Uric Acid and Urea in Human Sweat

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Abstract

The present study investigated whether thermal sweating may relieve elevated concentrations of serum uric acid or urea. Concentrations of uric acid and urea were measured in the sweat of sixteen male volunteers, who were treated with external heat after one hour of intense physical exercise. The same analytes were also measured in their urine and serum samples. Furthermore, creatinine and some electrolytes were determined in these specimens. The results show that the concentration of uric acid in the sweat is 24.5 μmol/L, which is only 6.3% of that in serum. The concentration of urea in the sweat is 22.2 mmol/L, which is 3.6 times that in serum. The results indicate that sweat uric acid concentration is quite minimal, and the estimated total uric acid excretion per day in normal physiological range is insignificant. However, the level of sweat urea was found at a much higher concentration than the serum level. No correlation could be established between the level of uric acid in sweat and in serum. There was also no correlation between the level of urea in sweat and that in serum. These results suggest it would not be effective to relieve the elevated serum uric acid concentration by thermal sweating when the renal excretion of uric acid is partly compromised. Nevertheless, the potential of urea excretion via profuse sweating is apparent particularly when the kidneys are damaged or their function is impaired. These findings also suggest that persons who take vigorous exercise or are exposed to hot environments should be well advised to drink adequate fluids since heavy sweating excretes only minimal uric acid, accompanied by significant diminution of urinary output and diminished urinary excretions of uric acid, which may induce elevated levels of serum uric acid.

Key Words: sweat, uric acid, urea, uric acid excretion

Introduction

Analyses of metabolites in human sweat have been performed in previous clinical studies (7,9). The eccrine sweat gland, whose principal function is thermoregulation in a hot environment or during physical exercise, is a secretory as well as an excretory organ. Eccrine sweat fluid is a dilute electrolyte solution that contains several biochemical compounds or metabolites of clinical interest. This sweat mainly contains sodium chloride (NaCl) and some potassium (K). In addition, it contains nitrogen metabolites such as urea, ammonia and uric acid (18, 24).

In humans, uric acid is the major product of the catabolism of the purine nucleosides, adenosine and guanosine. Catabolism of proteins and creatine result in formation of urea and creatinine. Most of these nitrogen metabolites are excreted through the kidneys.

To rid the body of waste materials is one of important functions of the kidney. A second function that is also critical, is to control the volume and composition of the body fluids. A variable intake of

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water must be carefully matched to the daily fluid losses from the body. The amount of fluid lost by sweating is highly variable, depending on physical activity and environmental temperature. The volume of sweat normally is only about 100 mL/day, but in very hot weather or during heavy exercise, water loss from sweating can increase to 1 to 2 liters/hour (11).

Al-Tamer *et al*. (1) found that the concentration of sweat urea in uremia patients is far higher than that of urine urea. Those findings initiated hypothesis of the present study, that the eccrine sweat gland assumes a natural alternative route for the excretion of uric acid, which may relieve the elevated serum uric acid concentration by profuse thermal sweating. It will do this especially when the excretion of uric acid by the kidney is partly compromised.

This study was carried out to determine the levels of uric acid and urea in human sweat, urine and serum. Creatinine and certain electrolytes were also measured in these specimens. The relation of uric acid in sweat and in serum from our observations may be applied to relieving the elevated serum uric acid in patients with hyperuricemia, and also may be useful in reducing risk of gout.

Materials and Methods

Subjects

Sixteen male volunteers living in Taichung, Taiwan, with age ranging from 40 to 50 years, gave informed consent for this study approved by the Institutional Review Board of the Veterans General Hospital-Taipei. None of the subjects took diuretics, uricosurics or xanthine oxidase inhibitors three month before the study. Some physical characteristics of the subjects are summarized in Table 1.

Table 1. Descriptive Characteristics of Experimental Subjects (n=16)

Variable	Mean±SD	Range
Age (yrs)	45.6±3.0	41-50
Height (cm)	167.4±6.2	153.1-176.2
Weight (kg)	71.2±6.1	60.2-80.3
BMI (kg/m^2)	25.4±2.5	22.6-32.0

Values are mean±SD of 16 subjects
BMI: Body mass index

Sample Collection

All volunteers played tennis in outdoor tennis court. The routine play session was 4:30-6:00 P.M., three times/week. Sweat, urine and serum samples were collected during the exercise session in August 2000. The air temperature of the subjects' tennis court was about 32°C in August. The sweat and urine samples were collected (about 5:30 P.M.) after the volunteers had played 1 h tennis game. Then after the game was over (about 6:00 P.M.), blood samples were collected.

Sweat Fluid

Sweat collections were performed in a small rest room near the tennis court. Windows and doors were closed to keep the room temperature in the range of 40-45°C heated by electric heaters, air movement below 0.1 m/s, and relative humidity 30-50% during the experimental periods.

The subjects' back and chest were thoroughly washed with deionized water and dried with clean towels before the collection of sweat samples. The newly produced sweat was collected using a plastic collector with dimensions of 15 cm (length) × 9 cm (width) × 2 cm (height). Five to ten mL of sweat was collected from each subject within 5 min by gently placing this collector in contact with the skin of the chest and back, letting the sweat drip into the collector. This procedure was repeated until enough sweat was obtained. The sweat could be obtained easily in the above-mentioned room immediately after exercise. These samples were then divided into three portions; each was placed in clean capped 10 mL plastic tube and kept frozen at -18°C for not more than 3 weeks before analysis.

Urine

Five to ten mL of urine was collected in a plastic container and a few drops of toluene were added as a preservative, and it was then stored in -18°C refrigerator for not more than 3 weeks before analysis.

Serum

Ten mL of venous blood samples of the volunteers were drawn, and the serum samples were collected by centrifuge. Each serum sample was divided into three portions, and then kept frozen at -18°C in capped 10 mL plastic tube for not more than 3 weeks before analysis.

Methods

The uricase-peroxidase method (8) was adopted to determine uric acid. Uric acid was oxidized by uricase to produce allantoin and hydrogen peroxide. The hydrogen peroxide reacted with 4-

Table 2. Concentrations of Each Analyte in Sweat, Urine and Serum from Subjects

(unit: mmol/L)

	Sweat	Urine	Serum
Uric acid	0.025±0.007	3.7±1.3	0.389±0.064
Urea	22.2±8.0	392.7±137.8	6.2±0.9
Creatinine	0.031±0.017	21.5±7.4	0.102±0.025
Sodium	66.3±46.0	109.9±84.1	140.5±2.2
Chloride	59.4±30.4	102.8±37.0	98.9±6.7
Potassium	9.0±4.8	69.2±27.7	4.8±0.8

Values are expressed as mean±SD

aminoantipyrine (4-AAP) and 3,5-dichloro-2-hydroxybenzene sulfonate (DCHBS) in a reaction catalyzed by peroxidase to produce a colored product. This change in absorbance at 520 nm was proportional to the concentration of uric acid in the sample. Urea measurement was performed using the urease glutamate dehydrogenase method (17). Urea was hydrolyzed by urease to ammonia and carbon dioxide. Glutamate dehydrogenase catalyzed the conversion of ammonium ion and 2-oxoglutarate to glutamate and water. Coupled with this conversion is the oxidation of nicotiamide adenine dinucleotide (NADH) to NAD. A decrease in absorbance resulting from the glutamate dehydrogenase reaction was monitored at 340 nm. In spite of our main aims to investigate uric acid and urea in sweat, we were also interested in some metabolites that could also be excreted via the sweat fluid. Creatinine and some electrolytes in sweat were analyzed as well. Creatinine was assayed using modified Jaff'e method (3). The creatinine combined with picrate in an alkaline solution to form a creatinine-picrate complex. This change in absorbance at 520 nm was proportional to the concentration of creatinine in the sample. Samples with a creatinine concentration of less than 0.5 gm/L were discarded. The ion concentration of sodium, chloride and potassium was determined by using ion selective electrode assay (23). All measurements were made in triplicate. Pooled human serum was used as a quality control sample. The coefficient of variation was less than 5% for tested quantities. Recovery of analytes in sweat was determined by adding an aqueous mixture of the analytes in a volume of 100 μL and followed by analysis. Recovery of each analyte across the range of concentration observed in sweat was within the range 93-108%. Reagents used in our six assays were obtained from Bcekman (Fullerton, CA, USA).

Statistical Analysis

The data obtained from the experiments were expressed as means±SD and range (minimum - maximum). Statistical analysis between two different variables was determined by using Pearson correlation coefficient. The statistical significance of correlation coefficient was determined using the Student's *t*-test (12). Statistical significance ($P<0.05$) was indicated.

Results

Subject Characteristics

Table 1 provides the physical details of subjects employed in the study. The age range of the volunteers is 40-50 years, and men in this age stratum can relatively suffer from gout with hyperuricemia (10).

Analytes in Sweat, Urine and Serum

The concentrations of each analyte in chest and back sweat from volunteer subjects are shown in Table 2. The concentration of uric acid in the sweat is only 0.0245 mmol/L, but the concentration of urea in the sweat is 22.2 mmol/L. The maximum concentration of uric acid in the sweat is 0.0357 mmol/L. The results of these analytes in urine and serum from volunteers are also presented in Table 2. The mean concentration uric acid in the urine and serum are 3.7 mmol/L and 0.3894 mmol/L.

Urea is the largest of these nitrogen metabolites in sweat, urine and serum. Sodium is always more than chloride and potassium in these specimens. The concentration of chloride is close to that of sodium.

Relationships and Comparison of Analytes between Sweat and Serum

Figure 1 shows the scatter plot of uric acid in sweat and serum. The Pearson product-moment correlation coefficient is 0.303. There is no statistical correlation found between the level of uric acid in the sweat and that in the serum.

Figure 2 shows the scatter plot of urea in sweat

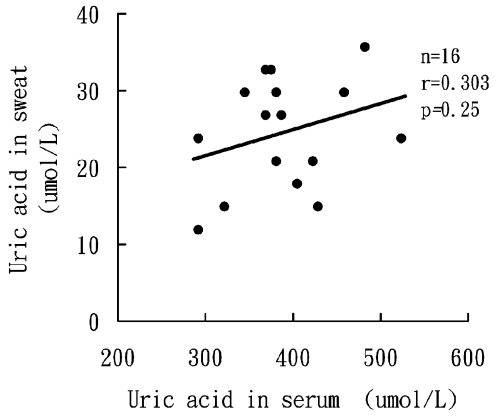

Fig. 1. Scatter plot of uric acid in sweat and serum. The linear regression line and correlation coefficient are shown by a solid line and r. p: significance level. n: total number of sample.

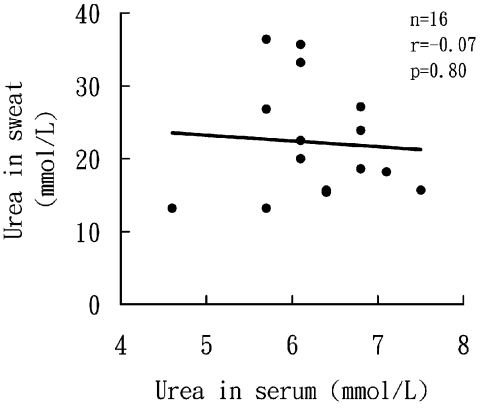

Fig. 2 Scatter plot of urea in sweat and serum. The linear regression line and correlation coefficient are shown by a solid line and r. p: significance level. n: total number of sample.

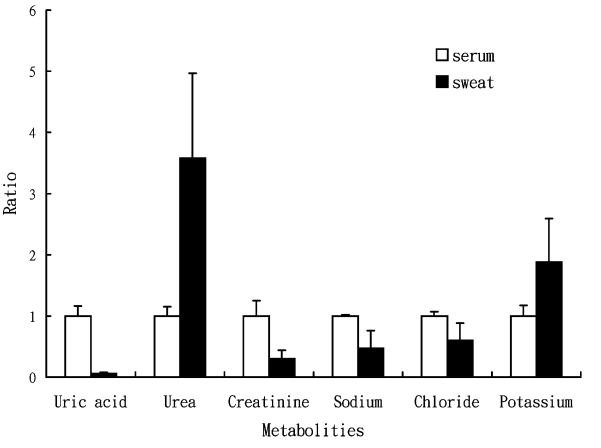

Fig. 3. Mean ratios of six metabolites measured in sweat to those in serum specimens. Each bar represents the mean±SD.

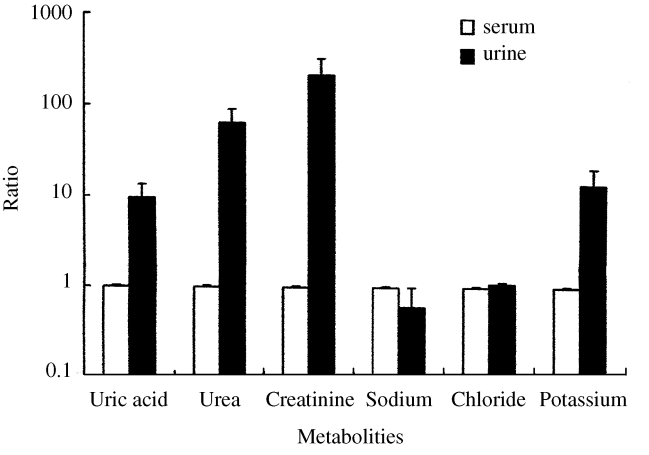

Fig. 4. Mean ratios of six metabolites measured in urine to those in serum specimens. Each bar represents the mean±SD.

and serum, indicating the relative levels of urea between sweat and serum. In other words, there appears to be no significant statistical correlation for urea between sweat and serum.

Figure 3 shows a comparison of mean ratio calculated from the concentration of these metabolites analyzed in sweat specimen to those in serum. The concentration of uric acid in the sweat is only 6.3% of that in serum. The maximum of the ratio from uric acid in sweat to that in serum is 9.7%. The results show that the excretion of uric acid in the sweat is insignificant, and that it is the same in the hyperuricemic subjects as in the normal subjects. The mean ratio of the concentration from creatinine in sweat to that in serum is about 42.6%, and the significance of that is not conclusive. However, urea can be excreted significantly via the sweat fluid, and the concentration of urea in the sweat is 3.6 times that in the serum. The minimum and the maximum of the ratio from urea in sweat to that in serum are 2.1 times and 5.9 times. The concentrations of sodium and chloride in sweat do not exceed those in serum. Nevertheless, the ratio of the concentration from potassium in sweat to that in serum exceeds 1. This may partly be attributed to the lower concentration of potassium in serum.

Figure 4 shows mean ratio calculated from the concentration of six metabolites analyzed in urine specimens to those in serum specimens. The elimination of uric acid, urea and creatinine by the kidney is more efficient than those excreted by the sweat gland.

Discussion

In this study, the concentration of uric acid in sweat is most interesting. In contrast to the lower

animals, humans and humanoids must contend with elevated serum levels of an insoluble and toxic end product of purine metabolism, uric acid. This elevation in serum uric acid level exists, in part, because of the absence of hepatic uricase and relative low urinary excretion rates (14).

This study hypothesizes that thermal sweating may relieve the elevated serum uric acid concentration. However, in this study the concentration of uric acid in the sweat is only 6.3% of that in serum. The maximum concentration of uric acid in the sweat is 35.7 μmol/L. The excretion of uric acid in the sweat is only about 178.5 μmol/day, even though water loss from sweat increases up to 5 liters/day during prolonged and heavy exercise (11). Such an excretion amount of uric acid via sweat is insignificant compared to the amount that is excreted about 1.5-4.5 mmol/day normally via urine (23).

Our study shows that the concentration of uric acid in the sweat is minimal, and the sweat flow rate is relatively rapid during the sweat collecting period in our study. The sweat gland is a tubular structure consisting of two parts. One is a deep-coiled portion that secretes the sweat, and the other is a duct to the surface of the skin. Sweat solute concentrations are determined by secretion of solutes into the secretion coil and by the subsequent ductal modification (either secretion or absorption) (15). Thus they are usually influenced by the sweating rate because the ductal modification often is a function of the flow rate. Taylor *et al*. (22) collected sweat at ambient temperature from the sacrum of health subjects and a patient with a history of pressure sores for about 9 h by cellulose chromatography paper covered with a water-impermeable sheet of thick polypropylene. It is apparent that sweat flow rate of their samples is smaller than ours. Their results showed that median uric acid concentration range in sweat is 27.0 μmol/L and 28.0 μmol/L separately for the two groups are slightly larger than our results. The slight difference is of no physiological importance. Therefore, the conclusion here is the concentration and amount of uric acid excreted by sweat fluid was not high enough to consider the sweat as an important route for excretion when the sweat rate is in normal physiological range. Thus it would be thoroughly impracticable to relieve an elevated concentration of serum uric acid by thermal sweating.

Uric acid excretion and clearance are increased at high rates of urine flow in normal subjects (4, 6). This causes sweating to be an ineffective means for elimination of uric acid, since there may be a reduction in the excretion of uric acid by the kidney because of the resulting diminution in urinary output. Hence there is an increase in the urate excess in the subjects exposed to heat. This data also enables us to understand the frequency of hyperuricemia in hot environments, and the necessity for surveillance of hyperuricemia in athletes. The prevention strategies of hyperuricemia and gout in athletes need considering the modification of provoking factor. For this reason, intense exercises and longer time training are restricted. Athletes also restrain exercising in hot environments. Life styles such as alcohol consumption and high-purine diets need to be controlled. Moreover, athletes need drinking enough fluids to prevent dehydration and maintain adequate (at least 1000 mL/day) urinary output.

Creatinine is a metabolic product of muscle metabolism and is produced at a constant rate by the body. It is well known that creatinine is primarily eliminated from the body by the kidney via the glomerular filtration mechanism. The consequence for creatinine excretion via sweat was the same as uric acid via sweat in our study. Therefore, sweat creatinine and uric acid may represent a simple leakage from the blood.

Urea is the major nitrogen-containing metabolic product of protein catabolism in human, accounting for 75% of the nonprotein nitrogen eventually excreted. In our study, sweat urea is the most significant metabolic product of these three nitrogen metabolites we analyzed in sweat. Sweat urea is thought to be derived mostly from serum urea and its concentration is inversely related to sweat rate (5, 13). Average sweat urea concentration range from 5.4 to 8.9 mmol/L in health subjects, as determined by Boysen *et al*. (2), is lower than the range from 13.2 to 36.4 mmol/L in our analyses. However, our sweat urea result is close to that of Taylor *et al*. (22). Because urea can readily cross the glandular wall and cell membranes (21), sweat urea concentration is always higher than that of plasma, regardless of the means of sweat collection.

In contrast with the results indicating that sweat urea concentration could reach 5.5 to 50 times the serum concentration in uremia patients (1), our data show that the mean sweat urea concentration reached 3.9 times the mean serum concentration, and that the former is at least 2.1 times the latter in healthy male subjects. These findings suggest that urea can be eliminated via sweating by exercise or thermal stimulation. Urea excretion via sweating is particularly important when the kidneys are damaged or their functions are impaired (1).

The correlation of urea and uric acid between sweat and serum could not be established according to our data. Al-Tamer *et al*. (1) has also noted lack of association between sweat urea and serum urea. As the above mentioned, sweat urea and uric acid concentrations are determined by secretion of solutes into the secretion coil and by the subsequent ductal

modification. Thus the final concentration depends upon the rate at which it is being producing, because the ductal secretion or absorption often is a function of the flow rate. When men are subjected to endogenous and exogenous heat loads, the sweating rate is not absolutely the same. No correlation of urea and uric acid between sweat and serum resulted from different sweating rate.

Sodium is the major cation of extracellular fluid, and chloride is the major extracellular anion. Na^+ and Cl^- together represent the majority of the osmotically active constituent of plasma. When the rate of sweat secretion is very low, the Na^+ and Cl^- concentrations in the sweat are also very low, because the most of these ions are reabsorbed in the duct from the precursor secretion before it reaches the surface of the body. It is known that aldosterone can increase ductal absorption (18), increasing the rate of active reabsorption of Na^+ by the duct. The reabsorption of Na^+ also carries Cl^- along, because of the electric pull that develops across the epithelium when positively charged Na^+ is reabsorbed. On the other hand, when the rate of secretion becomes progressively greater, the rate of Na^+ and Cl^- reabsorption does not increase commensurately, so that the concentrations in the sweat of the normal unacclimatized person then usually rise. The normal range of Na^+ concentrations is therefore between 10 to 20 mM at the relatively low sweat rate, but it can reach 100 mM near the maximal sweat rate (21). The mean concentration of Na^+ is 66. 3 mM, suggesting that the sweat rate is relatively rapid in our study. Cl^- concentration in the skin surface sweat also increases with sweat rate in proportion to sweat Na^+ concentration, except that Cl^- concentration is usually lower than Na^+ concentration in sweat.

Potassium is the major intracellular cation. In tissue cells, its mean concentration is 150 mmol/L, which is about 30 times the concentration in serum. The value of K^+ concentration in the pooled primary sweat nearly identical to plasma is 5 to 6 mmol/L (19). The mean concentration of sweat K^+ is 9 mmol/L in our study. The fact that the K^+ concentration is higher than 6 to 7 mmol/L in the final sweat may be due to K^+ secretion by the sweat duct. K^+ secretion by the duct may be partially controlled by the aldosterone (20), but other mechanisms, such as K^+ permeability of the ductal wall also may influence sweat K^+ concentration.

In order to collect the sweat from the chest and back very quickly, we used neither filter paper (16) nor macroduct (25). Although the sample collection of sweat fluid was as quick as possible in our study, nevertheless, inevitable evaporation during the collection cannot be ruled out. However, this was minimal and should not affect our general conclusions.

On the basis of these results we conclude that uric acid excretion via sweat is negligible, although, urea excretion via sweat is relatively meaningful. Persons who always take vigorous exercise or one exposed to hot environments would be well advised to drink adequate fluids since heavy sweating excretes only minimal uric acid and may diminish urinary excretions of uric acid. These results may be of further value in determining kidney uric acid clearance during exercise and afterwards because many athletes suffer from hyperuricemia and gout.

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