Regulatory T cells and vascular dysfunction

Francisco José Fernández-Fernández

I read with interest the excellent review '$CD4^+CD25^+$ $Foxp3^+$ regulatory T cells and vascular dysfunction in hypertension' by Kassan *et al.* [1]. They note that regulatory T cells (Tregs) imbalance may be a major factor in vascular endothelial dysfunction, and Tregs mediate their effects through an interleukin (IL)-10-dependent mechanism. They postulate that Tregs replacement by infusion might represent a new therapeutic strategy for the treatment of cardiovascular diseases. Another approach to the problem could be to restore the function of Tregs, if it is shown that their function is impaired. In this regard, I would like to comment on the role of vitamin D as an immunomodulator. Vitamin D from the skin and diet is metabolized in the liver to 25-hydroxyvitamin D, which is used to determine the patient's vitamin D status. 25-hydroxyvitamin D is metabolized in the kidneys by the 25-hydroxyvitamin D-1alfa-hydroxylase to its active form, 1,25-dihydroxyvitamin D. In contrast to the abundant availability of hepatic 25-hydroxylase, the renal capacity for 1-alfa-hydroxylation is limited, and already with a creatinine clearance of less than 65 ml/min, it is significantly reduced [2]. This is important because impairment of renal function is very frequent in the elderly and may be overlooked because of normal serum creatinine levels in most patients. Epidemiological studies have linked vitamin D deficiency to higher risk of hypertension, although controlled trials of vitamin D and blood pressure have yielded inconclusive results [3–5]. It is believed that vitamin D acts via the rennin–angiotensin–aldosterone system [6]. Likewise, vitamin D deficiency is associated with higher parathyroid hormone (PTH) levels, and elevated PTH levels are associated with higher blood pressure [7]. Vitamin D might also be beneficial for cardiovascular health by acting as a modulator of the immune system. Jeffery *et al.* [8] demonstrated that stimulation of CD4(+)CD25(−) T cells in the presence of 1,25-dihydroxyvitamin D inhibited production of proinflammatory cytokines, and induced development of Tregs expressing cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and forkhead box P3 (FoxP3). T cells cultured in the presence of both 1,25 dihydroxyvitamin D and IL-2 expressed the highest levels of CTLA-4 and FoxP3. Zold *et al.* [9] investigated the effects of alfacalcidol (1-alpha-hydroxycholecalciferol) to modify the regulatory T-cell functions in patients with undifferentiated connective disease and found that alfacalcidol repaired the $CD4^+CD25^{high}FoxP3^+$ natural Treg (nTreg)/Th17 balance and raised the capacity of nTreg cells to suppress the proliferation of autologous $CD4^+CD25^-$ cells. They showed that 1 μg/day alfacalcidol was the optimal dose in their patients. It could be interesting to evaluate, in experimental models, if alfacalcidol or other preparation of active vitamin D could be helpful to restore the functional activity of Treg cells.

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Conflicts of interest

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Left-ventricular hypertrophy in obesity

Franz H. Messerli[a,b] and Hector Ventura[a,b]

We read with interest the paper by Cuspidi *et al.* [1] on left-ventricular hypertrophy and obesity. The authors state in the 'Introduction' section that 'after this seminal study, a number of studies failed to provide unequivocal findings in terms of prevalence and characteristics of this cardiac phenotype' [2]. This may be correct; however, we would like to emphasize that a full decade

before this seminal study, we unequivocally documented that cardiac adaptation to obesity consists of left-ventricular dilatation and hypertrophy (eccentric hypertrophy) irrespective of arterial pressure levels. In contrast, we showed in the nonobese that hypertension solely produced concentric hypertrophy. These findings were established by M-mode echocardiography by comparing severely obese hypertensive and normotensive patients to lean normotensive and hypertensive patients who were carefully matched for mean arterial pressure, body weight and age. We concluded that 'These pathophysiologic observations give credence to the clinical experience indicating that the combined long-term effects of the two evils (hypertension and obesity) will heavily tax the heart and greatly enhance the patient's risk for developing congestive heart failure' – a conclusion that three decades ago was rather similar to the one put forward in the present meta-analysis by Cuspidi *et al.* [1].

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Response to 'Left ventricular hypertrophy in obesity'

Cesare Cuspidi[a,b], Marta Rescaldani[c], Carla Sala[c], and Guido Grassi[a,d]

We greatly appreciate the interest of Messerli and Ventura [1] in our meta-analysis documenting that left ventricular hypertrophy (LVH), an unhealthy cardiac phenotype associated with increased cardiovascular risk, occurs in more than 50% of obese individuals regardless of their blood pressure status [2]. In the pooled population including more than 5000 obese individuals of both sexes, we also found that eccentric hypertrophy was present in approximately two-thirds of individuals with elevated left ventricular mass.

In our analysis including 22 studies performed in the last decade according to most updated echocardiographic techniques, a notable fraction of obese individuals with LVH exhibited a concentric geometric pattern. At difference from what reported by Messerli *et al.* [3] in their historical article, we did not find that the eccentric pattern, characterized by left ventricular dilatation combined with wall thickening, was the exclusive cardiac response to obesity. In the study by Messerli *et al.* [3], both normotensive and hypertensive obese patients exhibited an eccentric hypertrophy as opposed to lean hypertensive patients who showed only a mild concentric LVH. Despite a careful design, the conclusions provided by the report of Messerli *et al.* [3] supporting a close association between eccentric hypertrophy and obesity should be taken with caution for several reasons. Their observations were based on a very small sample of patients; measurements of left ventricular diameter and thickness only performed by M-mode technique without two-dimensional control; LVH definition based on left ventricular posterior wall thickness (>1.1 cm) rather than on left ventricular mass, a parameter that has been shown to have a better agreement with necropsy-determined left ventricular mass than with nonindexed left ventricular wall thickness. Our analysis was restricted to the time-interval 2000–2013 and included only studies in which LVH phenotype was assessed by modern echocardiographic techniques and LVH was defined by left ventricular mass indexed to body size. For this reason, we cited the study by de Simone *et al.* [4] as the pioneering article in this area. These authors, examining a population-based sample of obese patients, reported that both the eccentric and concentric LVH phenotypes were more prevalent in obese patients than in normo-weighted counterparts. In keeping with the results by de Simone *et al.* [4], our meta-analysis indicated that eccentric LVH was the prevailing geometric response to obesity, but concentric LVH was detected in a notable fraction of obese patients. Finally, it is worth noting that prevalence rates of eccentric and concentric LVH showed a great variability across the studies, probably due to differences in demographic/clinical characteristics of obese individuals examined and echocardiographic criteria used to define left ventricular geometric patterns.

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The enigma of microvascular and macrovascular changes in mild essential hypertension

Eugenia Gkaliagkousi[a], Eleni Gavriilaki[b], and Stella Douma[b]

We read with interest the study by De Ciuceis *et al.* [1] regarding the effects of antihypertensive treatment on oxidative stress, microvascularand macrovascular alterations observed in patients with mild essential hypertension. Although the interplay between microcirculation and macrocirculation represents an innovative research field in the pathophysiology of essential hypertension [2], the present study raises some additional issues that should be taken into consideration.

First, the authors sought to investigate the role of oxidative stress in the development of microvascular and macrovascular alterations. Increased oxidative stress has been reported even in the early stages of essential hypertension [3], although its accurate measurement can be complicated, time-consuming and not representative of the total oxidative burden. In this study, no difference has been found in the markers of oxidative stress; hence, its possible contribution to the improvement of microvascular alterations can neither be confirmed nor be excluded. Methodological issues and the small number of patients may be responsible for these results. However, if the effect of lercanidipine cannot be attributed to its antioxidant properties, then its actual vasodilating effect seems a possible mechanism through which lercanidipine exerts its beneficial action in the vasculature. Bearing this in mind, the present study cannot shed any light on the pathogenetic mechanisms of the beneficial effects of any of the used antihypertensive agents.

Moreover, statistical significant differences were observed only in macrophage chemotactic factor-1, interleukin-18 and C-reactive protein levels in the group randomized to receive the combination of lercanidipine and enalapril. The different effect of the same treatment (lercanidipine alone for 4 weeks) in two randomized groups raises some methodological questions that need to be taken into consideration.

In addition, the authors do not comment on the lack of an anticipated statistically significant reduction in pulse wave velocity following 7 months of antihypertensive treatment. On the basis of previous larger studies regarding the effect of combination therapy on central hemodynamics [4,5], this lack of statistical significance may be attributed to the small sample size of the present study. Thus, the authors should rationalize and comment on their sample size calculation, which focused only on wall-to-lumen ratio of retinal arterioles.

Beyond sample size, another limitation of the present study refers to patient selection. The study population is a rather heterogeneous small group of previously treated patients with an unknown duration of essential hypertension and unknown previous treatments. These factors may also influence microvascular and macrovascular alterations observed in these patients and may account for the different response in antihypertensive agents.

In conclusion, we believe that several limitations of the present study need to be clarified. Further larger studies are warranted in order to address the hypothesized pathophysiological interplay between oxidative stress and vascular changes observed in essential hypertension. Beyond that, the role of microvascular alterations as a prognostic predictor during antihypertensive treatment remains questionable not only because of the lack of available evidence but also because of the limited applicability of laser Doppler flowmetry used in the present study.

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Reply to 'The enigma of micro- and macrovascular changes in mild essential hypertension'

Carolina De Ciuceis, Massimo Salvetti, Maria Lorenza Muiesan, Damiano Rizzoni, and Enrico Agabiti-Rosei

We thank Gkaliagkousi *et al.* [1] for their interest in our article [2]. Our replies to the main points they raised are as follows:

1. Oxidative stress and inflammation are well accepted mechanisms possibly involved in the development of microvascular structural alterations [3,4], although the association between oxidative stress and hypertension may be considered a complex one [5]. The difference observed between the two randomized group in the effects of lercanidipine alone on macrophage chemotactic peptide-1, interleukin-18 and C-reactive protein could be ascribed to the relatively small group of patients evaluated, together with a rather large dispersion of the parameters examined. However, it is our opinion that different effects on oxidative stress/inflammation of the therapeutic strategies explored in our study remain a possible explanation for the observed effects on microvascular and macrovascular structure, although clearly our data cannot directly prove it.
2. As correctly pointed out by Gkaliagkousi *et al.* [1], also the lack of a clear reduction in pulse wave velocity in the two treated groups could be, at least in part, because of the number of patients enrolled. In fact, the sample size calculation was performed on microvascular morphological parameters, as we thought that this was the most interesting and novel aim of the study.
3. In our study, we aimed to examine a real-life situation, enrolling the same kind of patients who are usually seen in an outpatient's clinic. Therefore, the majority of them were previously treated, as untreated patients are rarely seen in clinical practice; our hypertensive patients were, in general, referred to our centre by their general practitioners for optimization of treatment. Previous antihypertensive treatments included angiotensin converting enzyme inhibitors, calcium channel blockers, β-blockers, diuretics, α_1-blockers and angiotensin-receptor blockers, usually administered for short periods. Previous known duration of hypertension was, on average, 3.2 years. The criteria of patient selection could be regarded both as a limitation and as a strength of our study, as evidences obtained may be directly transferred to the average population of hypertensive patients. Frequently, the profile of the patients enrolled in intervention studies is far from being representative of what we see in daily clinical practice, and this may also be considered a problem [6].
4. Finally, the prognostic significance of indices of microvascular alterations, namely the media to lumen ratio of subcutaneous small resistance arteries, is widely accepted, as recognized also by the European Society of Hypertension/European Society of Cardiology guidelines for the management of arterial hypertension [7], in which the need of a noninvasive approach for the evaluation of microvascular morphology, suitable for general use, was also pointed out [7]. The approach used in our study (Scanning Laser Doppler Flowmetry of the retinal vascular district) represents a promising approach for the assessment of microvascular structure, as it appears to be closely related to the well settled micromyographic method [8]; however, a direct demonstration of its prognostic value is, at present, lacking.

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Resistant hypertension revisited: definition and true prevalence

Rodrigo Modolo, Ana P. de Faria, Andréa R. Sabbatini, and Heitor Moreno

Resistant hypertension (RHTN) is a clinical condition pertaining great cardiovascular risk. Its prevalence has been extensively debated and conflicting data regarding its value have been presented, especially because of the difficulties on correctly characterizing one as having true RHTN. These difficulties are mainly from the very strict criteria for determining this condition. We have read with great interest the article by Smith *et al.* [1] showing the predictors of RHTN in a population from the large previous study INVEST (The International Verapami–Trandolapril Study) [2]. Smith *et al.* showed with these data a high prevalence (38%) of RHTN among the 17 190 hypertensive patients included in his analysis.

Interestingly, the prevalence of RHTN shown in the article is especially high, in contrast with the prevalence found in studies dedicated to this specific condition. In fact, data from outcome studies such as the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) [3], Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [4], Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) [5] and Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) [6] show that RHTN may be more prevailing than it was believed. However, we would like to point out that the true prevalence of this condition may be much lower, and it is overestimated in the given study due to some specific inconsistencies in the methodology for assessing RHTN.

The definition widely used was proposed by Calhoun *et al.* [7], in which RHTN is when blood pressure levels remain uncontrolled despite the use of at least three antihypertensive drugs or when its control is dependent on the use of four or more drugs, ideally with one diuretic. Although Smith *et al.* used adequately this definition, they used data from a large previous study initiated over 10 years ago. Consequently, causes of pseudoresistance (that may be responsible for up to 90% of all cases [8]) were not properly assessed. Interpreting these data with focus on RHTN can be misleading, and must be done cautiously. Moreover, over 5000 patients (who had controlled BP and not taking more than three drugs) were excluded for the final analysis overestimating the real prevalence of RHTN.

The INVEST trial was not designed to investigate RHTN. RHTN has a much complex phenotype, demanding a strict protocol of adherence, exclusion of secondary causes, optimization of the prescribed drugs, and a previous follow-up to correctly diagnose this condition. For instance, some patients in a three-drug regime might have this prescription because either they did not control with two drugs in optimal doses or their prescribing physician chose to add a third or fourth drug to the previous regime only to have an antihypertensive combination even in lower doses – overestimating the prevalence of RHTN. Using strict criteria, Acelajado *et al.* [9] have graciously shown that only 9% of all patients referred to a RHTN clinic are in fact truly resistant.

When evaluating RHTN, analysis of the data from registries, cohorts and large trials designed for other purposes requires great caution. However, none of these raised criticisms diminishes the important message from the study conducted by Smith *et al.*

We feel that the associations found by Smith *et al.* are important in order to identify predictors of RHTN in a population at risk – such as coronary artery disease and hypertensive patients – in order to call more attention to their antihypertensive treatment.

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Reply to 'Resistant hypertension revisited: definition and true prevalence'

Steven M. Smith[a,b], Carl J. Pepine[c], and Rhonda M. Cooper-DeHoff[a,c]

We appreciate Dr Modolo *et al.*'s [1] interest in our recent work regarding resistant hypertension in patients with hypertension and coronary artery disease (CAD). They appear to be primarily concerned about the high prevalence of resistant hypertension (38%) that we observed, and suggest that figure may overestimate the true resistant hypertension prevalence [2].

It is critically important to understand that the epidemiology of resistant hypertension is highly specific to the characteristics of population under evaluation, as well as the intensity of treatment, since the latter is part of the definition. In the general outpatient population with newly diagnosed hypertension, the estimate of resistant hypertension incidence is very low (1% to <2% over a median 1.5 years) [3]. Likewise, in the general hypertensive population, resistant hypertension prevalence is estimated at only 8–12% [4]. However, in clinical situations specifically focused on achieving blood pressure (BP) control, the resistant hypertension prevalence is much higher. Studies of cohorts with multiple additional risk conditions, in which medications are provided free, titration required per protocol, and adherence to treatment monitored, document that resistant hypertension may be present in 30% or more of patients. For example, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), with more than 33 000 participants who were at least 55 years old with other cardiovascular disease (CVD) risk factors, 27% of all participants required at least three BP medications, and, in certain subgroups [e.g. those with left-ventricular hypertrophy (LVH) or creatinine $\geq$1.5 mg/dl], more than 40% of participants required at least three BP medications [5]. Similarly, as we observed in the International Verapamil-Trandolapril Study (INVEST), which included more than 22 500 patients with known CAD, 29% had above-goal BP and 50% required at least three BP medications [6]. These population characteristics result in a high prevalence of resistant hypertension as evidenced in our analysis [2]. Finally, in hypertension specialty clinics where up-titration of antihypertensive medications occurs regularly, the resistant hypertension prevalence may exceed 4 of every 10 patients [7]. These data also support our contention that cross-sectional reports of resistant hypertension prevalence, in many settings, underestimate the true prevalence of resistant hypertension. Said another way, undertreatment of hypertension masks the true prevalence of resistant hypertension.

The prevalence of resistant hypertension was predicted to increase due to increased life expectancy and increases in the prevalence of factors [e.g. obesity, diabetes, chronic kidney disease (CKD)] associated with resistant hypertension. Indeed, this seems to be the case based upon epidemiologic data from the National Health and Nutrition Examination Survey (NHANES), where the prevalence of resistant hypertension increased from 15.9% in 1998–2004 to approximately 28% in 2005–2008 [8].

More importantly, though, we must not lose sight of the primary reason to determine who has resistant hypertension: to identify those hypertensive patients at high risk for adverse outcomes. Clearly, many patients have multiple other conditions that reflect more severe cardiovascular disease (e.g. heart failure, LVH, prior stroke or transient ischemic attack, or peripheral arterial disease), and these risk conditions impart excess risk for adverse outcomes. But some may have only diabetes, CKD, obstructive sleep apnea, increased BMI or be of Black race, elderly or female, as we pointed out in our analysis [2].

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Conflicts of interest

There are no conflicts of interest.

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