THE ROLE OF LACTIC ACID IN THE REDUCED EXCRETION OF URIC ACID IN TOXEMIA OF PREGNANCY *

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When Chesley and Williams demonstrated low uric acid excretion in toxemic patients,[1] they noted that the reduction in renal urate clearance was relatively greater than the reduction in glomerular filtration rate (1). This relationship has been confirmed (2) and is striking when compared with observations on urate excretion in normal subjects and patients with renal disease. It is generally accepted that under normal circumstances serum urate is completely filtered at the glomerulus and that 5 to 10 per cent of filtered urate appears in the urine (3); net tubular reabsorption accounts for the other 90 to 95 per cent. Coombs and co-workers (4), in a study of subjects with various degrees of renal impairment, found that as glomerular filtration rate fell, a progressively larger portion of filtered urate was excreted in the urine, uric acid clearance increasing to over 20 per cent of glomerular filtration rate. In pre-eclamptic and eclamptic patients, although glomerular filtration rate is reduced, the ratio of urate clearance to glomerular filtration rate is often lower than normal. Unless there is a reduction in the filtrability of serum urate, explanation of the low ratio of uric acid clearance to glomerular filtration rate must invoke greater net tubular reabsorption of uric acid in these patients.

The ingestion of buffered lactic acid is normally folowed by reduced uric acid excretion (5). Quick confirmed this response to lactate (6) and suggested that lactate might be responsible for the hyperuricemia of pre-eclampsia and eclampsia (7). At that time there were a few reports in the literature of high blood concentrations of lactic acid in toxemic patients (8–10). However, Schaffer, Barker, Summerson and Stander (11) were unable to find a correlation between *blood levels* of uric acid and lactic acid in each patient with pre-eclampsia, although the mean concentration of each metabolite was higher in the group with pre-eclampsia than in their normal pregnancy group. More recently, Huckabee (12) has shown the importance of measuring lactic acid in arterial rather than in venous blood, as well as other refinements in technique.[2] Thus, failure to relate blood lactic acid concentration to hyperuricemia in toxemic patients may have been due to methodological deficiencies.

This study was initiated to re-evaluate the role of lactic acid in the reduced urate clearance of toxemia of late pregnancy. The results indicate an inverse relationship between arterial lactic acid concentration and uric acid excretion in normal and toxemic pregnancy.

MATERIAL AND METHODS

Twenty-eight patients were studied in the last trimester of pregnancy, before the onset of labor. All of the patients were Negro except N.M. and P.Z. Ten subjects were in a normal pregnancy. Edema, proteinuria, and a rise in blood pressure, or 2 of these abnormalities, were present in 11 patients classified as pre-eclamptic. Three patients with eclampsia had the aforementioned abnormalities; in addition, they convulsed. Four subjects who

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[1] The term "toxemia of late pregnancy" in this paper is intended to describe patients who manifest albuminuria, hypertension, and edema in the latter half of pregnancy. Since classification of patients into the categories of chronic renal disease, chronic hypertension, or pre-eclampsia is so often difficult, and is unnecessary for the purposes of this paper, toxemia will be used interchangeably with pre-eclampsia and eclampsia.

[2] The author is grateful to Dr. W. E. Huckabee for valuable suggestions regarding the measurement of lactic acid in blood.

were known to have hypertension very early in pregnancy as well as at the time of study, but who had no other abnormalities, were considered to have chronic hypertensive vascular disease. The length of the pregnancy in each case was based upon the date of the last normal menstrual period unless this was considered incorrect for other reasons.

All subjects were examined in the resting, hydrated, postabsorptive state, and the 3 eclamptic patients at least 12 hours after convulsing. A minimum of 1 hour was allowed to elapse between insertion of the Cournand arterial needle, used for blood sampling, and the start of collection periods. A urethral catheter was used to facilitate urine collection. Uric acid clearance (C_{urate}) and endogenous creatinine chromogen clearance (C_{cr}) were determined for 3 consecutive 15-minute periods. Blood samples were obtained midway in each collection period. Arterial whole blood specimens for lactic acid were collected by allowing blood to flow directly into a small chilled tube and immediately transferring 1 ml of blood into 10 ml of 10 per cent trichloroacetic acid in an ice bath. Specimens were shaken frequently and allowed to stand at 0°C for at least 2 hours. The precipitate was separated by centrifugation, and the supernatant fluid was run in triplicate using the method of Barker and Summerson (13). Recovery of lactic acid added to the trichloroacetic acid just before the blood was 100 per cent ± 5 per cent. Lactic acid concentrations are reported as milligrams of lactate per 100 ml of whole blood. According to Huckabee (12), the ratio of the lactate concentration in whole blood water to the lactate concentration in plasma water averages 1.08. Uric acid and creatinine were measured by the method of Praetorius and Poulsen (14), and Bonsnes and Taussky (15), respectively.

The effect of lactate on a normal pregnant subject near term was tested by an intravenous infusion of isotonic sodium lactate, 15 ml per minute for 45 minutes.

RESULTS

The response of four normal pregnant subjects near term to intravenous sodium lactate is listed in Table I. Lactate was infused after three control periods and was associated with a marked fall in urate clearance. There was no consistent change in creatinine clearance. Variations in the latter are probably due to collection errors which

TABLE I

The response of four normal pregnant subjects to an intravenous infusion of sodium lactate *

Patient	Month of pregnancy	Serum creatinine	Serum uric acid	C_{urate}	C_{cr}	$C_{urate}:C_{cr}$
		mg/100 ml	*mg/100 ml*	*ml/min*	*ml/min*	%
M.G.	9	0.78	4.9	7.6	103	7.4
				10.0	112	8.9
				13.8	139	10.0
				3.9	69	5.7
				1.9	86	2.2
				1.4	86	1.6
H.P.	8	0.60	2.5	5.2	65	8.0
				6.4	75	8.5
				5.6	70	8.0
				4.8	62	7.7
				1.8	73	2.5
				1.6	58	2.8
S.R.	8	0.73	4.9	12.4	148	8.4
				8.4	104	8.1
				13.4	150	8.9
				6.9	86	8.0
				4.1	125	3.3
				3.3	125	2.6
C.W.	9	0.69	4.1	9.4	112	8.4
				8.4	106	7.9
				12.0	142	8.5
				8.5	119	7.1
				4.5	174	2.6
				2.0	109	1.8

* The first three clearance periods for each patient were control observations. The lactate infusion was started and continued as the next three 15-minute collection periods were obtained. Abbreviations used: C_{urate} = clearance of urate; C_{cr} = clearance of creatinine; $C_{urate}:C_{cr}$ = ratio of C_{urate} to $C_{cr} \times 100$.

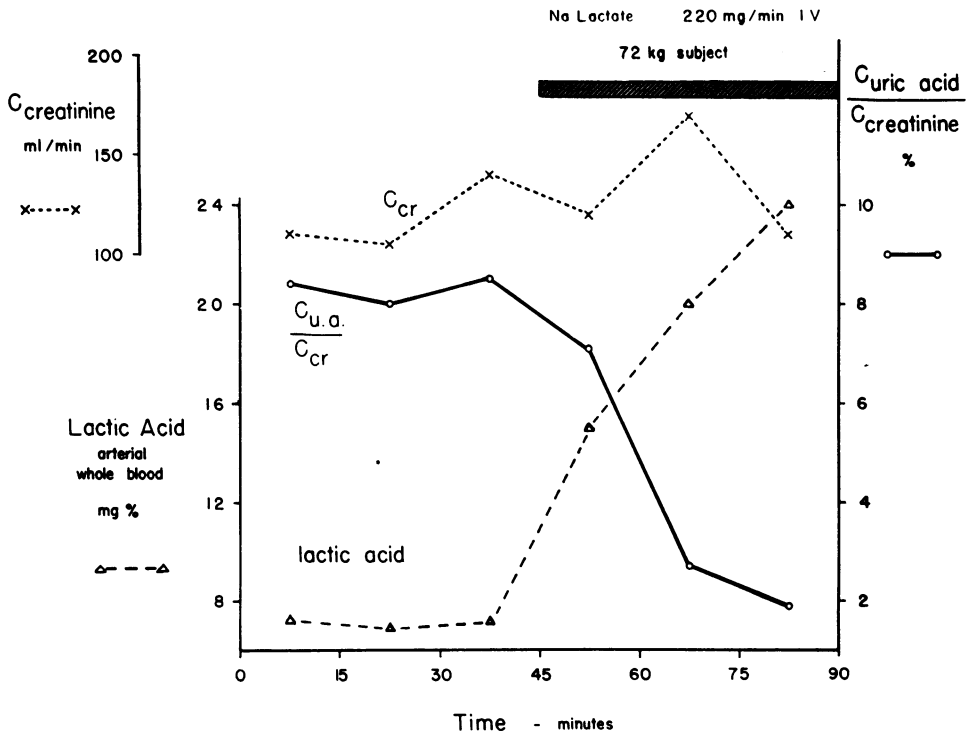

FIG. 1. RESPONSE OF A NORMAL PREGNANT SUBJECT TO AN INTRAVENOUS INFUSION OF ISOTONIC SODIUM LACTATE. Lactate infusion started at 45 minutes. As arterial lactic acid concentration rose, the ratio of uric acid clearance to creatinine clearance fell sharply.

would affect the simultaneous urate clearance in a similar manner. Arterial lactate concentrations were measured in Patient C.W. whose response is illustrated in Figure 1.

The clinical diagnosis, average resting endogenous arterial lactate concentration, and ratio $C_{urate}: C_{cr}$ for each patient are listed in Table II and plotted in Figure 2. There was a significant ($p < 0.005$) negative correlation ($R = -0.60$) between arterial lactate levels and the ratio $C_{urate}: C_{cr}$; i.e., the higher concentrations of whole blood lactate were associated with the lower ratios of urate clearance to creatinine clearance. If the three eclamptic patients are omitted from the analysis, a similar correlation is found ($R = -0.50$, $p < 0.05$). However, there was no correlation between arterial lactate concentrations and the clearance ratio in the normal subjects.

Four patients with low clearance ratios were restudied on their third or fourth postpartum day. In each case, abnormal prenatal lactate concentrations and clearance ratios had returned to the normal range (Table III, Figure 3). Patient N.M. had an abnormal antepartum clearance ratio which returned to normal in the postpartum period, although there was no significant change in her blood lactate concentration, which had not been elevated.

DISCUSSION

There are now several reports that blood lactic acid concentrations are higher in patients with toxemia than in patients during normal pregnancy (8–10, 16, 17). Differing methodology probably explains the differences in conclusions as to lactate concentrations in normal pregnancy. Arterial lactic acid concentrations in normal pregnant subjects in this study were in a range similar to those found in resting nonpregnant subjects by Huckabee (12) but were generally lower than the values reported by Hendricks (18) who measured the lactic acid content of maternal venous blood.

The reduction in the uric acid clearance of normal pregnant subjects in response to lactate infusion was similar to that observed in nonpregnant subjects by Yü and associates (19). This

TABLE II

Clinical diagnosis and laboratory data from 28 prenatal patients *

Patient	Clinical diagnosis	Month of pregnancy	Serum creatinine	Serum uric acid	Arterial whole blood lactic acid	C_{urate}	C_{cr}	$C_{urate}:C_{cr}$
			mg/100 ml	*mg/100 ml*	*mg/100 ml*	*ml/min*	*ml/min*	%
M.W.	Normal	9	0.83	4.9	10.0	11.6	135	8.2
M.H.	Normal	7	0.71	3.9	9.0	11.7	150	7.8
D.B.	Normal	8	0.92	4.4	6.2	5.2	94	5.5
E.S.	Normal	9	0.78	3.7	6.3	7.5	80	9.4
A.M.	Normal	9	1.0	4.9	7.2	7.9	94	8.4
N.M.†	Normal	9	0.86	7.2	8.5	1.5	89	1.7
H.B.	Normal	7	0.74	2.9	5.8	12.3	112	11.0
S.S.	Normal	9	0.70	3.6	7.3	10.2	102	10.0
C.W.	Normal	9	0.69	4.1	7.1	9.9	120	8.3
V.B.	Normal	7	0.68	3.0	7.7	9.9	118	8.4
W.W.	Chronic hypertension	9	0.73	5.0	5.8	9.5	124	7.7
B.P.	Chronic hypertension	8	0.70	4.1	5.7	10.0	110	9.1
T.S.	Chronic hypertension	8	0.71	3.8	7.1	10.6	127	8.3
B.M.†	Chronic hypertension	7	0.71	3.9	18.0	5.7	132	4.3
G.Rea.	Pre-eclampsia	9	0.79	4.7	9.0	16.7	152	11.0
M.Sa.	Pre-eclampsia	9	0.64	3.1	4.9	16.0	160	10.0
M.St.	Pre-eclampsia	9	0.85	5.1	9.6	5.2	80	6.5
P.Z.	Pre-eclampsia	9	0.48	2.8	7.3	16.4	126	13.0
R.F.	Pre-eclampsia	9	0.77	5.7	13.0	5.5	86	6.4
R.T.	Pre-eclampsia	9	0.86	6.5	8.3	4.5	98	4.6
M.B.	Pre-eclampsia	8	0.97	6.7	11.0	1.0	63	1.6
D.M.	Pre-eclampsia	8	1.0	6.3	6.5	10.5	177	5.8
E.N.	Pre-eclampsia	7	0.6	4.0	5.3	6.5	59	11.0
G.Ree.	Pre-eclampsia	9	1.0	7.0	7.4	3.4	66	5.2
B.O.	Pre-eclampsia	7	1.4	10.0	11.0	3.2	92	3.5
D.A.†	Eclampsia	8	0.96	9.1	18.0	3.3	65	5.1
F.W.†	Eclampsia	9	1.4	11.0	16.0	1.0	57	1.8
L.L.	Eclampsia	9	0.74	6.8	12.0	1.7	77	2.3

* See footnote to Table I for abbreviations.
† Studied again in postpartum period.

effect of lactate has been recognized for many years, but the mechanism has not been completely clarified. The alteration in urate clearance after lactate infusion does not depend upon changes in glomerular filtration rate as measured by inulin (19) or creatinine clearance, and it is unlikely that lactate causes a selective change in the filtrability of serum urate. The most likely possibility is that lactate evokes greater net tubular reabsorption of uric acid. This could be due to increased reabsorption of filtered urate, diminished tubular urate secretion, or a combination of tubular reabsorptive and secretory changes.

A large body of evidence demonstrating reduced glomerular filtration rate in toxemia of late pregnancy has been accumulated, and there is no reason to doubt that reduction in the filtered urate load would lead to low uric acid clearance. However, the available data suggest that increased net tubular reabsorption of urate is common in toxemia (1, 2). On the other hand, examination of the reports emphasizing the role of glomerular changes reveals that serum uric acid concentrations were elevated far more than was the relative elevation of other metabolites whose excretion depends primarily upon the rate of glomerular filtration (20), and that uric acid clearances were depressed relatively more than creatinine clearances were depressed (21). The data of this study suggest that the reduction in urate clearance due to increased net tubular reabsorption is related to the effect of excessive lactic acid. Other metabolites may also contribute to the phenomenon.

Evidence in the literature suggests that the uterus and its contents are a major source of lactic acid in pre-eclampsia and eclampsia. A marked reduction in uterine and placental blood flow in toxemic patients has been demonstrated by several workers (22–24). These observations probably explain the low oxygen content of umbilical cord blood of infants at delivery of toxemic mothers (25–27). Hendricks (18) found a gradi-

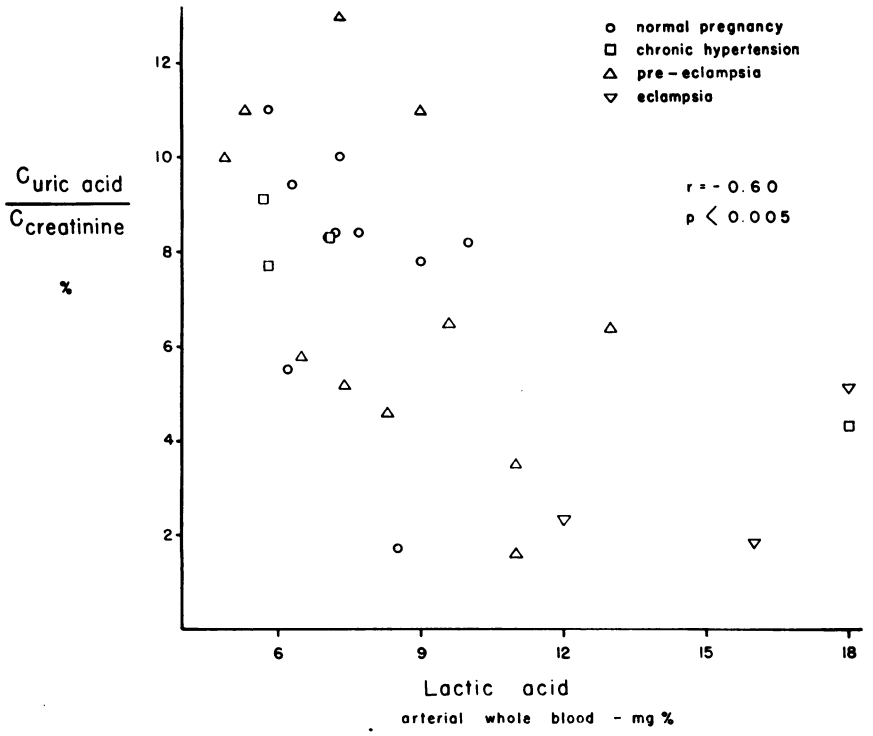

FIG. 2. RELATIONSHIP OF RESTING LACTIC ACID CONCENTRATION IN ARTERIAL BLOOD TO THE URIC ACID CLEARANCE: CREATININE CLEARANCE RATIO, IN NORMAL AND IN TOXEMIC PREGNANT PATIENTS. Data are shown from 10 normal, 11 pre-eclamptic, 3 eclamptic, and 4 chronic hypertensive pregnant patients. There is a statistically significant inverse relationship between the two parameters.

ent for lactic acid between normal fetus and normal mother at elective cesarian sections. Levels were highest in umbilical arterial blood and then in umbilical venous blood, maternal uterine venous blood and maternal peripheral venous blood, in descending order. The gradient was interpreted as evidence for net lactate transport from fetus to mother. However, Friedman and colleagues (28), working with normal pregnant rhesus monkeys at term, demonstrated bidirectional lactate exchange between fetal and maternal organisms. The authors felt that their results invalidated the concept of a unidirectional lactate transfer based on concentration gradients. The direction of net lactate

TABLE III

*Prenatal diagnosis and postnatal laboratory data from four subjects with low $C_{urate}:C_{cr}$ * in a prenatal study*

Patient	Prenatal clinical diagnosis	Serum creatinine	Serum uric acid	Arterial whole blood lactic acid	C_{urate}	C_{cr}	$C_{urate}:C_{cr}$
		mg/100 ml	*mg/100 ml*	*mg/100 ml*	*ml/min*	*ml/min*	%
N.M.	Normal	0.82	6.7	7.2	7.4	105	7.0
B.M.	Chronic hypertension	0.88	6.0	7.1	14.1	110	13.0
D.A.	Eclampsia	0.87	7.8	6.5	11.5	120	9.6
F.W.	Eclampsia	1.1	6.7	8.2	9.8	81	12.0

* See footnote to Table I for abbreviations.

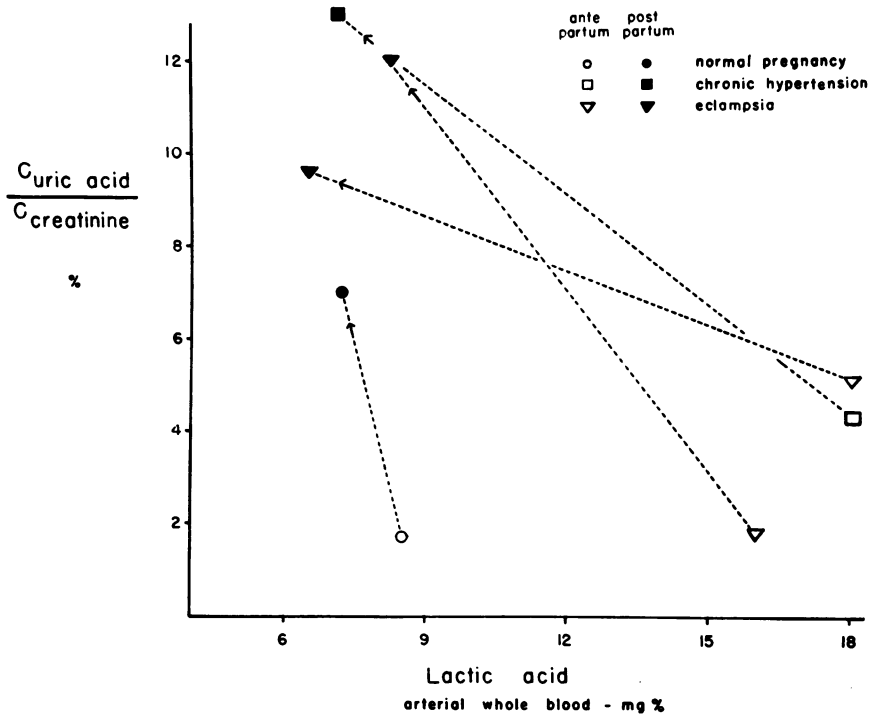

FIG. 3. RELATIONSHIP OF RESTING LACTIC ACID CONCENTRATION IN ARTERIAL BLOOD TO THE URIC ACID CLEARANCE: CREATININE CLEARANCE RATIO, BEFORE AND AFTER DELIVERY. The lactic acid level fell in three of four patients and the clearance ratio rose in all four patients, following delivery.

exchange and its quantitative characteristics are thus unresolved, but it would be reasonable to assume that the more hypoxic fetus of a pre-eclamptic patient, depending more upon anaerobic metabolism, produces greater than normal quantities of lactic acid which might then influence maternal-fetal exchange so that the rate of net lactate transfer into maternal blood is increased. Other tissues may also contribute to the lactate pool by increased production or diminished utilization. In any case, there is evidence that the concentration of lactic acid in the blood of toxemic patients is generally higher than that in normal pregnant subjects, and the data of this study suggest that the excessive lactate is at least partially responsible for the low urate clearance in these patients.

SUMMARY

The role of lactic acid in the low urate excretion in toxemia of pregnancy was studied. After obtaining the expected fall in the urate clearance of normal pregnant subjects by intravenous lactate infusion, determinations were made of endogenous arterial lactate concentrations and simultaneous urate and creatinine clearances in 28 (10 normal, 18 toxemic) subjects in late pregnancy.

There was a significant negative correlation between arterial whole blood lactic acid concentration and the ratio of uric acid clearance to endogenous creatinine clearance.

The correlation suggests that an increased level of lactic acid causes increased net renal tubular reabsorption of filtered urate and is responsible, at least in part, for the low uric acid clearance in toxemia of late pregnancy.

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