a functional Na\(^+\)/Mg\(^{2+}\) exchanger that functions to maintain low (Mg\(^{2+}\)) in cytotrophoblast cells. In addition (Mg\(^{2+}\)) is acutely regulated by (Mg\(^{2+}\)). Because placental trophoblasts are sites of maternal–fetal ion exchange, and (Mg\(^{2+}\)) is altered in preeclampsia, derangements in or modulation of this exchanger may contribute to complications of pregnancy such as pregnancy-induced hypertension, preeclampsia, and preterm labor.

If a Na\(^+\)/Mg\(^{2+}\) antiporter is defective in the preeclamptic placenta, it may contribute to the hypomagnesemia and vasoconstriction observed in these patients. Future studies are needed to characterize a Na\(^+\)/Mg\(^{2+}\) antiporter in isolated term trophoblast cells.

In this context we found lowered plasma, intracellular, and membrane Mg\(^{2+}\) concentrations in preeclampsia contributing to the development of hypertension in pregnancy similar to investigations by Kisters and Bardicef and their colleagues. In another study performed by our group, we measured decreased intracellular Na\(^+\) and increased Mg\(^{2+}\) concentrations in smooth muscle cells in spontaneously hypertensive rats determined by electron-probe X-ray microanalysis. The Mg\(^{2+}\) deficiency hypothesis in essential hypertension has been studied at both the extracellular and intracellular level. At the extracellular level, serum Mg\(^{2+}\) values have been reported higher, lower, or unchanged in hypertensive patients, compared with normotensive subjects. Nevertheless, several investigations have found a decreased intracellular Mg\(^{2+}\) content in red blood cells in essential hypertension and animals. One of the most important mechanisms contributing to the intracellular Mg\(^{2+}\) homeostasis is a Na\(^+\)-dependent Mg\(^{2+}\) efflux through the plasmalemmal membranes. This mechanism was described by Feray and Garay in human and rat erythrocytes. Evidence for a Mg\(^{2+}\)/Na\(^+\) exchanger has been obtained in giant squid axon, and the existence of a similar mechanism in liver cells, thymocytes, and myocardiocytes has been suggested. The increased Na\(^+\) concentration in different hypertensive cells has been previously attributed to a reduced Na\(^+\)-K\(^+\)-ATPase activity, and increased activity of the Na\(^+\)-H\(^+\) exchanger.

In conclusion, the excellent study of Stantley et al is similar to our results, showing the existence of a human Na\(^+\)/Mg\(^{2+}\) exchanger. Concerning hypertension in pregnancy, further investigations in other cell models should be performed, to stress the importance of the Na\(^+\)/Mg\(^{2+}\) exchanger in hypertension.

KLAUS KISTERS
FARUK TOKMAK
Medical Clinic I
St. Anna-Hospital
Herne
MARKUS KOSCH
MARTIN HAUSBERG
Medical University Policlinic

References


Left Ventricular Changes in Primary Aldosteronism

In their report Goldkorn et al compared patients with primary aldosteronism (PA) and patients with essential
hypertension (EH) and concluded that left ventricular (LV) mass index was not increased in the latter compared to the former patients. On the basis of this finding and on the lack of an association of LV mass with plasma or urine aldosterone, they concluded that there is no evidence for an association of aldosterone with LV structure or geometry. This conclusion is at variance with previous studies from our4 and other groups,3 which they did not mention.

Several considerations concur, in our view, to suggest caution in drawing such conclusion. First, experience during the past decades has shown that although the diagnosis of Conn’s adenoma can be conclusively made, that of idiopathic hyperaldosteronism cannot.4 It has been established three decades ago that this latter condition is almost indistinguishable from low renin EH,5,6 unless a combination of dynamic tests, imaging studies, and adrenal vein sampling,7 which apparently were not performed in the series studied by Goldkorn et al, is carefully used to diagnose this condition. Only 7 of 19 patients in the New York cohort and 12 of 16 in the Moscow cohort had Conn’s adenoma, but, unfortunately, they did not provide any information on how this diagnosis was made. They also did not furnish any data on blood pressure (BP), serum potassium, plasma renin activity, aldosterone and, more important, LV mass after adrenalec-tomy. Thus, one wonders how the diagnosis of idiopathic hyperaldosteronism was made and uncertainties remain on the diagnosis in the Conn’s adenoma group.

Second, this was a two-center study and, therefore, it is likely that differences in diagnostic criteria for PA, as well as in the assessment of echocardiographic parameters did occur. For example, the plasma aldosterone levels were unavailable in the New York cohort, and the urine aldosterone values were not reported in the Moscow cohort.

Third, a prerequisite for the validity of this type of comparative cross-sectional studies is the lack of biases in the selection of the patients for the two groups. Goldkorn et al claim that their PA and EH groups were well matched for gender, age, and BP. However, the patients were not matched for the known duration of hypertension, a variable that notoriously affects LV geometry and structure. Furthermore, the groups differed remarkably in terms of ongoing antihypertensive treatment. As they stated, 14 PA and 2 EH in the New York cohort and 12 PA v 9 EH patients in the Moscow cohort were on treatment; collectively 74% PA patients were treated versus 31% EH patients ($\chi^2 = 4.49, P < .05$). Needless to say that this difference might have also precluded detection of any differences in LV structure or geometry.

Fourth, as already mentioned, the plasma and urine aldosterone levels were unavailable in the New York and Moscow cohort, respectively. Thus, the regression analysis could not be performed in the entire group. Consequently, it appears evident that the failure to detect an association between the hormone and LV mass can simply be due to the lack of statistical power.

In the only study of ours that Goldkorn et al quoted,2 we carefully matched PA patients and EH patients for demography and BP values and, most important, our two groups did not differ significantly for duration of hypertension. Although all of our PA patients had previously been on regular antihypertensive treatment, whereas only 2 of the 34 EH had been treated, we found a higher LV mass index in PA than EH patients. In another study, which Goldkorn et al ignored, on a large series of patients ($n = 26$) with proven Conn’s adenoma, not only did we confirm this finding, but also found a significant relationship of plasma aldosterone with both interventricular septum and LV posterior wall thickness.9 The occurrence of excess LV hypertrophy in PA patients was also confirmed in a Japanese study by Shigematsu et al,3 another article that Goldkorn et al evidently ignored, which documented that LV hypertrophy, mostly of the eccentric type, preceded the other signs of target organ damage in PA patients. With regard to the hypothesis that aldosterone might be associated with changes of LV diastolic function, which Goldkorn et al put forward in their discussion, in both our studies, as well as in another study,9 we documented clear-cut changes in LV diastolic filling that indicated the greater dependency of the LV on the atrial contraction for its filling in PA compared to EH patients. Thus, this hypothesis has already been tested, albeit Goldkorn et al were evidently unaware of it.

Incidentally, we would like to recall that in an additional report, which Goldkorn et al failed to mention, extensive cardiovascular fibrosis was reported at necropsy in a patient with aldosterone-producing adenoma.10

In addition, we would like to point out that the LV midwall shortening that Goldkorn et al claimed they measured for the first time in PA patients, was already reported in another study from our group in 1998, again not quoted. We are pleased to see that Goldkorn et al’s finding of similar values in PA and EH patients, confirms our earlier report.9

Finally, the hypothesis that aldosterone exerts a pivotal role in causing cardiac fibrosis stands not only on a wealth of experimental studies, but also on a more recent study from our group. Using video-densitometry to assess LV texture, we found a significant decrease in cyclic variation index in the interventricular septum of PA patients, as compared to EH.11 This index was found to correlate with cardiac fibrosis in a few studies.

Thus, in our view, because of a number of methodologic flaws as well as failure to adequately mention and discuss previous published findings, the conclusions of Goldkorn et al are unwarranted.

GIAN PAOLO ROSSI
MAURIZIO CESARI
ACHILLE C. PESSINA
Department of Clinical & Experimental Medicine
Clinica Medica 4
University of Padova
Padova, Italy
gianpaolo.rossi@inipd.it
that obese patients have a 50% increased risk for lacking
treatment are notoriously low in overweight or obese pa-
therapies for the treatment of obesity hypertension that go
beyond the rather general recommendation to reduce body
weight.1 Furthermore, response rates to antihypertensive
treatment over the standard dose of 5 mg daily in obese
hypertensive patients.

Our study included overweight or obese (body mass
index [BMI], 28–45 kg/m²) patients with mild-to-moderate
treated or untreated essential hypertension (systolic BP
SBP ≥140 mm Hg and diastolic BP [DBP] ≥90 mm Hg)
who were otherwise healthy and between 18 and 80 years
of age. Target criteria for study completion were a fall in
SBP of ≥20 mm Hg or normotension (SBP ≤130 mm Hg
and DBP ≤85 mm Hg). After screening, antihypertensive
therapy was withdrawn in previously treated patients. Pa-
tients then received placebo for 2 weeks, followed by 5 mg
nebivolol for 4 weeks. The dose was increased to 10 mg
for 2 weeks, and again to 20 mg for 2 weeks if target
criteria were not reached with the preceding dose. If target
criteria were met, patients were classified as responders
and otherwise as nonresponders. The analysis was based
on a Macrov-chain design with three points in time (weeks
4, 6, and 8) and two conditions (nonresponse, response).

Mean BP and heart rate were calculated of five mea-
surements with an automatic oscillometric BP measure-
dment device (Dinamap 1846 SX, Critikon, Germany) at
intervals of 2 min in a sitting position after 10 min rest; the
cuff was placed on the right arm, with an individual cuff
size depending upon circumference. Body weight was
measured with the Tanita TBF-305 scale (Tanita Corp.,
Tokyo, Japan) and blood and urine samples were analyzed
with standard laboratory techniques. Quality of life was
assessed with the Short Form–36 (SF-36) questionnaire.5
Patients were asked regarding adverse events, and com-
pliance was checked at every visit. The study was ap-
proved by the Institutional Ethics Committee and was
performed in accordance with the Guidelines for Good
Clinical Practice (GCP). Written informed consent was
obtained from all participants.

A total of 66 patients were screened, 46 of whom met
the inclusion criteria at baseline (Table 1). Of the 41
patients who completed the first dose per protocol, 18
responded to 5 mg nebivolol (response rate 43.9% [95%
confidence interval, 28.5% to 60.3%]). In all, 21 patients
completed the second titration step per protocol. Of these,
three (14.3% [0.3% to 36.3%]) responded to 10 mg nebivo-
lool. The last titration step was completed per protocol by
16 patients. Of these, none (0% [0% to 0.21%]) responded
to 20 mg nebivolol. During the verum phase, nine patients
were excluded from the study: five on 5 mg nebivolol

**Effect of Forced Titration of Nebivolol on Response Rate in
Obese Hypertensive Patients**

Although hypertension is a common finding in obesity,
current guidelines do not provide specific recommenda-
tions for the treatment of obesity hypertension that go
beyond the rather general recommendation to reduce body
weight.1 Furthermore, response rates to antihypertensive
treatment are notoriously low in overweight or obese pa-
tients. For example, a study by Lloyd-Jones et al reported
that obese patients have a 50% increased risk for lacking
blood pressure (BP) control on antihypertensive treatment
compared to lean patients.2 Nebivolol is a lipophilic selective βι blocker that also
induces endothelial nitric oxide release.3 It is currently
licensed for use in arterial hypertension with a recom-
mended daily dose of 5 mg, but is also used for treatment
of angina pectoris, heart failure, and cardiac arrhythmias.4

Given the larger volume of distribution that can be ex-
pected in obese individuals, the primary purpose of the
present study was to assess whether higher doses of
nebivolol (10 or 20 mg) would increase the response to
treatment over the standard dose of 5 mg daily in obese
hypertensive patients.

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