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Original Paper

Plasma ET-1 Concentrations are Elevated in Patients with Hypertension – Meta-Analysis of Clinical Studies

Mei Xu[a] Yong-Ping Lu[b,c] Ahmed Abdallah Hasan[b,d] Berthold Hocher[b,e,f]

[a]Department of Traditional Chinese Medicine, Medical School of the Jinan University, The First Affiliated Hospital of Jinan University, Jinan University, Guangzhou, China; [b]Institute of Nutritional Science, University of Potsdam, Potsdam-Rehbrücke; [c]Department of Nephrology, Charité - Universitätsmedizin Berlin, Campus Mitte, Berlin, Germany; [d]Department of Biochemistry, Faculty of Pharmacy, Zagazig University, Egypt; [e]Department of Embryology, Medical School of the Jinan University, Guangzhou, China; [f]IFLb, Institut für Labormedizin Berlin, Berlin, Germany

Key Words
Hypertension • ET-1 • Meta-analysis

Abstract
Background/Aims: A recent study revealed that global overexpression of ET-1 causes a slight reduction in systemic blood pressure. Moreover, heterozygous ET-1 knockout mice are hypertensive. The role of ET-1 in human hypertension was so far not addressed by a strict meta-analysis of published human clinical studies. ***Methods:*** We included studies published between January 1, 1990 and February 28, 2017. We included case control studies analyzing untreated essential hypertension or hypertensive patients where antihypertensive medication was discontinued for at least two weeks. Based on the principle of Cochrane systematic reviews, case control studies (CCSs) in PubMed (Medline) and Google Scholar designed to identify the role of endothelin-1 (ET-1) in the pathophysiological of hypertension were screened. Review Manager Version 5.0 (Rev-Man 5.0) was applied for statistical analysis. Mean difference and 95% confidence interval (CI) were shown in inverse variance (IV) fixed-effects model or IV random-effects models. ***Results:*** Eleven studies fulfilling our in- and exclusion criteria were eligible for this meta-analysis. These studies included 450 hypertensive patients and 328 controls. Our meta-analysis revealed that ET-1 plasma concentrations were higher in hypertensive patients as compared to the control patients [mean difference between groups 1.57 pg/mL, 95%CI [0.47~2.68, P = 0.005]. These finding were driven by patients having systolic blood pressure higher than 160 mmHg and diastolic blood pressure higher than 100 mmHg. ***Conclusions:*** This meta-analysis showed that hypertensive patients do have elevated plasma

M. Xu and Y. Lu contributed equally to this article and therefore share first authorship.

Prof. Dr. Berthold Hocher
Institute of Nutritional Science, University of Potsdam, Potsdam-Rehbrücke
Arthur-Scheunert-Allee 114-116, 14558 Nuthetal, Potsdam (Germany),
Homepage: http://www.uni-potsdam.de/eem; E-Mail hocher@uni-potsdam.de

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ET-1 concentrations. This finding is driven by those patients with high systolic/diastolic blood pressure. Given that the ET-1 gene did not appear in any of the whole genome association studies searching for hypertension associated gene loci, it is very likely that the elevated plasma ET-1 concentrations in hypertensive patients are secondary to hypertension and may reflect endothelial cell damage.

Introduction

Thirty-two years ago Hickey et al. [1] found an endothelium-derived constricting factor by analyzing the supernatant of bovine aortic endothelial cells. This factor was thought to be a peptide hormone, since trypsin abolished the vasoconstrictive property of this new factor [1]. The molecular structure of this endothelium-derived constricting factor was identified later by Yanagisawa et al. [2] They named it endothelin, because it was isolated from the supernatant of porcine aortic endothelial cells. Endothelin was a very strong vasoconstrictor. It produces powerful, very long-lasting constrictions of a range of mammalian blood vessels in vitro including human arteries and veins. It also causes long-lasting elevation of blood pressure when injected into rodents [2]. Because of these observation, scientists at this time were of the opinion that this peptide - nowadays called endothelin-1 (ET-1), since there are two further endothelin isoforms that were discovered shortly after the initial discovery of ET-1 - plays a pivotal role in the pathogenesis of arterial hypertension [3]. It was thus an unexpected finding that ET-1 transgenic mice do not develop hypertension. This was first shown by our group in Berlin, Germany [4]. ET-2 overexpressing rats likewise do not develop hypertension [5]. Both rat and mouse ET overexpression models develop renal intestinal fibrosis and glomerulosclerosis in a blood pressure independent manner [4-10]. When going to the original publications, it was always noted that numerically the blood pressure was even somewhat lower in ET-1 transgenic mice as compared to their WT control counterparts. The difference was numerically small and always detectable, When applying appreciate statistical testing of this hypothesis, however, statistical differences between blood pressure in ET-1 transgenic mice and their controls could not be verified in these individual studies. To address this topic in more detail, we recently performed a meta-analsis about blood pressure in ET-1 transgenic mice studies reported in the past 20 years. This meta-analysis provides robust evidence that global ET-1 overexpression in mice lowers blood pressure in an age-dependent manner. Older ET-1+/+ mice had even a somewhat more pronounced reduction of blood pressure as compared to younger ET-1 transgenic mice when comparing these mice to their age-matched controls [11]. Given this findings in transgenic endothelin rodent models, the aim of the current study therefore was to perform a systematic review and meta-analysis of all published studies on ET-1 plasma concentrations in human patients with hypertension published so far. We likewise analyzed data on age and body mass index with regard to blood ET-1 concentrations in humans.

Materials and Methods

Search strategy

Two authors screened for clinical studies in PubMed (Medline) and Google Scholar for studies relevant to the topic of ET-1 and hypertension in humans. We included studies published between January 1, 1990 and February 28, 2017. Searching keywords were “endothelin-1”, and “hypertension”.

Inclusion and exclusion criteria

The first phases, we included all case control studies (CCSs) published in English. Inclusion criteria were established as following: untreated essential hypertension or antihypertensive medication was discontinued for at least two weeks. We checked all published papers fulfilling the above mentioned

criteria. The ET-1 concentration varied from 0.1 to 1000 pg/mL. Most of the studies reported mean ET-1 concentration between 0.5 and 100 pg/mL. We thus excluded studies reporting either extreme low or extreme high mean ET-1 concentrations in controls or hypertensive patients, because we assume quality issues of the used ET-1 assay systems in these studies reporting extreme values. We also excluded duplicate publications, abstracts, and review articles. Studies without comparison of hypertensive with normotensive subjects were likewise excluded. We used the following definition for hypertension: systolic blood pressure >140 mmHg and/or diastolic blood pressure 90 mmHg.

Data extraction and quality assessment

Two authors selected relevant articles, abstracted data, and evaluated the quality of enrolled studies independently. Questionable studies were resolved by discussion or consensus based on the views of a third reviewer. We contacted the authors when we encountered information that was unclear or incomplete.

The following data were extracted from the included articles: ET-1 blood concentrations, age, BMI, SBP, DBP. Data were given as mean ± SD. When encountered data given as mean ± SEM, we calculated SD form SEM (the formula is $SD = SEM \times n^{1/2}$, n is the number of subjects in each group); When data ere given as mean and range (a,b), $SD \approx [(b-a)^2 + (a-2m+b)^2/4]^{1/2}/12^{1/2}$ ($n \leq 15$) or $SD \approx (b-a)/4$ ($15 < n \leq 70$) [12]. We unified the ET-1 concentration unit as pg/mL, 1 pg/mL ET-1 = 2.4919 × pmol/L = 2.4919 × fmol/mL, because reported ET-1 concentrations in the individual studies were not reported using the same units.

Statistical processing

Statistical analyses were conducted by Review Manager Version 5.0 (Rev-Man 5.0) software, devised by Co-chrane Collaboration as described earlier [11]. Heterogeneity was assessed by *P* value and I^2. If there was no heterogeneity ($P \geq 0.1$, $I^2 \leq 50\%$), we used the IV fixed-effects model. If there was high heterogeneity ($P < 0.1$, $I^2 > 50\%$), we chose IV random-effects model. Binary outcomes were expressed as the risk ratio (RR) with 95%CI. Continuous variables were expressed as mean difference (MD) with 95% CI. In test for overall effect, the $P \leq 0.05$ was considered statistically difference.

We performed also a subgroup analysis of the hypertensive patients. In the 11 studies in the topic of ET-1 and hypertension, we conducted subgroups analysis according mean SBP in hypertensive group: subgroup 1, mean SBP < 160mmHg; subgroup 2 mean SBP > 160mmHg; subgroup 3 mean SBP unclear. A comparable classification was used for diastolic blood subgroups: subgroup 1, mean DBP < 100mmHg; subgroup 2 mean DBP > 100mmHg; subgroup 3 mean DBP unclear.

Results

Basic information

Based on the principle of Cochrane systematic reviews, and the inclusion and exclusion criteria of our meta-analysis, eleven [13-23] CCSs published studies included were in the present meta-analysis (450 patients in the hypertensive group, 328 controls in the normotensive group). A more detailed description of the clinical characteristics of the included studies is given in Table 1. Overall characteristics of included studies are given in Table 2. The study design/flow chart is given in Figure 1.

ET-1 and blood pressure

Eleven studies [13-23] reporting data on ET-1 and blood pressure could be included into the meta-analysis reporting data in patients without antihypertensive drug treatment.

The overall effect of the 11 studies [13-23] showed that hypertensive patients had higher ET-1 plasma concentrations than normotensive controls (mean difference 1.57 pg/mL, 95%CI [0.47~2.68], $P = 0.005$, with high heterogeneity ($P < 0.00001$, $I^2 = 99\%$), Figure 2). A subgroups analysis according to mean SBP in the hypertensive group revealed that hypertensive patients with SBP > 160mmHg hypertensive had higher ET-1 level than normotensive group (mean difference 2.03, 95%CI [0.10~3.97], $P = 0.04$, with high heterogeneity ($P < 0.00001$, $I^2 = 95\%$), Figure 2), whereas patient with mild hypertension (SBP between 140 and 160 mmHg) had similar ET-1 plasma concentrations as their normotensive controls (mean difference 0.70 pg/mL, 95%CI [-0.28~1.67], $P = 0.16$, with high heterogeneity ($P < 0.00001$, $I^2 = 92\%$), Figure 2).

Table 1. Characteristics of the included studies

Study ID	Study type	Type of patients	
		Hypertensive	Normonaltensive
Saito, 1990 [13]	CCS	Untreated essential hypertension. Age: 51.7±2.8	Age: 50±0.6
Kohno, 1990 [14]	CSC	Untreated or antihypertensive discontinued for at least 2 weeks. Stage Ⅰ hypertension age:49±7 Stage Ⅱ hypertension age:52±7	Age:50±7
Hoffman, 1994 [15]	CCS	All patients stopped medications 2 weeks. 52±16.5	Age:45±13.1
Januszewicz, 1994 [16]	CSC	Antihypertensive medication was discontinued for at least 2 weeks. Age:38.2±9.7 BMI:28±3.6 SBP:146±24.3 DBP:100±12.2	Age:35.6±6.4 BMI:24.5±7.8 SBP:126±9.2 DBP:80±9.2
Lemne, 1994 [17]	CCS	Untreated essential hypertension. Age:50±6 BMI:25.9±2.9 SBP:141±9 DBP:89±2	Age:50±6 BMI:24.6±2.8 SBP:125±11 DBP:76±4
Parrinello, 1996 [18]	CCS	Untreated essential hypertension. Age:37.5±4 BMI:35±7	Age:34±6 BMI:34±5
Cottone, 1998 [19]	CSC	Untreated essential hypertension. Age:42±4 SBP:168±4.4 DBP:105±4.8	Age:41±3 SBP:122±8.5 DBP:77±7.0
Hwang, 1998 [20]	CCS	Most essential hypertension were untreated. Or antihypertensive medication was discontinued for 2 weeks. Age:48±10.3 SBP:145±3 DBP:93±2	Age:47.2±12.1 SBP:131±3 DBP:84±2
Parissis, 2001 [21]	CCS	Untreated essential hypertension. Age:56±7 BMI:26.2±1.1 SBP:170±7 DBP:105±5	Age:55±6 BMI:25.8±0.9 SBP:120±4 DBP:85±4
Bruno, 2011 [22]	CSC	Untreated essential hypertension. Age:45.8±6.8 BMI:23.8±4.1 SBP:150.7±11.7 DBP:105±5	Age:43.5±5.6 BMI:22.2±3.5 SBP:130.1±7.1 DBP:85±4
Gu, 2015 [23]	CCS	Untreated essential hypertension. Age:64±11.4 BMI:23.5±2.6 SBP:164.2±16.7 DBP:85.3±15.5	Age:60.5±11.1 BMI:22.2±3.2 SBP:112.5±12.2 DBP:70.7±8.3

A subgroups analysis according DBP showed that hypertensive patients with DBP > 100mmHg had higher ET-1 plasma concentrations as compared to normotensive subjects: (mean difference 4.79 pg/mL, 95%CI [2.22~7.35], P = 0.0003, with medium heterogeneity (P = 0.08, I^2 = 61%), Figure 3); hypertensive patients with DBP between 90 and 100mmHg had similar ET-1 plasma concentrations as compared to normotensive controls (mean difference 0.45 pg/mL, 95%CI [-0.30~1.21], P = 0.24, with high heterogeneity (P < 0.00001, I^2 = 95%), Figure 3).

Table 2. Overall characteristics of the patients in the included studies

	Hypertensive group	Normotensive group
Age, year	51.8	48.8
BMI, kg/m^2	26.0	25.1
SBP, mmHg	148.2	119.4
DBP, mmHg	91.0	75.2
ET-1 concentration, pg/mL	5.4	3.8

Data are shown as mean

BMI

Six [16-18, 21-23] studies reported also data on BMI. The overall effect of the six studies showed that hypertensive patients had higher BMI than normotensive controls (mean difference 0.71 kg/m^2, 95%CI [0.36~1.06], P < 0.0001, with minimum heterogeneity (P = 0.16, I^2 = 37%), Figure 4 and Figure 5). A subgroup analysis according SBP in hypertensive group showed that patients with SBP between 140 and 160mmHg (mean difference 1.45 kg/m^2,

95%CI [0.61~2.30], P = 0.005, with minimum heterogeneity (P = 0.49, I^2 = 0%), Figure 4) as well as patients with SBP > 160mmHg (mean difference between groups: 0.55 kg/m^2, 95%CI [0.16~0.94], P = 0.005, with medium heterogeneity (P = 0.09, I^2 = 66%), Figure 4) had a higher BMI than normotensive group. Similar findings were seen when using DBP to differentiate the hypertensive patients. Patients with DBP between 90 and 100 mmHg (mean difference 1.31 kg/m^2,

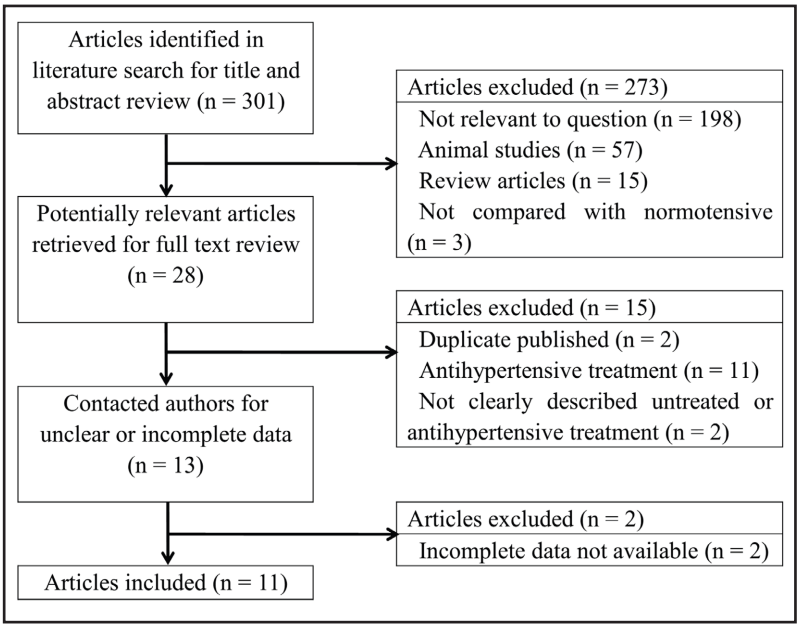

Fig. 1. Flow chart of the selection process defining the included sties in this meta-analysis.

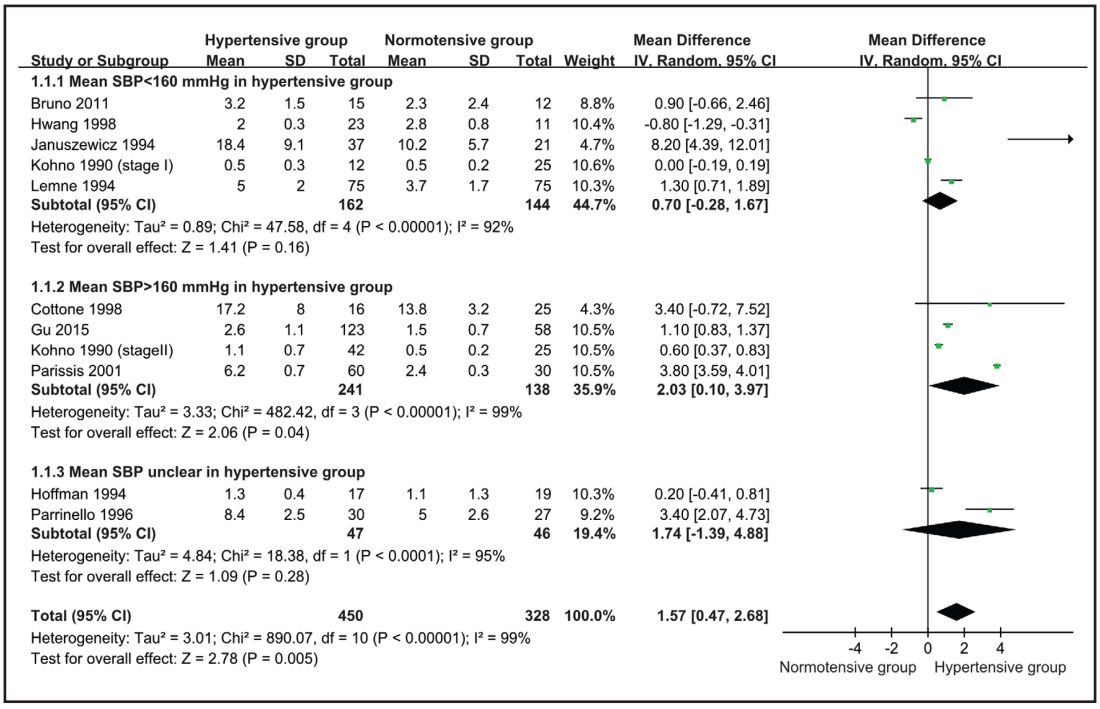

Fig. 2. Forrest blot showing the result of the meta-analysis of ET-1 plasma concentrations according to mean SBP in hypertensive and normotensive subjects.

95%CI [0.68~1.95], P < 0.0001, with minimum heterogeneity (P = 0.98, I^2 = 0%), Figure 5) as well as patients with DBP > 100mmHg (mean difference 0.44 kg/m^2, 95%CI [0.02~0.87], P = 0.04, with medium heterogeneity (P = 0.09, I^2 = 66%), Figure 5) had a higher BMI as compared to the normotensive controls.

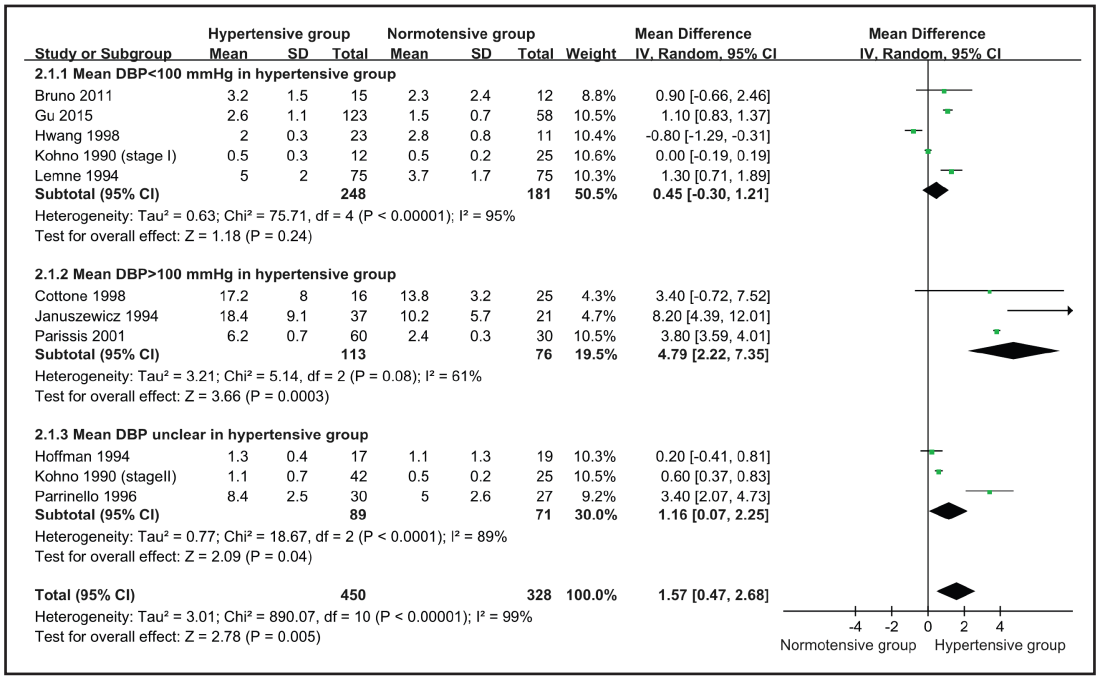

Fig. 3. Forrest blot showing the result of the meta-analysis of ET-1 plasma concentrations according to mean DBP in hypertensive and normotensive subjects.

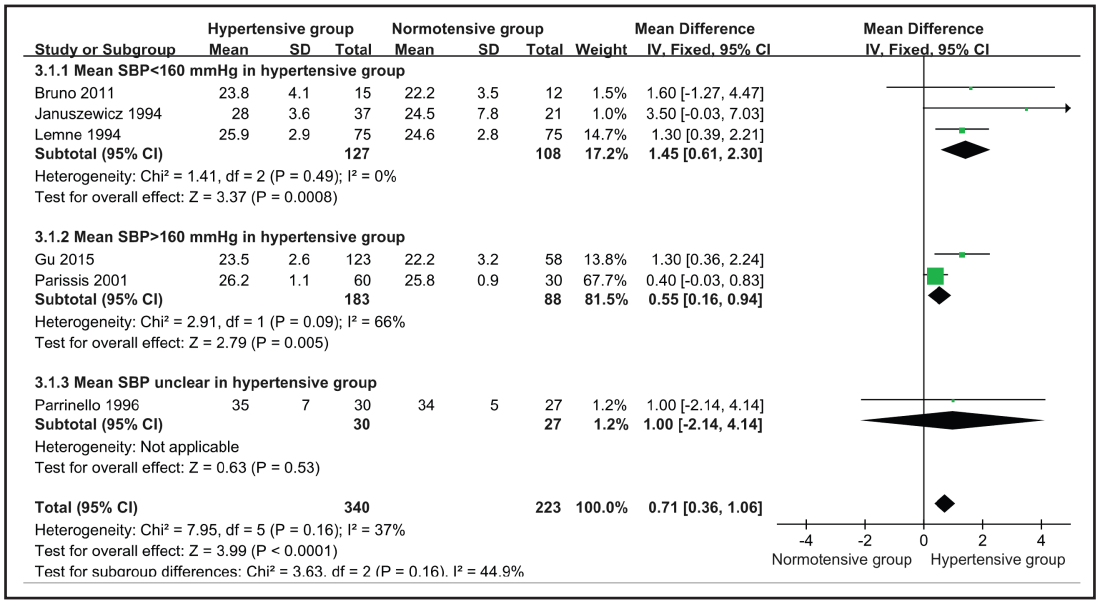

Fig. 4. Forrest blot showing the result of the meta-analysis of ET-1 plasma concentrations according to mean BMI in hypertensive and normotensive subjects when using SBP to define hypertensive patients.

Discussion

Key findings

The current meta-analysis in untreated patients with essential hypertension (450 hypertensive patients, 328 normotensive controls) revealed that ET-1 plasma concentrations were 42 % (= 1.57 pg/mL) higher in hypertensive patients as compared to the control patients. The body mass index was slightly higher in the hypertensive patients. These

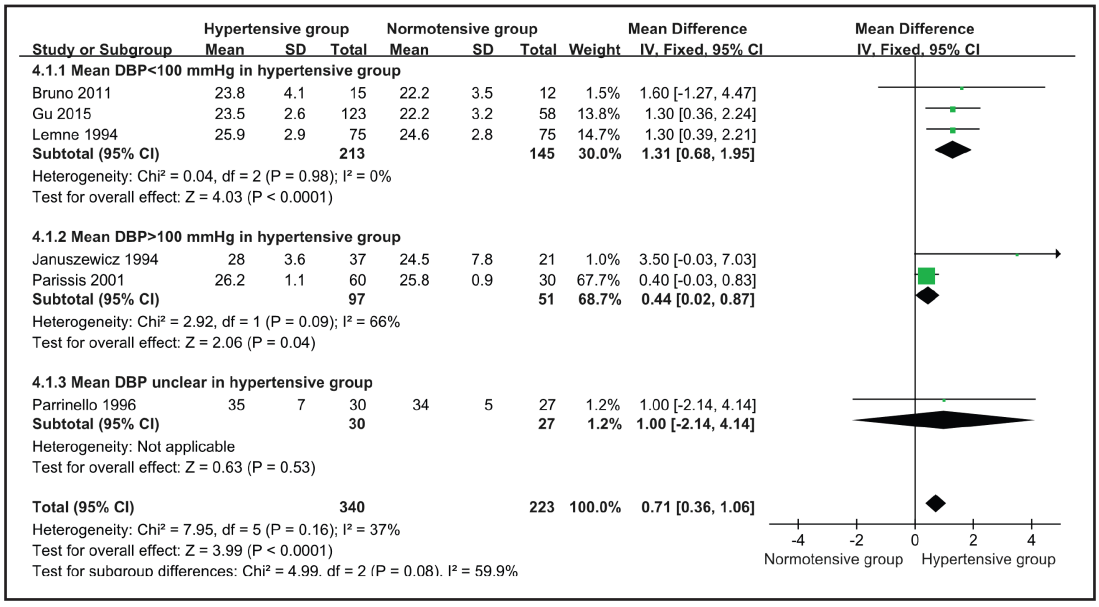

Fig. 5. Forrest blot showing the result of the meta-analysis of ET-1 plasma concentrations according to mean BMI in hypertensive and normotensive subjects when using DBP to define hypertensive patients.

finding were driven by patients having systolic blood pressure higher than 160 mmHg and/or diastolic blood pressure higher than 100 mmHg.

Study population

We identified 28 studies reporting data on ET-1 plasma levels in hypertensive patients (Figure 1). However, when applying the in- and exclusion criteria, only 11 studies were eligible for our meta-analysis due to various reasons such as incomplete reporting of data, reporting unrealistic high or low ET-1 plasma concentrations, duplication publications of studies and measurements of ET-1 concentration while the patients were treated with anti-hypertensive drugs. We excluded studies where patients were on anti-hypertensive medication, since it is well known that there is a close interaction for example of the renin-angiotensin-aldosterone system and the ET-1 system [24-28]. RAAS blocking agents thus might influence ET-1 plasma concentrations independent of the actual blood pressure. It was likewise shown that also beta blockers [29, 30] and calcium channel blockers [31-32] alter the paracrine ET-1 system. The majority of the remaining studies reported plasma ET-1 concentrations in treatment naive hypertensive patients, see table 1. We also included studies where the antihypertensive medication was stopped for at least two weeks. Plasma ET-1 concentrations did not behave differently in treatment naive patients and patients where antihypertensive treatment was stopped, we thus analyzed both groups together. It is of note that all hypertensive patients had a higher BMI as compared to the controls. This is consistent with the statement in the analyzed studies that patients with essential – and not secondary forms of hypertension – were included only, since essential hypertension is associated frequently with an increased BMI.

ET-1 and blood pressure

A recent study showed that global ET-1 overexpression in mice lowers blood pressure in an age-dependent manner [11]. This fits well with the observation that a global heterozygous ET-1 knockout in mice causes hypertension (the complete knockout in homozygous ET-1 knockout mice is lethal due to craniofacial malformations [23]). This landmark study was recently confirmed by another independent group showing that a decrease in systemic ET-1 level of up to 35 % of that in the control mice causes hypertension [33]. Notably, in this model blood pressure could be normalized by epithelial sodium channel blockers, indicating

that renal tubular sodium transport plays a key role in the pathogenesis of hypertension in these settings. These animal studies showed that ET-1 has numerous independent effects on blood pressure regulation in vivo, it is involved in tubular water and salt excretion, promotes constriction of smooth muscle cells, modulates sympathetic nerve activity, and activates the liberation of nitric oxide via an ETB receptor-mediated pathway from endothelial cells. [3, 34, 35]. In mice, the net effect of these partially counteracting mechanisms on blood pressure is a slight reduction of blood pressure [11]. The current meta-analysis of human studies – on the other hand - showed that ET-1 plasma concentrations were 42 % higher in hypertensive patients as compared to the control patients. The human ET-1 gene located on chromosome 6 (https://www.ncbi.nlm.nih.gov/gene/1906), however, was not associated to human hypertension in any of the large scale genome wide association studies searching for hypertension associated gene loci (37.38.39). The elevation of plasma ET-1 in the hypertensive patients seen in our meta-analysis thus rather reflects hypertension induced endothelial cell damage due to hypertension rather than the primary cause of hypertension. This hypothesis is supported by the finding that the evasion of ET-1 was seen in the subgroup of patient with very high systolic and/or diastolic blood pressure (= patients with most likely blood pressure induced endothelial damage) , but not in the patients with milder forms of hypertension.

Study limitations

The underlying reason for hypertension was not proven in most of the analyzed studies. The authors simply assumed that they have analyzed patients with essential hypertension based on patient's medical records, but did not check the quality of the records in detail. In addition, we had no systematic information's about the duration of hypertension in the analyzed studies in our meta-analysis. Some patients were newly diagnosed or untreated essential hypertension, some other were hypertensive patients who stopped medications at least 2 weeks before study entry. However, it is not clear whether this time in enough to eliminate the potential confounding effect of antihypertensive treatment. It is thus not possible to state what was first hypertension followed by an elevation of ET-1 or elevated ET-1. The renal tubular ET system is involved in water and salt transport and hence an increased salt reuptake in the kidney may contribute to the pathogeneses of hypertension. Salt intake, however, was not measured in the studies included into the meta-analysis.

Conclusion

This meta-analysis revealed that treatment naive hypertensive patients and patient who stopped blood pressure medication for at least two weeks do have slightly elevated plasma ET-1 concentration. This finding is driven by these patients with high systolic/diastolic blood pressure. Given that the ET-1 gene did not appear in any of the whole genome association studies searching for hypertension associated gene loci, it is very likely that the elevated plasma ET-1 concentrations in hypertensive patients are secondary to hypertension and may reflect endothelial cell damage.

Disclosure Statement

The authors of this manuscript state that they do not have any conflict of interests and nothing to disclose.

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