

The Impact of Antihypertensive Drug Therapy on Endotoxemia in Elderly Patients with Chronic Kidney Disease

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Summary

Background and objectives Endotoxin (ET) is recognized to cause adverse effects on cardiovascular (CV) structure. Circulatory translocation of gut bacterial ET is described in heart failure. Chronic kidney disease (CKD) is common in older people and aggressive BP control is the cornerstone of management. We therefore studied ET after improvement of the overall CV milieu with introduction of optimized antihypertensive therapy (AHT).

Design, setting, participants, & measurements We recruited 40 hypertensive nondiabetic patients (≥ 70 years) with CKD stages 3 and 4 and hypertensive non-CKD matched controls. Assessment was performed after complete AHT washout and repeated after AHT reintroduction to target BP 130/80 mmHg. Pulse wave velocity (PWV) and analysis were assessed by applanation tonometry, central hemodynamics by continuous digital pulse wave analysis, vascular calcification (VC) by superficial femoral artery CT, and serum ET by Limulus Amebocyte assay.

Results Mean age was 76 ± 5 years, estimated GFR (eGFR) (CKD group) was 40 ± 14 ml/min per 1.73 m^2 , and achieved BP was 128/69 mmHg. Washout ET was 0.042 ± 0.011 EU/ml and was independent of renal function, gender, age, BP, VC, arterial stiffness, and high-sensitivity C-reactive protein. ET significantly decreased with AHT (to 0.020 ± 0.028 EU/ml; $P < 0.001$) and was associated with eGFR ($R = -0.38$; $P = 0.02$), arterial wave reflection (Augmentation Index $R = -0.42$; $P = 0.01$), and degree of tonic vasodilatation (total peripheral resistance $R = -0.37$; $P = 0.03$), but not VC, PWV, gender, age, BP, or high-sensitivity C-reactive protein.

Conclusions Elderly patients with hypertension have elevated serum ET. Improvement of their CV status with optimized AHT is associated with a significant reduction in endotoxemia. Further investigation of the potential pathophysiological mechanisms linking CV disease and CKD with this previously unappreciated effect of AHT appears warranted.

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Introduction

Translocation of endotoxin across the gut wall is well described in severe heart failure (1), and occurs both in the setting of shock and in severe decompensated hepatic impairment with portal hypertension (2). Endotoxemia is associated with a wide range of well recognized pathophysiological processes; it is a profoundly proinflammatory stimulus (3) and is seen in pathologic conditions associated with malnutrition and wasting (1,2).

Endotoxin (without sepsis) was initially proposed as a stimulus for immune activation in the proinflammatory state in congestive heart failure (CHF) (4). Endotoxin enters the circulation by translocation from the gut, with bowel edema and hypoperfusion being the two main factors thought to influence bowel wall

permeability in CHF (5). A study of clinically stable CHF patients has shown structurally and functionally altered gut, with increased bowel wall thickness suggestive of edema, and increased intestinal mucosal permeability suggestive of inadequate bowel mucosal perfusion (6). Endotoxin and cytokine levels are elevated in CHF patients with recent-onset edema compared with stable CHF patients, with a significant reduction in endotoxin levels following diuretic treatment (7). In decompensated CHF, endotoxin levels are significantly higher in the hepatic veins compared with the left ventricle, suggesting endotoxin translocation from the gut is the probable source (8).

Endotoxemia has been previously recognized in patients on dialysis and with nondialyzed chronic kidney disease (CKD) (9–12). We have recently re-

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ported significant incremental endotoxemia across the full range of CKD patients. Although patients receiving dialysis were particularly affected, levels of serum endotoxin were markedly higher in CKD stage 3 and 4 patients when compared with hypertensive non-CKD patient controls (13). Acutely, haemodialysis (HD) with ultrafiltration causes a reduction in splanchnic blood volume. This associated reduction may occur with or without hypotension (14,15), with the resulting mesenteric ischemia leading to disrupted gut mucosal structure and function (with increased gut permeability) (16). Circulating endotoxin levels are around 500 to 1000 times greater than in non-CKD patients, levels roughly triple after initiation of HD (as compared with patients with stable cardiac troponin T CKD stage 5). These elevated levels in HD patients correlate with intradialytic instability, systemic inflammation, cardiac troponin T levels, ultrafiltration volumes, dialysis-induced myocardial stunning, and risk of subsequent mortality (13). The biologic fate of endotoxin is well known and is not related to renal clearance (17–20).

Such recurrent acute circulatory stress, however, does not account for endotoxemia in either peritoneal dialysis (PD) patients or in nondialyzed CKD patients. In common with CHF, CKD is characterized by fluid overload, with management limited to drug therapy in those not yet dialyzed. We hypothesize that factors relating to ischemic potential or predisposing to intestinal vascular congestion (in the absence of overt CHF) may be associated with endotoxemia, and that addressing these factors with antihypertensive medication is capable of modulating systemic endotoxin exposure by optimization of fluid status and/or reduction in circulatory stress with concomitant improvement in endothelial dysfunction.

Materials and Methods

We recruited a subset of BP-controlled hypertensive patients with CKD stages 3 and 4 from a previous observational study (13) to participate in a study of the effect of antihypertensive treatment (AHT) on endotoxemia. The

effects of AHT in these patients were compared with a control group of hypertensive non-CKD control patients (characteristics summarized in Table 1). Diabetics and patients with heart failure, ischemic heart disease, or malignant-phase hypertension likely to be destabilized by current therapy withdrawal were excluded. This study received additional approval by Local Regional Ethics Committee and was issued with a full clinical trials certificate by the Medicines and Healthcare products Regulatory Agency. Informed consent was obtained from all patients, who were recruited after being identified on primary care CKD chronic disease registers.

All subjects underwent a full initial assessment after having had all current antihypertensive agents withdrawn with a minimum washout period of 2 weeks. Circulating endotoxin levels were measured at this point. AHT was then reintroduced and escalated to achieve current guidelines (130/80 mmHg). All BP measurements were performed with an appropriately calibrated, serviced, and approved oscillometric device (as above). BP was measured in both arms, with the higher arm used for all subsequent measurements. At all visits, three measurements were performed, at least 2 minutes apart. The mean was used for further analysis. Postural BP was recorded at all visits. A single set of measurements was taken at sitting (0), 1, and 3 minutes. If there was a postural drop of $>20/10$ mmHg, AHT was reduced.

In the washout period, BP was checked after 2 weeks. If systolic BP was >180 mm Hg or diastolic BP >110 mm Hg during the washout period, AHT was restarted and the patient was withdrawn from the study. Reintroduction of AHT was based on renin-angiotensin-aldosterone system (RAAS) inhibition but was guided by knowledge of previously tolerated and effective agents within the individuals. If BP was $<110/60$ mmHg after an increase in treatment, that increase was reversed. Once a patient's BP was stable for 4 weeks at this target, he or she attended for a further visit to allow evaluation of the CV system and repeat

Table 1. Description of baseline patient characteristics

	Non-CKD (15)	CKD (21)	Overall	P value
Age (yrs)	77 \pm 5	76 \pm 5	76 \pm 5	0.53
eGFR (ml/min per 1.73 m ²)	—	40 \pm 14	40 \pm 14	—
Proteinuria (%)	0	33	19	0.03
Optimal BP (mmHg)	130/71	126/68	128/69	0.42
Male	67%	57%	61%	0.73
Smoker	27%	10%	17%	0.21
Alcohol (U/wk)	3 \pm 12	3 \pm 8	3 \pm 7	0.52
Albumin (g/L)	39 \pm 5	39 \pm 4	39 \pm 4	0.90
Corrected calcium (mmol/L)	2.39 \pm 0.09	2.34 \pm 0.09	2.36 \pm 0.09	0.13
Phosphate (mmol/L)	1.05 \pm 0.16	1.10 \pm 0.15	1.08 \pm 0.15	0.36
Hemoglobin (g/dl)	14.2 \pm 1.8	12.8 \pm 1.8	13.4 \pm 1.9	0.04
AIx (%)	29 \pm 8	26 \pm 6	27 \pm 7	0.29
PWVcr (m/s)	10 \pm 1	10 \pm 1	10 \pm 1	0.13
PWVcf (m/s)	14 \pm 3	13 \pm 3	13 \pm 3	0.17
SFA VC (units)	4 \pm 30	4 \pm 116	4 \pm 75	0.89

All continuous data are presented as mean \pm SD except alcohol and VC, which are median \pm interquartile range. CKD, chronic kidney disease; eGFR, estimated GFR (modification of diet in renal disease 4-variable); AIx, augmentation index; PWVcr, carotid-radial pulse wave velocity; PWVcf, carotid-femoral pulse wave velocity; SFA VC, superficial femoral artery vascular calcification.

measurement of circulating endotoxin levels. A maximum period of 3 months was allowed to achieve target BP.

Body Composition Assessment

Bioelectrical impedance (BIA) was measured using In-Body S20® body composition analyzer (Biospace, Korea) to detect changes in total body water and soft tissue composition.

Circulating Endotoxin Level Measurement

The method of plasma lipopolysaccharide (LPS) quantification has been described previously (21). Briefly, serum samples were diluted to 20% with endotoxin-free water and then heated to 70°C for 10 minutes to inactivate plasma proteins. We then quantified serum LPS with a commercially available Limulus Amebocyte assay (Cambrex, Verviers, Belgium), according to the manufacturer's protocol. The detection limit of this assay was 0.01 EU/ml. Samples with LPS level below the detection limit were taken as 0.01 EU/ml. All samples were run in duplicate and background subtracted.

Blood and Urine Samples Collected

Blood samples were collected at baseline after AHT washout and after retitration. Serum sodium, potassium, urea, creatinine, 25-OH vitamin D, phosphate (PO₄), albumin corrected calcium (CCa), albumin, and intact parathyroid hormone (PTH) were analyzed using standard auto-analyzer techniques (Roche diagnostics modular IIP®). Serum PTH was measured using the immunometric Immulite® 2000 assay (normal range 7 to 53 pg/ml). Commercially available enzyme-linked immunosorbent assay (ELISA) kits (DRG instruments, Germany) were used to assess high-sensitivity C-reactive protein (hsCRP). The detection limit was 0.1 mg/L with the coefficient of variation (CoV was 7.2%). Patients were staged on four-variable modification of diet in renal disease estimated GFR (eGFR). Proteinuria was quantified by the average of three sequential early morning urine samples for protein-creatinine ratio. All blood samples were taken in the hospital at an investigatory visit to allow for rapid separation of serum and storage at –85°C before endotoxin measurement.

Assessment of Vascular Calcification and Arterial Stiffness

Multislice computed tomography (MSCT) and measurement of hemodynamic variables were performed by a single observer. Briefly, MSCT was used to quantify calcification in a standardized section of the superficial femoral artery. Each slice was scored individually and a calcification score was generated. Calcification was considered to be present if an area ≥ 1 mm (2) displayed a density >130 Hounsfield units (22). Validation studies confirmed that the scoring technique is highly reproducible. Interobserver reproducibility between the investigator and a consultant radiologist was assessed in a 1-in-20 sample. The intraclass correlation was 1 (confidence interval [CI] 1 to 1) and the CoV was 3.9%. Repeatedly scored scans showed an intraobserver intraclass correlation of 1 (CI 1 to 1) and a CoV of 2.4%.

Applanation tonometry was performed at the radial artery using a SphygmoCor® (AtCor Medical Pty Ltd., Australia).

Augmentation was assessed as a derived central pressure wave. Electrocardiogram gated PWV was assessed between the carotid and radial as well as the carotid and femoral arteries.

Measurement of Hemodynamic Variables

Noninvasive continuous pulse wave analysis was used to determine hemodynamic variables. The Finometer® (FMS, Amsterdam, The Netherlands) utilizes photoplethysmography to derive a pulse wave from a finger pressure cuff containing an infrared optical source and detection unit. The pulse wave is then subject to mathematical analysis based on the transport characteristics of peripheral blood vessels to reconstruct a central pressure waveform. This, in turn, is analyzed to calculate a wide variety of hemodynamic variables, including systolic BP, diastolic BP, mean arterial pressure, heart rate, cardiac output, stroke volume, and total peripheral resistance on a beat-to-beat basis. All data were subsequently downloaded to a personal computer-based analysis program (Beatscope™), allowing averaging of results over the 10-minute assessment period. Patients were assessed while supine after at least 15 minutes of rest.

Statistical Analysis and Sample Size Justification

The principal primary end point was to detect a 50% difference in circulating endotoxin levels after reintroduction of AHT. A sample size of at least 36 patients was needed to detect this difference at 90% power.

Group data are presented as mean \pm SD, unless otherwise stated. All data were tested for normality. Analysis was performed using SPSS v12.0.1 (SPSS Inc., Chicago, IL). Categorical data were compared using the chi-squared test, continuous data using the paired or the unpaired *t* test, the Mann-Whitney U test, or the Wilcoxon test, as appropriate. Correlation between continuous variables was examined by the Spearman rank correlation coefficient. A two-tailed *P* value of less than 0.05 was considered significant.

Results

The patient characteristics and achieved BP after drug reintroduction, and agents utilized to achieve this, are summarized in Tables 1 and 2. The patient groups were well matched for all factors other than renal function. Achieved mean BP was 128/69 mmHg. Washout median (\pm interquartile range[IQR]) endotoxin level was 0.042 \pm 0.010 EU/ml and was not associated with renal function,

Table 2. Agents used during antihypertensive reintroduction in the study

% Use	Non-CKD (15)	CKD (21)	<i>P</i> Value
ACEi/ARB	40	57	0.31
Calcium blocker	47	48	0.96
Beta blocker	27	24	0.85
Diuretic	33	33	1.00
Alpha blocker	33	24	0.53

CKD, chronic kidney disease; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

hemoglobin, gender, age, BP, vascular calcification, arterial stiffness, or hsCRP (non-CKD, 0.042 ± 0.010 ; CKD, 0.042 ± 0.011 EU/ml). Circulating endotoxin level significantly decreased with the reintroduction and optimization of AHT (to 0.020 ± 0.028 EU/ml, $P < 0.001$, Figure 1) in both CKD and non-CKD groups (non-CKD, 0.011 ± 0.006 , $P = 0.008$; CKD, 0.032 ± 0.028 EU/ml, $P = 0.002$). This reduction was greater by 50% in the non-CKD patients (0.032 versus 0.010 EU/ml), despite similar drug usage and achieved BP.

Antihypertensive reintroduction resulted in a reduction in mean carotid-femoral PWV (-1.1 m/s, $P < 0.001$) and rate-corrected augmentation index (-3.2% , $P < 0.001$). Mean BIA measured intracellular and extracellular water tended to be lower (400 ml, $P = 0.05$; 223 ml, $P = 0.07$, respectively), lean mass decreased (837 g, $P < 0.05$), but body fat mass was unchanged with AHT reintroduction. Significant VC was present in 17 of 36 patients, median (\pm IQR) VC score 4 ± 75 units.

After reintroduction of antihypertensive medications, circulating endotoxin was associated with eGFR ($R = -0.38$; $P = 0.02$) as well as arterial wave reflection (Augmentation Index $R = -0.42$; $P = 0.01$; Figure 2) and degree of tonic vasodilatation (total peripheral resistance, $R = -0.37$; $P = 0.03$), but not VC, PWV (carotid-radial or carotid-femoral), gender, age, BP, or hsCRP. There were no associations between the degree of ET reduction and change in hemoglobin, arterial stiffness, central hemodynamics, renal function, or hsCRP. There was, however, little evidence of significant systemic inflammation within

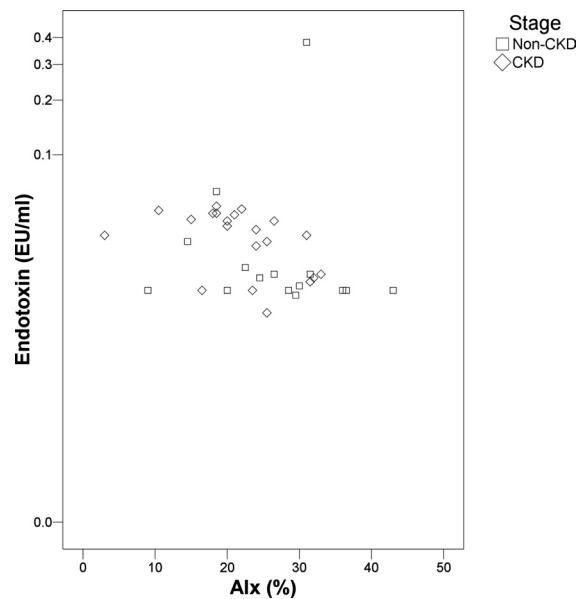


Figure 2. | Relationship of endotoxemia with arterial stiffness (augmentation index; Alx) after reintroduction of antihypertensive therapy in the entire cohort. CKD, chronic kidney disease.

this group with median (\pm IQR) hsCRP being only 2.3 ± 3.2 mg/ml, which was similar in non-CKD and CKD groups.

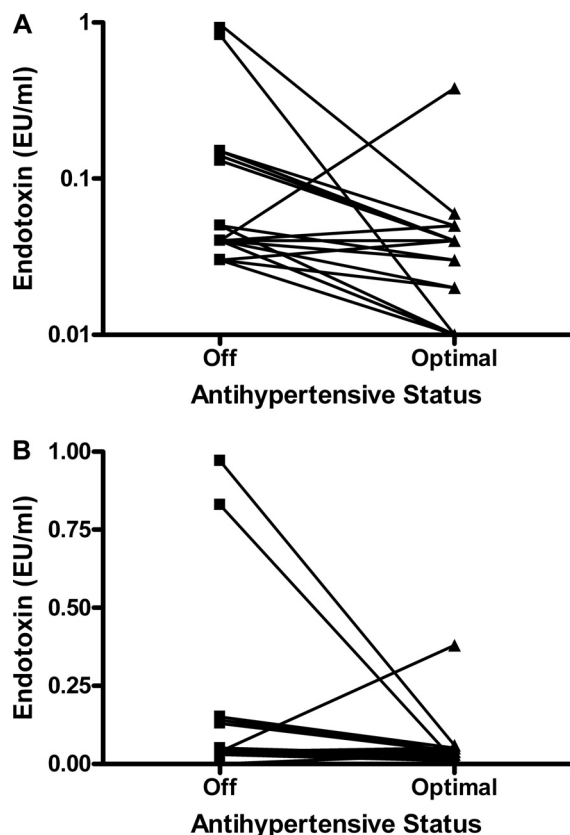


Figure 1. | Effect of optimization of BP with antihypertensive therapy on circulating endotoxemia in the entire cohort.

Discussion

This is the first study to recognize that serum endotoxin levels in hypertensive patients with CKD can be modified by AHT therapy use. This reduction in endotoxemia is associated with an improvement of factors previously implicated in CV health.

The biologic fate of plasma-free endotoxin is not dependent on the kidney. Clearance of endotoxin is affected both by humoral inactivation and through uptake into liver and mononuclear phagocyte cells (17–20), and is influenced by both host and LPS-specific factors (23,24). There is a complex relationship among binding of endotoxin to antibodies, to platelets, and to lipoproteins in the modulation of its biologic effects and clearance (23,24). Endotoxemia has been initially recognized in severe decompensated heart failure (4). Significant heart failure (New York Heart Association 3 to 4) was an exclusion criterion in this study, as was any recent decompensating acute illness. The degree of venous congestion has been reported as being increased with reducing GFR, but only in the setting of previously diagnosed significant CHF (25).

AHT appears to be able to reduce endotoxin levels. This is the first report that a pharmacologic intervention targeted at the cardiovascular system is capable of modulating such a potentially important factor as the intestinal translocation of preformed endotoxin in the pathophysiology of CV disease. Almost all of the patients studied had a reduction in endotoxemia after reintroduction of AHT. This resulted in around a halving of the levels of circulating endotoxin as compared with values obtained after full washout of AHT. Most patients were treated with RAAS inhibition, but a variety of agents were utilized. There were

a variety of effects resulting from introduction of these agents, which might have influenced the exposure to intestinal endotoxin translocation. Reduction in BP itself is capable of modifying endothelial vascular function (26) and altering potential for relative gut ischemia; a variety of the agents utilized (particularly angiotensin-converting enzyme inhibitors) also directly influence vascular biology, potentially reducing demand ischemia (27,28). There was a modest reduction in extracellular water with drug introduction, and a potential reduction in venous congestion may have played a role, but the patients with established CHF were specifically excluded from study, and the absolute change in extracellular water was small. PWV and augmentation index both improved with reintroduction of antihypertensive medication; reduction in arterial stiffness is known to reduce demand ischemia (29). There was a correlation between augmentation index (as a composite measure of cardiac performance and peripheral arterial structure and function) and the degree of endotoxemia, but not with PWV as measure of arterial compliance itself. A reduction in endotoxemia was seen in all of the hypertensive patients, but the reduction was reduced in percentage terms in those with the added factor of CKD. Given the potential biologic effects and influence of endotoxin at many levels of vascular biology (NO production, direct vasodilatation, Pro-inflammatory cytokine production, etc.) further investigation of potential pathophysiological mechanisms appears warranted.

Limitations

This study is limited by a variety of factors. Although the sample size is sufficient to meet the primary end point of detecting the reduction in circulating endotoxin level, the sample size is inadequate to fully resolve factors relating to the degree of endotoxemia or associated outcomes. The study would have been enhanced if further assessment of endothelial function had been performed. Although the groups were well matched, hemoglobin was lower in the CKD group. However, Hb levels were not associated with endotoxin in this study or previously across the spectrum of CKD (13). Endotoxin is also recognized to be a driver of atherosclerosis and is associated with increased intimal medial thickness measurements in peritoneal dialysis patients (11). This study did not include a direct measure of atherosclerotic burden. Plaque disease and classic thrombotic complications appear, however, to be significantly less important in the genesis of CV outcomes in this patient group compared with nonuremic patients.

Conclusions

Endotoxemia in CKD stage 3 and 4 patients appears to be modifiable by the use of pharmacologic intervention primarily directed at reducing BP. The observed reduction is associated with an improvement in factors associated with cardiovascular health and a subclinical reduction in overall hydration status. This previously unappreciated effect of AHT may be of significant importance in the pathophysiology of CV disease and progressive loss of renal function in patients with CKD.

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Disclosures

Dr. C.W. McIntyre was previously chief medical officer of INEOS healthcare.

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