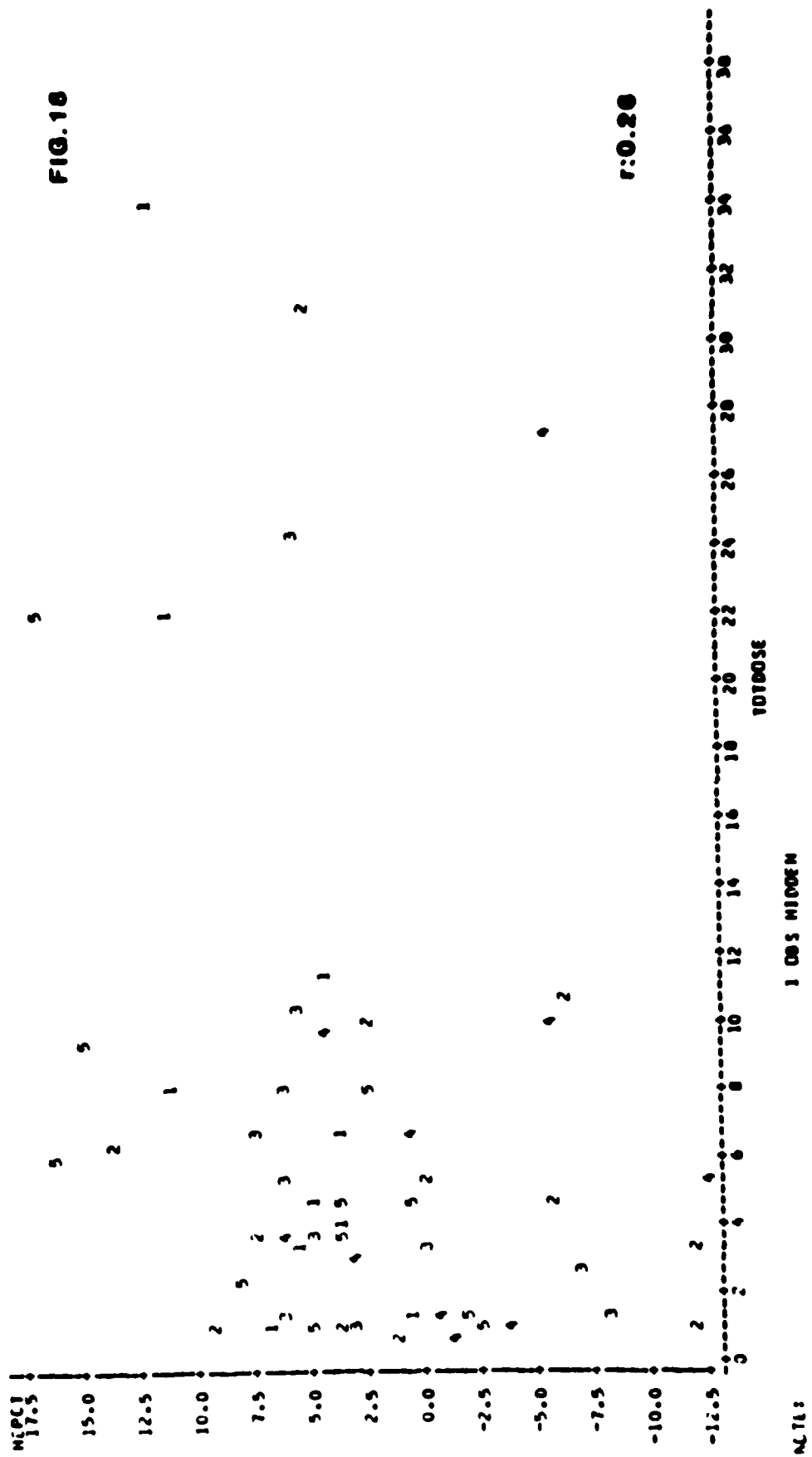


TABLE 1. EFFECT OF ATP-MgCl₂ ON CARDIAC OUTPUT AND PERIPHERAL VASCULAR RESISTANCE

ATP-MgCl ₂ Infusion rate (mg/kg/min)	Heart Rate	Mean Blood Pressure	Cardiac Output	SVI	SVR
0 - 0.01 (Group 1)	74.3±1.6	92.3±1.0	7.7±0.4	0.057±0.002	12.2±0.53
0.10 - 0.19 (Group 2)	72.3±3.2	91.6±2.0	9.0±1.0	0.062±0.004	11.5±1.18
0.22 - 0.28 (Group 3)	97.7±2.9***	91.1±1.8	12.8±0.6***	0.068±0.003**	7.3±0.72***
0.31 - 0.40 (Group 4)	107.3±3.6***	93.6±2.3	13.6±0.7***	0.065±0.003*	6.8±0.83***

***p<0.0001 compared to Group 1

**p<0.004 compared to Group 1

*p<0.05 compared to Group 1

Cardiac output and peripheral vascular resistance measurements in each of the 5 volunteers at 4 separate occasions were performed in the absence and presence of various rates of ATP-MgCl₂ infusion. Values are mean ± S.E. SVI = Stroke Volume Index, SVR = systemic vascular resistance. Statistical analysis were performed with ANOVA and co-efficients of correlation.

TABLE II. EFFECT OF ATP-MgCl₂ INFUSION ON SERUM GOT AND GPT LEVELS (KARMAN UNITS/ML)

<u>3rd ATP-MgCl₂ INFUSION SERIES</u>						
		Volunteer #				
		1	2	3	4	5
Pre-ATP-MgCl ₂ Infusion	GOT	12.19	14.38	15.37	29.90	16.25
	GPT	11.66	5.43	5.83	26.0	9.75
<u>ATP - M g C l ₂ I N F U S I O N R A T E</u>						
		<u>0.37mg/kg/min</u>	<u>0.37mg/kg/min</u>	<u>0.37mg/kg/min</u>	<u>0.33mg/kg/min</u>	<u>0.4mg/kg/min</u>
During ATP-MgCl ₂ Infusion	GOT	14.84	14.31	10.07	28.60	17.55
	GPT	14.31	5.83	6.36	24.70	7.80
7 days Post ATP-MgCl ₂ Infusion	GOT	18.02	14.30	16.90	26.40	15.85
	GPT	12.72	5.85	7.15	25.30	8.82
<u>4th ATP-MgCl₂ INFUSION SERIES</u>						
		Volunteer #				
		1	2	3	4	5
Pre-ATP-MgCl ₂ Infusion	GOT	12.50	20.82	18.62		17.40
	GPT	4.00	6.25	5.62		10.02
<u>ATP - M g C l ₂ I N F U S I O N R A T E</u>						
		<u>0.23mg/kg/min</u>	<u>0.37mg/kg/min</u>	<u>0.32mg/kg/min</u>		<u>0.2mg/kg/min</u>
During ATP-MgCl ₂ Infusion	GOT	16.90	18.00	17.50	SAMPLES HEMOLYZED	14.50
	GPT	7.80	5.62	5.00		10.02
7 days Post ATP-MgCl ₂ Infusion	GOT	13.80	17.60	16.85		17.65
	GPT	8.01	5.75	5.35		10.80

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