

Red Blood Cell Sodium-Lithium Countertransport and Risk of Future Hypertension

The Olivetti Prospective Heart Study

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Abstract—An elevated red blood cell (RBC) sodium-lithium countertransport (Na-Li CT) is associated with high blood pressure (BP) in cross-sectional investigations; however, its value as a predictor of future hypertension, and thus of cardiovascular risk, has not been defined. The present study evaluated the association between Na-Li CT and risk of future hypertension in a sample of 106 untreated normotensive middle-aged men participating in the Olivetti Prospective Heart Study in southern Italy. BP, anthropometric and metabolic variables, and RBC Na-Li CT were measured at baseline in 1987 and at a follow-up visit in 1994 through 1995. Na-Li CT was stable over time ($r=0.85$) and was significantly associated to systolic BP in both visits. Of the 106 initially normotensive participants, 14 were found to be hypertensive at the 8-year follow-up examination. Eleven of these 14 hypertensives were in the highest tertile of systolic BP at baseline, and 9 of 11 also had an elevated baseline Na-Li CT. In multiple logistic regression analysis, baseline BP, Na-Li CT, and age were all significant predictors of the risk of future hypertension. Individuals with baseline systolic BP in the highest tertile had a 60% risk of developing hypertension if their Na-Li CT was also high, whereas their risk was only 5% if Na-Li CT was in the two lowest tertiles ($P=0.003$). RBC Na-Li CT was a valuable predictor of subsequent hypertension in middle-aged men with a high-normal BP level for their age. (*Hypertension*. 1998;31:1284-1289.)

Key Words: hypertension, essential ■ blood pressure ■ risk factors ■ ion transport ■ genetics ■ erythrocytes

The Na-Li CT is an ion transport system that exchanges sodium for sodium or other univalent cations.¹ It was brought to clinical attention by Canessa and coworkers,² who reported that its activity was enhanced in erythrocytes of patients with essential hypertension, a finding confirmed by many epidemiological and clinical studies thereafter.³⁻⁶ The interest in this membrane transport system was enhanced by the notion that its activity was under tight genetic control⁷⁻⁹ and that it was remarkably stable within individuals.¹⁰ Because of these properties, even though its physiological role in vivo has not been fully clarified,⁵ Na-Li CT is considered a genetic marker of essential hypertension¹¹ and, in particular, of those clinical forms of hypertension that are associated with resistance to the metabolic effects of insulin.^{4,12-14}

The majority of the studies exploring the relationship of Na-Li CT to human disease have been cross-sectional population-based observations or case-control investigations comparing hypertensive versus normotensive individuals.^{5,6} Very few studies have tried to identify whether Na-Li CT predicts the risk of future hypertension, and their results have been controversial.¹⁵⁻¹⁷ We attempted to provide an answer to this

question by analyzing a data set from the Olivetti Heart Study, a prospective investigation on the prevalence of risk factors for cardiovascular disease in southern Italy initiated in 1975 and involving the participation of the Olivetti factory male workforce.¹⁸

Methods

After the first examination in 1975, study participants underwent a first follow-up visit in 1987, when 841 employees were examined; they represented 95% of the factory male workforce after exclusion of those receiving chronic medical treatment.¹⁸ On that occasion, Na-Li CT was measured for the first time (hereafter referred to as the baseline measurement) in a randomly selected sample of 216 study participants^{13,19}; complete demographic, anthropometric, and biochemical data were available for 188 of the participants. Of this group, 124 were normotensive (BP <140/90 mm Hg).

A second follow-up visit took place in 1994 through 1995. At this time, 110 of these 124 previously normotensive subjects were examined, and 106 (87%) had Na-Li CT measured again; in four cases, Na/Li CT was not measured for technical reasons. The average length of follow-up was 8 years. This group of participants are the subjects of the present report. Fourteen subjects were lost to follow-up: 8 were not willing to participate, 3 were no longer working in the factory, 1 had moved to a different city, and 2 died of

Received December 12, 1997; first decision January 5, 1998; revision accepted January 16, 1998.

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Selected Abbreviations and Acronyms

BMI = body mass index
BP = blood pressure
Na-Li CT = sodium-lithium countertransport
RBC = red blood cell

neoplastic disease. They were comparable to the 106 subjects reexamined with regard to all relevant baseline characteristics.

At both visits, in 1987 and 1994–1995, the participants were seen in the morning, after fasting for at least 13 hours, in a comfortable environment within the factory premises in Pozzuoli and Marcanise (two suburban areas of Naples). Anthropometric indices and BP were measured according to a carefully standardized protocol as previously reported.^{18,19} A fasting venous blood specimen was obtained for the measurement of RBC Na-Li CT and levels of plasma glucose, serum cholesterol, triglyceride, and uric acid. The rate of sodium-stimulated lithium efflux from lithium-loaded erythrocytes was measured at 150 mmol/L external sodium concentration according to Canessa et al² with slight modification as described.¹⁹ This parameter has for a long time been considered as the Na-Li CT maximal velocity. However, more recently it has been recognized that in a few individuals with lower affinity of the transporter for external sodium, the transporter may not be fully saturated at 150 mmol/L external sodium, and thus the rate of lithium efflux measured under these experimental conditions may not reflect true maximal velocity.^{14,20–22} Technical error and day-to-day within-individual coefficient of variation were consistently below 10% throughout the study.

Serum cholesterol, triglyceride, glucose, and uric acid levels were measured with automated methods (Cobas Mira, Roche) as previously described.¹³

All medical and technical operators involved in the field and laboratory measurements on the occasion of the follow-up visit were unaware of the results of the baseline examination.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS-PC). The distributions of serum triglyceride and blood glucose were normalized by log transformation, and log-transformed values were used in the analysis. Pearson linear correlation was used to test the univariate associations of Na-Li CT with the other variables under study, and multiple logistic regression analysis was used to test the ability of selected variables measured at baseline to predict the risk of future hypertension accounting for the effects of the others. Two-tailed paired or unpaired Student's *t* test was used as appropriate to evaluate differences in the mean values of specified variables between groups. Cross-tabulation analysis with Fisher's exact test was used to analyze the distribution of cases of incident hypertension across tertiles of specified variables. Two-tailed values of $P < 0.05$ were taken as statistically significant.

TABLE 1. Descriptive Statistics for Study Population at Baseline Examination (1987) and at 8-Year Follow-up (1994–1995)

Variable	Baseline (1987)	Follow-up (1994)	Change	<i>R</i>
Age, y	45.3 (6.9)	53.2 (7.0)	8.0	...
BMI, kg/m ²	25.5 (2.8)	26.7 (3.6)	1.2 (2.8)†	0.65
Systolic BP, mm Hg	117.9 (10.3)	124.0 (13.8)	6.1 (11.7)†	0.51
Diastolic BP, mm Hg	80.5 (5.7)	79.8 (9.2)	−0.7 (8.3)	0.45
Na-Li CT, μmol/L RBC/h	276 (96)	289 (111)	13 (60)*	0.85
Serum cholesterol, mmol/L	5.55 (0.99)	5.68 (0.97)	0.13 (0.75)	0.71
Serum triglyceride, mmol/L	1.53 (0.79)	1.66 (0.78)	0.13 (0.72)	0.58
Plasma glucose, mmol/L	5.14 (0.65)	5.74 (1.57)	0.61 (1.20)†	0.71
Serum uric acid, μmol/L	302 (52)	319 (62)	17 (43)†	0.73

* $P < 0.05$, † $P < 0.001$.

TABLE 2. Pearson Correlation Coefficients of RBC Na-Li CT to Other Variables in the Study at Baseline Examination (1987) and at 8-Year Follow-up (1994–1995)

Variable	Baseline (1987)	Follow-up (1994)
Age	0.017	−0.067
BMI	0.066	0.127
Systolic BP	0.179*	0.284†
Diastolic BP	0.043	0.171*
Serum cholesterol	−0.061	0.067
Serum triglyceride	0.124	0.232†
Plasma glucose	0.172*	0.264*‡
Serum uric acid	0.032	0.123

* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$.

To evaluate the power of Na-Li CT as a screening test for future hypertension, sensitivity, specificity, and predictive values were estimated by standard calculations.²³

All data is expressed as mean ± SD or 95% confidence intervals.

Results

The study population included 106 normotensive men aged from 22 to 57 years (Table 1). During the 8-year follow-up period, systolic BP increased by an average of 6 mm Hg, whereas diastolic BP remained unchanged. Body weight and BMI also increased. Serum uric acid and fasting blood glucose in 1994–1995 were significantly higher than at baseline: 6 subjects had glucose values in the diabetic range (ie, >7.8 mmol/L) at this time compared with only 1 at the baseline visit in 1987. There was also an increase in RBC Na-Li CT. The last column in Table 1 gives the simple correlation coefficients between the two measurements performed on each variable 8 years apart: the highest correlation coefficient was that of Na-Li CT, whereas the lowest coefficients were those of systolic and diastolic pressures.

In univariate analysis (Table 2), RBC Na-Li CT was significantly and positively associated with systolic pressure and fasting blood glucose in the baseline examination in 1987.

These associations were confirmed and became stronger at the follow-up visit in 1994–1995, at which time significant and positive correlations were also observed between Na-Li CT and diastolic pressure and serum triglyceride concentration, respectively.

TABLE 3. Baseline and Follow-up Characteristics of Newly Detected Hypertensive Participants and Participants Who Remained Normotensive

Variable	Normotensive (n=92)			Newly Detected Hypertensive (n=14)		
	Baseline	Follow-up	Change	Baseline	Follow-up	Change
Age, y	44.8 (7.0)	52.7 (7.1)	8.0 (1.6)‡	48.4 (5.5)§	56.4 (5.4)§	7.9 (2.0)‡
BMI, kg/m ²	25.4 (2.9)	26.6 (3.8)	1.22 (2.85)‡	26.0 (2.3)	27.2 (1.9)	1.15 (2.63)
Systolic BP, mm Hg	116.1 (9.3)	119.9 (8.5)	3.9 (10.3)‡	130.1 (8.4)¶	150.9 (11.9)¶	20.8 (9.9)‡
Diastolic BP, mm Hg	79.8 (5.7)	77.8 (7.7)	-2.03 (7.6)*	84.8 (3.3)¶	93.0 (6.9)¶	8.2 (7.6)†
Na-Li CT, $\mu\text{mol/L RBC/h}$	269 (87)	273 (100)	4 (57)	356 (123)§	393 (126)¶	37 (67)
Serum cholesterol, mmol/L	5.62 (1.00)	5.71 (1.00)	0.08 (0.77)	5.09 (0.74)§	5.54 (0.69)	0.51 (0.50)†
Serum triglyceride, mmol/L	1.53 (0.83)	1.65 (0.81)	0.12 (0.77)	1.47 (0.49)	1.68 (0.56)	0.16 (0.34)
Fasting blood glucose, mmol/L	5.09 (0.53)	5.59 (1.11)	0.50 (0.90)‡	5.48 (1.10)	6.82 (3.22)	1.36 (2.35)*
Serum uric acid, $\mu\text{mol/L}$	301 (53)	317 (64)	16 (42)†	300 (43)	335 (41)	35 (44)†

* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$, baseline vs follow-up; § $P < 0.05$, ¶ $P < 0.01$, ¶¶ $P < 0.001$, newly detected hypertensive vs normotensive participants.

At the follow-up visit in 1994–1995, 14 untreated and previously normotensive individuals were classified as hypertensive (systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg). The subjects in the hypertensive group were older and had higher BP at the baseline visit (Table 3). They also tended to have higher fasting blood glucose levels and to be heavier than persons who remained normotensive, although these differences were not statistically significant. A tendency to lower serum cholesterol concentration in this group at baseline was no longer significant at follow-up examination. RBC Na-Li CT was significantly higher in those who became hypertensive, both at baseline and at the follow-up visit. In general, the differences between the two groups, including that in Na-Li CT, were amplified across the 8-year observation period because BP, glucose, uric acid, and RBC Na-Li CT increased only or to a larger extent in those who became hypertensive.

Multiple logistic regression analysis was performed to assess the relative influence of baseline RBC Na-Li CT, BP, age, BMI, serum triglyceride level, and glucose concentration on the risk of future hypertension. Two different models were used with the alternative inclusion of systolic or diastolic pressure (Table 4). This analysis confirmed that BP and Na-Li CT were both significant independent predictors of the risk of future hypertension. In particular, placement in the higher tertile of Na-Li CT was associated with an approximate threefold increase in the risk of future hypertension in comparison to placement in the two lower tertiles. Systolic and diastolic BPs were both significant predictors of the risk of becoming hypertensive, and age also gave a small independent contribution in this sample of middle-aged individuals with a narrow age range.

When the whole study population was divided into tertiles of baseline systolic pressure (Table 5), it was found that 11 of the 14 subjects who became hypertensive during the follow-up period were in the upper tertile (systolic pressure between 121 and 139 mm Hg), 3 subjects were in the second tertile, and none were in the lowest tertile (Fisher's exact test, $P = 0.005$). Similar data were obtained when the population was divided into tertiles of diastolic BP (10, 4, and 0 subjects, respectively).

Table 6 shows the distribution of the 14 cases of incident hypertension when the whole population was divided by tertile of baseline RBC Na-Li CT. Similar to the findings for BP, over two thirds of the newly discovered hypertensive subjects belonged to the upper tertile of the distribution of baseline Na-Li CT (Fisher's exact test, $P = 0.004$).

As shown in Tables 5 and 6, all the newly discovered hypertensive subjects who were in the upper tertile of baseline Na-Li CT were also in the upper tertile of baseline systolic pressure. On the other hand, although most of the incident cases of hypertension came from the upper tertile of baseline systolic pressure, the majority of persons in this tertile (26 of 37 subjects) did not actually develop high BP during the 8-year observation period (Table 5). We asked therefore whether baseline Na-Li CT could be of value in discriminating further, among persons in the upper tertile of baseline BP, who would become hypertensive from those who would remain normotensive after 8 years. As shown in

TABLE 4. Multiple Logistic Regression Analysis: Relative Risk of Hypertension by Baseline Values of RBC Na-Li CT and Other Selected Variables

Variable	Relative Risk (95% Confidence Interval)
Model 1, including baseline systolic BP	
Systolic BP, tertile*	3.151 (1.525–6.847)
Na-Li CT, tertile*	2.699 (1.234–5.900)
Age, y	1.159 (1.01–1.330)
BMI, kg/m ²	1.121 (0.875–1.435)
Fasting blood glucose, mmol/L	1.041 (0.998–1.097)
Serum triglyceride, mmol/L	0.995 (0.998–1.097)
Model 2, including baseline diastolic BP	
Diastolic BP, tertile*	2.963 (1.363–6.442)
Na-Li CT, tertile*	3.229 (1.481–7.042)
Age, y	1.208 (1.044–1.399)
BMI, kg/m ²	1.132 (0.889–1.441)
Fasting blood glucose, mmol/L	1.018 (0.600–1.724)
Serum triglyceride, mmol/L	0.994 (0.983–1.006)

*III vs I+II tertile.

TABLE 5. Distribution of Newly Discovered Hypertensive Subjects by Tertile of Baseline Systolic BP

	Systolic BP Tertile and Level, mm Hg		
	I (<112)	II (112-121)	III (>121)
No. in tertile	35	34	37
No. hypertensive at follow-up examination	0	3	11*
No. still normotensive at follow-up examination	35	31	26

*Two-tailed Fisher's exact test, $P=0.0005$.

the Figure, this analysis showed that 9 of the 11 newly discovered hypertensives who were in the upper tertile of baseline BP also had a baseline Na-Li CT in the upper tertile of the distribution, and only 2 of these hypertensive subjects had a countertransport in the two lower tertiles (two-tailed Fisher's exact test, $P=0.003$).

From this data and the data shown in Tables 5 and 6, the power of baseline RBC Na-Li CT to predict the risk of future hypertension in our study population was calculated. In Table 7, sensitivity, specificity, and predictive values are given under the two circumstances in which the test of Na-Li CT is applied to the whole study population or only to those who had a systolic BP at baseline in the upper third of the distribution (high-normal BP). The test was considered positive if Na-Li CT was above the cutoff level for the upper tertile (ie, $>311 \mu\text{mol/L}$ RBC per hour). The sensitivity of the test improved significantly when its application was restricted to persons with high-normal BP at baseline; in turn, its positive predictive value was enhanced. The data thus lead to the estimation that among middle-aged men with high-normal BP, an elevated Na-Li CT (ie, a Na-Li CT in the highest tertile) confers a 60% probability of becoming hypertensive in 8 years. More important, however, is the result of the negative predictive value of Na-Li CT, since an individual with Na-Li CT in the low-mid ("normal") range had only a 5% probability of becoming hypertensive even if he had a BP level in the high-normal range.

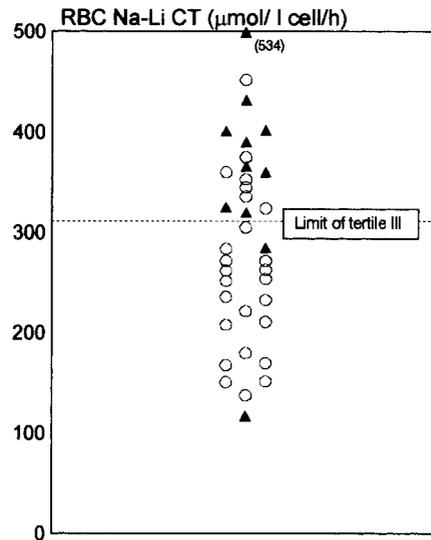
Discussion

The interest in Na-Li CT in the cardiovascular research arena is still very much alive⁶ 16 years after the report by Canessa and coworkers.² The academic interest in this marker of hypertension and of insulin resistance, however, has not been matched by a proportionate attention from clinicians and

TABLE 6. Distribution of Newly Discovered Hypertensive Subjects by Tertile of Baseline Na-Li CT

	Na-Li CT Tertile and Level, $\mu\text{mol/L}$ RBC/h		
	I (<220)	II (220-311)	III (>311)
No. in tertile	34	36	36
No. hypertensive at follow-up examination	2	2	10*
No. still normotensive at follow-up examination	32	34	26

*Two-tailed Fisher's exact test, $P=0.004$.



Distribution of RBC Na-Li CT in subjects with high-normal systolic pressure at baseline ($n=37$). ▲ indicates subjects who developed high BP during follow-up ($n=11$); ○, subjects who remained normotensive ($n=26$).

health professionals, because its practical value as a predictor of future hypertension, and thus of cardiovascular risk, has not been defined.⁵

The ongoing Olivetti Prospective Heart Study offered a good opportunity to investigate the prospective relationship between Na-Li CT and BP in a sample of untreated normotensive middle-aged men. In the analysis of the available data set, we tried to answer the question of whether the measurement of Na-Li CT may or may not be of practical value in predicting the risk of future hypertension in normotensive individuals.

Although the number of participants was relatively small, the study had a long follow-up and included only untreated individuals in whom BP was directly measured both at baseline and at follow-up examination and in whom Na-Li CT was measured twice 8 years apart with an identical protocol in the same laboratory.

The study confirmed that Na-Li CT has very small intra-individual variability and great stability over time, two properties that make it an ideal candidate as a marker of future disease. It also confirmed the statistical associations between Na-Li CT and a number of biochemical variables related to lipid and carbohydrate metabolism, in agreement with previous studies.^{4,13}

TABLE 7. Predictive Power of Baseline RBC Na-Li CT on Risk of Future Hypertension When Applied to Whole Study Population or Persons in Upper Tertile of Baseline Systolic BP (High-Normal)

	Whole Population	High-Normal BP
n	106	37
Sensitivity, %	71	90
Specificity, %	72	77
Predictive value positive, %	28	60
Predictive value negative, %	94	95

Baseline BP (particularly systolic pressure) was a significant predictor of the risk of the development of hypertension, and most of the newly discovered hypertensive subjects had a BP value in the so-called "high-normal" range at baseline. The tracking of BP is a well-recognized phenomenon^{24,25}; it implies that those who will become hypertensive tend to have, at any time earlier in their life, a BP value in the upper part of the distribution for their gender and age. Nevertheless, in multivariate analysis accounting for the effects of BP, age, body mass, serum glucose, and triglyceride concentration, Na-Li CT maintained a large independent effect in predicting the risk of future hypertension in this population of untreated and initially normotensive middle-aged men.

Cross-tabulation of the cases of incident hypertension by tertile of baseline Na-Li CT showed that over two thirds of the cases came from the highest tertile. Moreover, if one looks specifically at the group of participants with high-normal BP at baseline (those at particularly high risk), the sensitivity of Na-Li CT in predicting the risk of future hypertension in this group increased further, since 9 of 11 cases had a high Na-Li CT at baseline (Figure).

The most important finding of the study is the very high negative predictive value of Na-Li CT among persons with high-normal BP, inasmuch as an individual with Na-Li CT in the low-mid range had only a 5% probability of becoming hypertensive, despite his high-normal BP level. This finding may have important practical implications because the majority of persons with high-normal BP (based on a casual BP measurement) do not become hypertensive; our study supports the view that these individuals could be identified through the measurement of Na-Li CT. This property confers to Na-Li CT a predictive power that is additive to that of BP.

In our study, only the standard assay of Na-Li CT was performed with no evaluation of the kinetic parameters of the transporter, the significance of which was not fully appreciated at the time the study was originally planned and that would have hardly been compatible with the constraints of the work in the field. Nevertheless, in careful kinetics studies, a very high correlation ($r=0.90$) has been found between the conventionally measured lithium transport rate and the true maximal velocity of the transporter. In particular, it has been noted that for countertransport values in the low-mid range, the transporter true maximal velocity tends to be only slightly higher than the activity measured with the standard assay, whereas for values in the upper part of the distribution (thus mostly in hypertensive subjects), the difference between the two values becomes larger.¹⁴ This means that measuring the true maximal velocity can be expected to lead to a better separation between normotensive and hypertensive individuals; in turn, the ability of the test to predict the risk of future hypertension could be further enhanced. Its cost-effectiveness, however, would be substantially reduced because of the longer time needed to carry out a kinetic study.

Other potential limitations of the present study include the small sample size, particularly for those participants with high-normal BP. This would lead to a lack of sufficient statistical power to detect a difference. Our study, however, had sufficient statistical power to detect a significant association between Na-Li CT and incidence of hypertension. The

relatively narrow age range of our participants and the lack of information on women may represent another limitation of our study as to its generalizability. Some recent studies reported conflicting data concerning the association between an elevated Na-Li CT and high BP in women.^{17,26} Therefore, caution should be used in extrapolating our findings to a broader segment of the population not included in our study.

Little and controversial information exists on the ability of the RBC Na-Li CT to predict the risk of future hypertension.¹⁵⁻¹⁷ In a 7-year follow-up study by Hunt and coworkers¹⁵ on a large cohort of adult members of Utah pedigrees with a high prevalence of cardiovascular disease, Na-Li CT was found not to be a significant predictor of future hypertension; however, in that study BP was not directly measured, with the outcome being based on the participants' responses to a questionnaire asking whether they had been given antihypertensive therapy by a physician. The number of cases detected in this way was surprisingly low (40 of 1482 participants). Moreover, as acknowledged by the authors, the particular cohort studied was not representative of the general population. In another article, the same authors reported that a subset of individuals identified as carriers of a "high countertransport genotype" experienced a four to five times higher rate of hypertension.¹⁶

A more recent study focused on the relationship between baseline Na-Li CT and development of hypertension over a 6-year period in a large adult population sample in central Italy.¹⁷ In this survey, the incidence of hypertension was higher in individuals with Na-Li CT in the upper quartile than those in the three lower quartiles; however, the predictive ability of Na-Li CT appeared to be weaker compared with our data, and statistical significance was reached in female but not male participants. There may be several possible explanation for these discrepancies: methodological variability in the measurement of Na-Li CT, broader age range enhancing population heterogeneity, and shorter duration of follow-up in the Gubbio study.

Speculation about the mechanism(s) of the association between Na-Li CT and risk of future hypertension is beyond the scope of this article. It is not clear whether an abnormal countertransport activity is the expression of a genetic defect etiologically related to hypertension or of a genotype that is associated but not causally related to hypertension or a step in the pathogenetic chain leading to high BP. In this regard, it may be of interest that the newly discovered hypertensive subjects had, as a group, a higher fasting blood glucose level at baseline than those who remained normotensive (Table 3). The increase in their blood glucose, occurring during the 8-year observation period at the same time that BP increased, was remarkable: such an increase was almost threefold that observed in the normotensive group. It should also be noted that among the 6 subjects who developed diabetes during the follow-up period, those who had an RBC Na-Li CT in the upper tertile at baseline (3 of 6) were those who also developed hypertension. The concomitance between the development of high BP and this metabolic perturbation might be related to the recognized relationship between altered Na-Li CT and diminished insulin sensitivity.^{12,13,27,28}

In conclusion, our findings indicate that high-normal BP and elevated RBC Na-Li CT were both significant and independent predictors of future development of hypertension in a group of middle-aged men. In particular, Na-Li CT was especially useful in discriminating participants with high-normal BP who did progress to develop hypertension from those whose BP remained within the normal range over time. Continued follow-up of our study population and other prospective investigations involving women and younger age groups are warranted to reinforce these results.

Acknowledgments

This study is dedicated to the memory of Dr Mitzy Canessa, who inspired us along this research line. The study was supported in part by a grant from the Italian Ministry of University and Scientific Research and by Modinform s.p.a. (Olivetti group). The authors are grateful to Drs Umberto Candura and Antonio Scottoni, chiefs of the Olivetti factory medical staff in Marcianise and Pozzuoli, respectively, for their valuable collaboration in the organization and coordination of the study; we also thank the Olivetti employees for their enthusiastic participation. The excellent cooperation of Drs Francesco Stinga and Franco Noviello and Maria Bartolomei for field work, and Paola Cipriano and Elisabetta Della Valle for laboratory help is gratefully acknowledged.

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