A MODEL FOR PLASMA VOLUME CHANGES DURING SHORT DURATION SPACEFLIGHT

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ABSTRACT

It is well established that plasma volume decreases during spaceflight and simulated weightlessness (bedrest). The decrement in plasma volume is thought to contribute to the orthostatic intolerance that has been observed in some crew members following spaceflight. To date, no studies have evaluated the effectiveness of fluid countermeasures of varying osmolality in the restoration of plasma volume and orthostatic tolerance in a controlled study. The overall objectives of this project were to: 1) provide a model that would rapidly and safely produce a fluid loss comparable to that which occurs during short duration spaceflight and 2) design a study that would determine the optimal drink solution to restore orthostatic tolerance and describe the mechanism(s) whereby orthostatic tolerance is restored. In the first part of the study, we used a diuretic (Lasix) as a model for the plasma volume changes that occur during short duration spaceflight. Four subjects (3 males and 1 female) participated in the study. Blood samples were drawn before Lasix administration (IV) and every 30 minutes for 3 hours after Lasix administration. Changes in plasma volume and plasma osmolarity were determined for each blood sample. Urine flow was followed for 3 hours after Lasix injection. Plasma volume decreased by an average of 11.5 $\pm$ .78% by hour 2 and then leveled off. Most of the loss of plasma occurred in the first 30 minutes after Lasix administration (-9.5 $\pm$ .45%). Plasma volume was lowest at 2 hours and increased slightly between 2 and 3 hours (11.5 $\pm$ .85% to 10.35 $\pm$ .95%). This might be a result of fluid shifting from other fluid compartments (interstitial and intracellular) into the plasma. There was a slight decrease in plasma osmolality during the three hours following lasix (286.3 to 283.6 $\pm$.85 mosm), thus the fluid loss was primarily isotonic. Urine flows peaked at approximately 40-60 minutes after lasix (14.7 $\pm$ 2.4 ml/min) and returned to pre-lasix values by 3 hours. These data suggest that Lasix can be used as a model for fluid loss during short duration spaceflight where other models (i.e., bedrest) are not appropriate because of the experimental design. In the second part of the study, we have designed an experiment to examine the effectiveness of fluid countermeasures in the restoration of plasma volume and orthostatic tolerance. For each subject, a euhydrated control orthostatic challenge (lower body negative pressure - LBNP) will be performed in order to establish a baseline response. A second condition will involve dehydration by Lasix administration (20 mg IV). Two subsequent dehydration experiments will be performed where LBNP will be administered following rehydration with a hypertonic saline solution and an isotonic saline solution. This will be done to produce a range of plasma volumes and osmolarities to compare LBNP responses. Plasma volume, leg volume, plasma osmolarity, forearm blood flow, heart rate, blood pressure and cardiac dimensions (echocardiography) will be measured during rest, LBNP exposure, and recovery. During spaceflight, man is subjected to gravitational extremes (weightlessness to high G+ force). It will be important to document the effectiveness of countermeasures that could potentially minimize the negative effects of spaceflight.

INTRODUCTION

The cardiovascular system adapts to the weightless environment of space. This is sometimes referred to as cardiovascular deconditioning. The extent of the deconditioning and the mechanism of deconditioning vary with the individual and the duration of spaceflight. The effects of the deconditioning are manifested upon return to the earth's atmosphere. Crewmembers have experienced orthostatic intolerance when they are re-exposed to the +1 G environment. Symptoms include tachycardia, a reduction in systolic blood pressure and pulse pressure, and a reduction in exercise capacity. In order to maintain crew safety, it is necessary to understand the mechanisms that underlie this cardiovascular deconditioning and find potential countermeasures to minimize its negative effects.

During spaceflight, there is a redistribution of fluid from the lower extremities to the head and upper body. It is thought that this central blood volume expansion results in a suppression of antidiuretic hormone (ADH) and a potentiated diuresis. This has been reported to decrease plasma volume by 8-15% (13). Current techniques to simulate the fluid shifts during spaceflight are limited to bedrest and water immersion. Both of these are time consuming and expensive and not appropriate for those studies that involve repetitive testing.

As a result of the plasma volume loss, the central hypervolemia that occurs initially is compensated for and thus an individual is well suited to a weightless environment. However, upon reentry crewmembers are exposed to 1.2 to 2 +Gz, and at this point due to the hypovolemia, some individuals experience cardiovascular instability. This is characterized by decreased blood pressure, decreased brain blood flow and in some cases syncope. The potential for these to occur continues and is further manifested upon egress from the spacecraft.

Countermeasures are currently being developed to minimize the cardiovascular deconditioning that occurs during spaceflight. These include exercise, lower body negative pressure (LBNP) during spaceflight, and fluid ingestion. In short duration flight it is thought that the primary factor involved in deconditioning is the loss of plasma volume. In longer duration flights, there could be venous compliance or baroreceptor sensitivity changes that contribute to the cardiovascular deconditioning.

Fluid countermeasures have been used for the past 15 years in both the Russian and US space programs. The initial countermeasures included water and saline in the form of bouillon to offset the natriuresis and diuresis that were thought to occur in response to the headward fluid shift. Since that time the makeup of the countermeasure has changed considerably including a wide variety of electrolyte supplements. The current US countermeasure is salt tablets and water to make an isotonic solution (0.9% saline) taken 2 hours before reentry. One recent study by Bungo

and Charles (2) has indicated that crewmembers who ingested a salt and water solution before reentry had fewer incidences of orthostatic intolerance upon re-exposure to gravity than those that did not use the countermeasure. This has yet to be validated in well controlled ground based research. In addition, we dont know if the mechanism for the restoration of orthostatic tolerance is the restoration of plasma volume. It is possible that there is a restoration of hydration status in other body fluid compartments and that this is restoring orthostatic tolerance. In order to evaluate the use of different drink solutions, it is first necessary to first develop a model for spaceflight fluid loss that can be used in a repeated treatment design.

Purpose of Research

The overall objectives of this study were: 1) develop a ground based simulation of changes in plasma volume during short duration spaceflight and 2) develop a research protocol that would determine the optimal drink solution to restore orthostatic responses and describe the mechanism(s) whereby orthostatic tolerance is restored.

HISTORICAL BACKGROUND

The fluid shift that occurs during spaceflight can be as much as 2 liters. This shift is thought to increase central venous pressure at least transiently, although this remains quite controversial (15). Atrial receptors are sensitive to changes in atrial pressure. Increasing stretch on these receptors decreases output to the anterior pituitary and thus decreases the output of ADH (6). This in turn decreases the reabsorption of water in the distal tubule of the kidney. In the non-human primate, this mechanism has been questioned (8). There was no suppression of ADH in response to volume expansion in the monkey. A study on Skylab failed to observe a diuresis. They report that urine flow was actually suppressed during spaceflight (16).

Recent evidence suggests that the increase in CVP is transient and might not be sufficient to stimulate a suppresion of ADH (21). However, it might be sufficient to stimulate an increase in the release of ANF. There are several resports of increased levels of ANF in response to central volume expansion by head-out water immersion (4, 22). There have also has been reports of a decrease in fluid intake during flight, which could also contribute to a reduction in plasma volume. Whatever the mechanism, there is a decline in plasma volume during spaceflight and simulated weightlessness. The decrease in plasma volume has been reported to be between 8-15% depending on the length of the flight (13). During simulated weightlessness (bedrest), the blood volume loss is equivalent to what is observed in spaceflight however, the plasma volume losses after horizontal bedrest are greater (13). Greenleaf et al. (10) reported an average plasma volume decrease of 15.2% following 14 days of bedrest.

Other studies have demonstrated that dehydration either as a result of heat stress (18), diuretic administration (19), or long duration exercise (11) decreases LBNP tolerance. Luft et al. (18) found that leg volume increased and arm volume decreased progressively with LBNP, but these changes were significantly less after dehydration. In a separate study, Luft et al. (19) found that LBNP tolerance was reduced following oral Lasix administration. The Lasix produced a 16.8% reduction in plasma volume. Hilton et al. (11) found that after dehydration as a result of 60 minutes of moderate exercise, LBNP intolerance occurred even after subjects were rehydrated.

To date, there have been no studies that have identified the source of the fluid loss. Total body water has been shown to decrease by 3% in short duration shuttle flights (17). It has been previously mentioned that plasma volume decreases by approximately 10-15% during spaceflight. It is unlikely that all of the fluid was coming solely from the plasma. There must be equilibration of body fluid compartments in the latter portions of the flight. It has yet to be determined how much fluid is coming from the interstitial space (ISF) and/or intracellular space (ICF).

As a result of cardiovascular deconditioning that occurs during spaceflight, there is an impairment of orthostatic responses (7,14). Several studies have indicated that orthostatic tolerance following bedrest is also impaired (10,12). In an attempt to reduce some of the potentially debilitating cardiovascular deconditioning of spaceflight and its effect on orthostatic tolerance, three potential countermeasures have been developed: exercise, LBNP during spaceflight, and fluid ingestion before reentry. The effects of exercise on cardiovascular deconditioning have yet to be documented. However, anecdotal information collected on the Skylab missions indicates that recovery from spaceflight was faster in those who participated in an inflight exercise program (20). Inflight LBNP has been used during Skylab with mixed results (14). However, a ground based bedrest study where LBNP was applied daily has demonstrated that LBNP can be used to offset some of the effects of weightlessness (12).

Several countermeasures have been used to offset the naturesis and diuresis that was observed during spaceflight. One of the first ingested countermeasures was 9-alpha-fluorohydrocortisone which minimized bed rest orthostatic intolerance (1). Hyatt and West (12) used one of the first fluid countermeasures and found that the combined use of oral saline and LBNP was quite effective in returning the heart rate and blood pressure responses to LBNP to prebedrest values, but saline ingestion alone was less effective. Greenleaf et al.(10) reported that saline consumption improves acceleration tolerance after bedrest by restoring plasma volume. Recently, Bungo et al. (2) examined the use of fluid countermeasures in several shuttle flights. They found that crew members that ingested a salt and water solution before reentry had fewer incidences of orthostatic intolerance upon re-exposure to gravity than those that did not use the countermeasure. In a recent study by Fry et al. (5), different drink solutions were ingested in order to determine the solution that produced

the greatest elevation in plasma volume and maintained the increase the longest. They found that a slightly hypertonic saline solution (1.07%) was most effective in increasing and maintaining the higher plasma volume. It was superior to a number of drink solutions including an isotonic saline solution (the present countermeasure). It has yet to be determined whether the hypertonic solution will increase plasma volume after dehydration and whether it will improve orthostatic tolerance as well as the isotonic saline fluid countermeasure.

There are various techniques to assess orthostatic responses. These include the stand test, tilt table test, human centrifugation, and lower body negative pressure (LBNP). The NASA stand test has the subject lie supine for 5 minutes and then stand quickly. Heart rate and blood pressure are then monitored for 5 minutes. This is a simple test, however, it does not rule out the confounding effects of muscle contraction and the resulting volume redistribution associated with it. By putting an individual on a tilt table and positioning the table to various inclines, the gravitational effects on the cardiovasular system can be varied. However, this test has limited usefulness in that it can only place a +1 Gz stress on the individual and it is difficult to get many physiological measurements during this type of testing. Human centrifugation is expensive and data collection is limited by the size of the centrifuge.

Lower body negative pressure allows for the gradation of the orthostatic stress while the subject is in the supine position. This technique facilitates data collection and allows for high +Gz forces to be applied to the subject. Lower body negative pressure results in venous pooling in the lower extremities. This in turn decreases cardiac filling pressure, end diastolic volume, and ultimately via the Frank-Starling mechanism stroke volume. Reflex mechanisms from both the carotid baroreceptors and cardiopulmonary receptors are activated which act to increase heart rate and total peripheral resistance to maintain arterial pressure. In addition, there is an increased sympathetic outflow and catecholamine release resulting in a reduction in end-systolic volume, thus maintaining stroke volume and cardiac output (24).

To date, no studies have evaluated the effectiveness of fluid countermeasures of varying osmolality in the restoration of plasma volume and LBNP tolerance in a controlled study. Studies of this nature have been limited by the need to do repetitive spaceflight simulations. For bedrest, there is an effect of one bedrest on the next bedrest making it impossible to look at independent effects of drink solutions in subsequent bedrests. Diuretics will cause a dehydration as a result of increasing fluid loss in the urine. Lasix is a commonly used diuretic for the treatment of hypertension that uses furosimide as its active ingredient. Furosimide acts to inhibit the reabsorption of sodium and chloride in the proximal and distal tubules, and the loop of henle. Its action is independent of any inhibitory effects of carbonic anhydrase or aldosterone (9). It is quick acting and has few side effects. For these reasons, we tried Lasix as a model for the fluid losses that occur during spaceflight.

METHODS

Model for Plasma Volume Changes During Spaceflight

In order to determine the total loss of plasma volume as a result of diuretic administration (Lasix), the time course of PV changes, the optimal time for fluid ingestion, and whether the loss of fluid with the diuretic is isotonic, four subjects were recruited and participated after obtaining informed consent (3 males and 1 female). Subjects entered the laboratory after a small meal in the euhydrated state. Subjects voided their bladder and were weighed. They then sat for 30 minutes to control for posture before blood sampling. An intracath was inserted in a superficial arm vein. A preliminary blood sample (5 ml) was drawn without stasis. Twenty mg of Lasix was injected IV. Urine samples were collected for 3 hours after Lasix injection for urine flow determinations. Blood samples were obtained every 30 minutes after Lasix. Hematocrit was determined by microcentrifugation, hemoglobin was determined by a Coulter Counter, osmolality was determined by freezing point depression on all samples. From the hematocrit (HCT) and hemoglobin (HG), relative changes in plasma volume were determined using the formula of Dill and Costill (3).

Fluid Countermeasure and Orthostatic Tolerance

Eight volunteers will be recruited for this part of the study. Subjects will be given several practice LBNP tests prior to the start of the experimental phase of the study. For each subject, control LBNP test(s) will be performed in order to establish a baseline response to LBNP. In a second condition, dehydration will be produced by a 20 mg IV injection of Lasix. This will produce approximately an 11% reduction in plasma volume from euhydrated plasma volume as has been determined from the first part of this project. Two subsequent experiments will be performed where each subject is rehydrated after dehydration by Lasix with a 14 ml/kg solution of a hypertonic saline solution and an isotonic saline solution. For the dehydration and two rehydration experiments an LBNP test will be performed. This will give us a range of plasma volumes and osmolarities to compare LBNP reponses. Each subject will complete all tests. Below is a summary of the 4 conditions:

1. Control LBNP
2. LBNP following dehydration
3. LBNP following dehydration and rehydration with hypertonic saline
4. LBNP following dehydration and rehydration with isotonic saline

The order of treatments will be randomized in order to eliminate any order effects on the LBNP results. All experiments will begin at the same time of day for each individual subject to eliminate any circadian effects on the findings. Testing will begin 2 hours after the ingestion of a small meal. LBNP will be performed 60 minutes after ingestion of fluids. At least 72 hours will be allowed between testing.

LBNP Protocol

Lower body negative pressure will be applied using a plywood chamber sealed at the waist with a rubber gasket. A vacuum cleaner is then used to withdraw air out of the box. The following protocol will be used:

	Pressure (Torr)	Time at Stage(min)
Rest	0	10
Stage 1	-5	5
Stage 2	-10	5
Stage 3	-20	5
Stage 4	-30	5
Stage 5	-40	5
Stage 6	-50	5
Stage 7	-60	5
Recovery	0	10

The test will be terminated if the subject's systolic blood pressure drops suddenly (greater than 25 mmHg in 1 minute), systolic pressure reaches 80 mmHg, bradycardia occurs (drop in HR greater than 15 BPM), subject distress or subject request.

Before, during, and immediately after LBNP the parameters described below will be measured.

Leg volume is calculated from leg circumference measurements made every minute with a mercury-in-silastic strain gauge. The changes in leg volume during LBNP exposure will be used to approximate the amount of venous pooling in the legs.

A blood sample will be taken from an antecubital vein before drink ingestion, 30 minutes after drink ingestion, immediately before, and immediately after LBNP (a total of seven blood samples). Changes in plasma volume will be calculated from hematocrit (microhematocrit technique) and hemoglobin (Coulter Counter) ratios using the formula of Dill and Costill (3). A direct measurement of plasma volume will be performed once (human serum labeled 125-I) in each subject before the first experimental testing. This value will be used as the absolute plasma volume and changes will be expressed relative to that value. Plasma osmolality will be determined using freezing point depression on all blood samples. A 5 ml sample will be required to do all of the hematological analysis. Plasma levels of antidiuretic hormone (ADH), atrial natriuretic factor (ANF), aldosterone, and catecholamines (epinephrine, norepinephrine) will be measured for each blood sample. These assays require a blood sample of 15 ml.

Venous occlusion plethysmography with a mercury-in-silastic strain gauge will be used to measure forearm blood flow. The forearm vasoconstrictor response as indicated by this technique will be measured at each step of LBNP, and plotted as a function of systolic blood pressure. The slope of this response will be used to estimate vasoconstrictor responses to

baroreceptor (cardiopulmonary and sinoaortic) activation induced by the decreasing blood pressure. Heart rate will be determined using a three lead EKG. The R-R interval will be determined for each stage of LBNP. The change in R-R interval will be plotted as a function of the systolic blood pressure. The slope of this relationship will be used as an estimate of overall baroreceptor function. Blood pressure will be measured once a minute using a standard auscultatory technique. 2-D and M-Mode echocardiography (ATL 4000 S/LC ultrasound system, ATL, Botheli, WA.) will be performed at each stage of LBNP in order to assess relative changes in left ventricular dimensions with LBNP.

EMG will be used to assess abdominal and leg muscle tension in order to control for muscle tensing. The subject will be asked to maintain a resting EMG level throughout all LBNP tests.

Urine will be collected 30 minutes after drinking and immediately after LBNP in order to calculate urine flow rates.

RESULTS

Model for Changes in Plasma Volume During Short Duration Spaceflight

Plasma volume decreased in the first 30 minutes after Lasix administration (Figure 1). The loss of plasma volume leveled off at 2 hours (11 $\pm$ .78%). By 3 hours, the plasma volume was partially restored, most likely as a result of fluid shifting from the ISF and ICF compartments into the plasma.

There were no major changes in plasma osmolality for three hours after Lasix in comparison to pre-lasix injection (Figure 2). There was a slight fall in plasma osmolality (286.3 to 283.6 $\pm$ .85 mosm), indicating a slightly hyperosmotic urine.

Urine flow for each subject is displayed in Figure 3. For all of the subjects, urine flow peaked between 30 and 60 minutes, then decreased back to control level. By 3 hours, urine flow had returned to the control value.

In an attempt to determine the source of the fluid loss, the % loss of fluid from the plasma was estimated. We assumed that the plasma volume was 45 ml/kg for men and 35 ml/kg for women. These results are displayed in Table 1. Overall, for the 3 male subjects, one third of the fluid loss was from the plasma, and thus the other two thirds must have been from the ISF or ICF. The level of dehydration (-11% of the plasma) and the time (2-3 hours) would indicate that most of the fluid was coming from the ISF and not the ICF.

DISCUSSION

Six degree head down bedrest is currently the standard simulation of weightlessness. However, it is expensive and can not be used in repetitive designs. Results from the present study indicate that Lasix produces

comparable losses of plasma volume (11%) to that observed following spaceflight (10-15%) (13). This is also comparable to oral Lasix administration. Luft et al. (19) reported plasma volume decreased 16.8% by 3 hours after oral Lasix. However, they did not follow the time course of the response. Lasix is fast acting as most of the loss of plasma volume occured in the present study in the first 45 minutes following IV injection. By 2 hours the loss of plasma had peaked. Thus for the second part of this study, fluid ingestion should take place approximately 2 hours after lasix administration. As is the case during spaceflight the loss of fluid as a result of the lasix is primarily isotonic. Although, it is not known during spaceflight where the fluid loss is coming from, it is probably coming from the ISF first and then the ICF. In the present study, we found that approximately 1/3 of the total fluid loss was coming from the plasma and the rest from the other two fluid compartments (ICF and ISF).

There is the possibility that Lasix could influence the control of blood pressure independent of the plasma volume changes. Lasix does alter renal blood flow. It can increase or decrease renal blood flow depending on the experimental conditions (9). Furosimide has also been shown to increase atrial natriuretic factor and renin in plasma (23). However, it is difficult to separate out the hypovolemic effects of furosimide and its direct effect on the kidney and other vascular areas. This needs to be taken into account when using Lasix under these conditions. Given these limitations, Lasix can be used to simulate the plasma volume losses that occur during short duration spaceflight.

The design presented should determine the optimal drink solution to restore orthostatic tolerance and the mechanism whereby orthostatic tolerance is restored. We would anticipate, based on the study by Fry et al.(5), that the optimal drink solution should be the hypertonic saline solution if the mechanism for restoring orthostatic tolerance is the restoration of plasma volume. However, it is possible that other mechanisms might be operational. It is possible that fluid ingested moves through the plasma into the ISF and ultimately the ICF, thus restoring hydration in cells. This could in some way restore orthostatic tolerance independent of restoring plasma volume.

CONCLUSIONS

In summary, Lasix can be used as a way of simulating the plasma volume changes that occur during short duration spaceflight. The total loss of plasma is comparable to spaceflight. Lasix is fast acting, and has relatively few side effects.

The present design for evaluating the optimal fluid countermeasures will have important implications in restoring orthostatic tolerance and function in the latter stages of spaceflight when it is essential for safe operation of the spacecraft.

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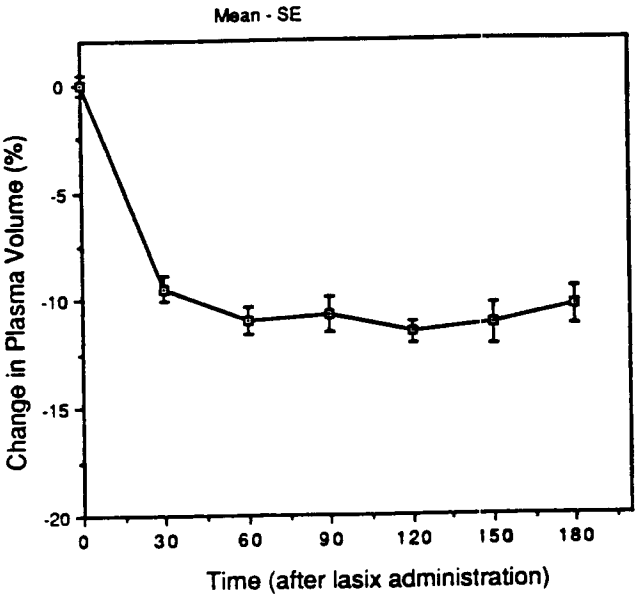

Figure 1. - Change in plasma volume as a function of time after Lasix administration. Means are plotted ± 1 SE.

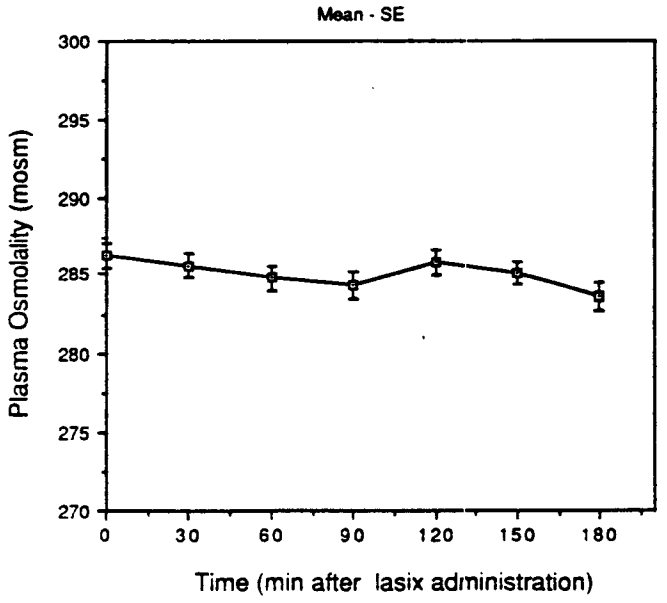

Figure 2. - Plasma osmolality as a function of time after Lasix administration. Means are plotted ± 1 SE.

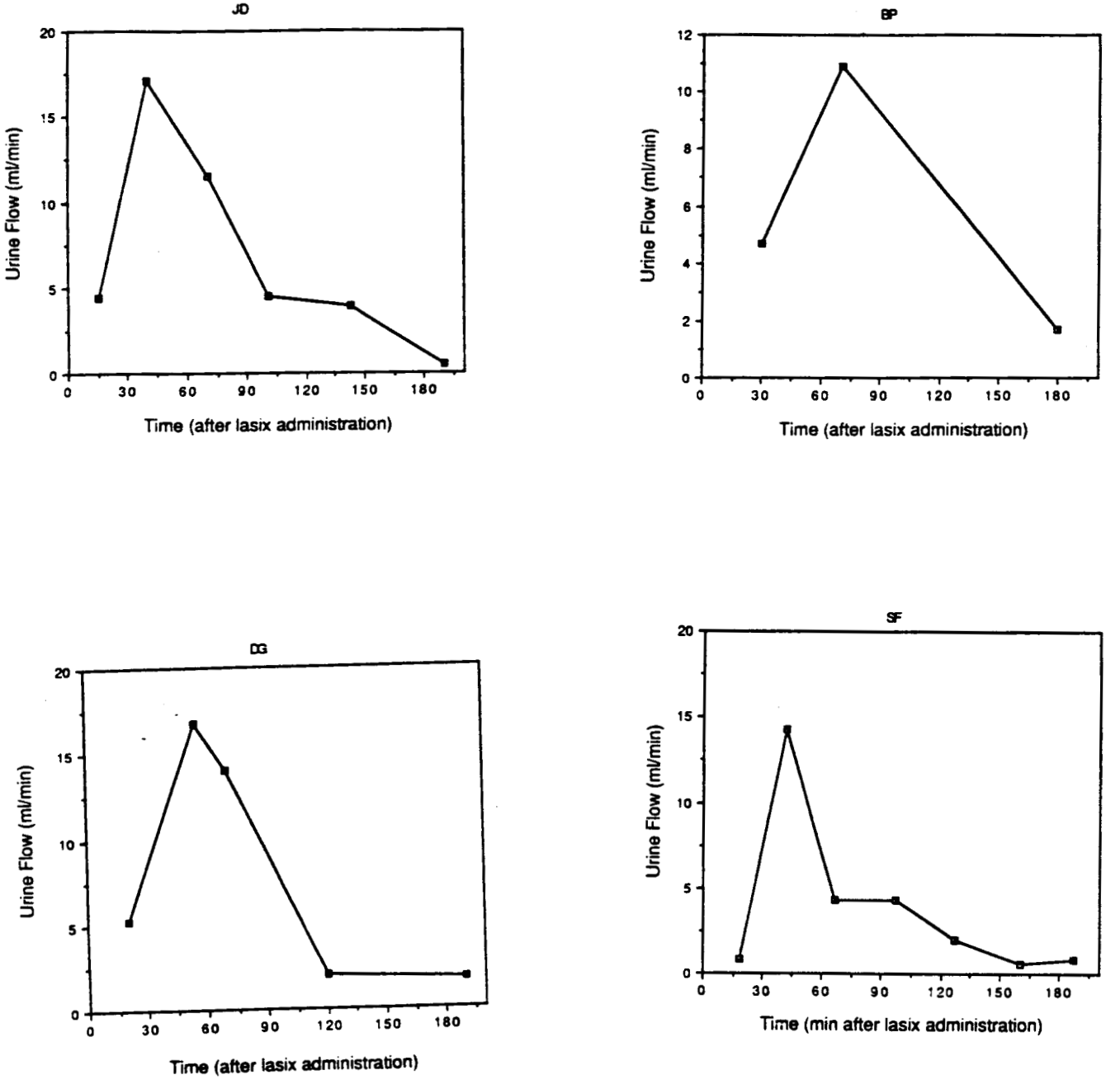

Figure 3. - Urine flow rate as a function of time after Lasix administration. Individual responses are displayed.

Table 1. - Total urine output and % loss of fluid from plasma for each subject.

SUBJECT	TOTAL URINE OUTPUT (LITERS)	% FROM PLASMA
1	1.58	34.5
2	1.13	35.8
3	1.40	31.6
4	0.72	51.7

CALCULATIONS:

$$\%\ \text{LOSS FROM PLASMA} = \frac{\text{EST. PV (ML)} \times \%\ \text{LOSS OF PV}}{\text{TOTAL URINE OUTPUT (L)}}$$