Review Article

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Refractory and Resistant Hypertension: Antihypertensive Treatment Failure versus Treatment Resistance

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Resistant hypertension has for many decades been defined as difficult-to-treat hypertension in order to identify patients who may benefit from special diagnostic and/or therapeutic considerations. Recently, the term "refractory hypertension" has been proposed as a novel phenotype of antihypertensive failure, that is, patients whose blood pressure cannot be controlled with maximal treatment. Early studies of this phenotype indicate that it is uncommon, affecting less than 5% of patients with resistant hypertension. Risk factors for refractory hypertension include obesity, diabetes, chronic kidney disease, and especially, being of African origin. Patients with refractory are at high cardiovascular risk based on increased rates of known heart disease, prior stroke, and prior episodes of congestive heart failure. Mechanisms of refractory hypertension need exploration, but early studies suggest a possible role of heightened sympathetic tone as evidenced by increased office and ambulatory heart rates and higher urinary excretion of norepinephrine compared to patients with controlled resistant hypertension. Important negative findings argue against refractory hypertension being fluid dependent as is typical of resistant hypertension, including aldosterone levels, dietary sodium intake, and brain natriuretic peptide levels being similar or even less than patients with resistant hypertension and the failure to control blood pressure with use of intensive diuretic therapy, including both a long-acting thiazide diuretic and a mineralocorticoid receptor antagonist. Further studies, especially longitudinal assessments, are needed to better characterize this extreme phenotype in terms of risk factors and outcomes and hopefully to identify effective treatment strategies. **(Korean Circ J 2016;46(5):593-600)**

KEY WORDS: Resistant hypertension; Refractory hypertension; Sympathetic nervous system; Spironolactone.

Introduction

The term "resistant hypertension" has been used for many decades to identify a group of patients with difficult-to-treat hypertension.[1] The phenotype has been largely defined as failure to control blood pressure in spite of use of 3 or more antihypertensive agents, including, if possible, a diuretic.[2] Especially early on when the terms were first being applied, refractory hypertension was used interchangeably with resistant hypertension to refer to the same group of difficult-to-treat patients.[3][4] While there continues to be overlap, it seems recently that the term resistant hypertension has been used more preferentially and refractory hypertension is being used less frequently.

Recently it has been proposed that the two terms be applied in a divergent fashion, with refractory hypertension being applied to an even more extreme phenotype of antihypertensive failure.[5] As such, refractory hypertension would represent a severe subgroup of resistant hypertension. In this review article, we discuss the emerging data pertaining to this novel phenotype of antihypertensive treatment failure and how it compares and contrasts with resistant hypertension in terms of definition, prevalence, patient characteristics, risk factors, comorbidities, and possible underling etiologies.

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Definition

Resistant hypertension

Resistant hypertension has been consistently defined for many decades as high blood pressure requiring more than 3 medications for treatment, ideally, one of which, is a diuretic.[1)6)] The American Heart Association (AHA) Scientific Statement published in 1988, expanded the definition to include patients whose blood pressure is eventually controlled, but required 4 or more medications to do so, i.e., so-called "controlled resistant hypertension".[2)]

Refractory hypertension

The term "refractory hypertension" has been applied with reference to an extreme subgroup of patients failing antihypertensive treatment in four separate scientific publications. Already, during the short duration between these four publications, the definition of refractory hypertension has evolved. While in all cases the term was applied in an attempt to identify patients failing maximum antihypertensive therapy, in the first iteration of the term, refractory hypertension was defined as hypertension uncontrolled with use of five or more antihypertensive agents from different classes that were otherwise unspecified.[5)7)8)] Based on published studies demonstrating the superiority of chlorthalidone over hydrochlorothiazide (HCTZ) and a large body literature strongly confirming the preferential benefit of spironolactone for treatment of resistant hypertension, with the most recent application of the term, the definition of refractory hypertension required absence of blood pressure control when treated with five or more antihypertensive agents, including specifically, use of a long-acting thiazide diuretric such as chlorthalidone and a mineralocorticoid receptor antagonist (MRA), such as spironolactone.[9)] As such, the most recent working definition of the term has become more specific in requiring, in addition to a combined total of five or more antihypertensive classes of agents, failure of an intensive antidiuretic combination as such chlorthalidone and spironolactone.

Prevalence

Resistant hypertension

Cross-sectional studies have been largely consistent in indicating that resistant hypertension based solely on the number of medications prescribed has a prevalence of 10-20% of patients being treated for hypertension. For example, in a cross-sectional analysis of a very large, ethnically diverse cohort in the United States, Sim et al.[10)] evaluated individuals enrolled in the Kaiser Permanente South California health care system. Over 470000 individuals were included in the analysis, of whom, 15.3% had resistant hypertension based on the AHA definition. In a European based study, de la Sierra et al.[11)] analyzed a database of hypertensive patients that had been included in the Spanish Ambulatory Blood Pressure Monitoring Registry. Of the 68045 included in the analysis that were being treated for hypertension, approximately 15% had resistant hypertension also based on the AHA definition of resistant hypertension, i.e., clinic blood pressure levels >140/90 mmHg while receiving 3 or more antihypertensive agents, including a diuretic, or clinic blood pressure levels <140/90 mmHg on four or more antihypertensive agents.

Longitudinal analyses indicate that the prevalence of resistant hypertension has increased dramatically over the last several decades. Utilizing data from the ongoing National Health and Nutrition Examination Survey (NHANES), Roberie and Elliott[12)] estimated that the prevalence of apparent resistant hypertension in the United States increased from 8.8% in 1988-1994 to 14.5% in 1999-2004, and then most recently, up to 20.7% in the years 2005-2008. The rapid increase in the estimated prevalence rates suggests that resistant hypertension may represent one of the fasting growing subgroups of hypertension. Explanation for the increasing rates of resistant hypertension have not been fully elucidated, but are no doubt related to associated increases in common risk factors for development of resistant hypertension, including older age, obesity, and chronic kidney disease (CKD).

Refractory hypertension

Among the four currently published studies on refractory hypertension, the estimated prevalence rates have ranged from approximately 5 to 30% of patients with resistant hypertension. In the initial study of refractory hypertension,[5)7-9)] a retrospective analysis of over 300 patients referred to the University of Alabama at Birmingham Hypertension Clinic for resistant hypertension, approximately 10% of the patients with adequate follow-up never achieved blood pressure control in spite of us of five or more antihypertensive agents.[5)] Later, when the same group of investigators at the University of Alabama at Birmingham published a prospective analysis of over 700 patients referred for resistant hypertension, only 29 or approximately 4% were identified as having refractory hypertension.[9)] There was an important distinction between studies in how refractory hypertension was defined. In the earlier, retrospective analysis, refractory hypertension was based only on needing five or more antihypertensive medications, without specifying classes of agents used. In the later, prospective analysis, refractory hypertension was defined more stringently, that is, patients had to be failing regimens incorporating five or more agents, including, chlorthalidone and spironolactone. That

requirement of obligatory use of an intensive diuretic regimen likely facilitated better control rates, resulting in less cases of treatment failure.

In the study by Modolo et al.,[8] refractory hypertension was also based solely on the number of medications, i.e., five or more. In this cross-sectional analysis of 116 patients with resistant hypertension, 31% were uncontrolled on five more medications. All of the refractory patients were receiving a diuretic and most were receiving spironolactone (76%).

The remaining study of refractory hypertension published so far was a cross-sectional evaluation of participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a large (n=30239), community-based cohort study.[7] In this analysis, refractory hypertension was defined as uncontrolled hypertension office blood pressure despite use of 5 or more different classes of agents. Diuretic use, including specifically chlorthalidone and spironolactone, was not required as part of the definition. The prevalence of refractory hypertension was 3.6% of patients with resistant hypertension (uncontrolled with three or more medications or controlled on four or more medications) and 0.5% of all hypertensive participants. While all of the REGARDS participants identified as having refractory hypertension were receiving a diuretic (either HCTZ or furosemide), none were receiving chlorthalidone or spironolactone.

The currently published studies of refractory hypertension have so far indicated a wide, estimated prevalence from as low as 5% to as high as 30% of patients originally referred for resistant hypertension. The wide discrepancy is no doubt related to important differences in the analyzed cohorts and to how refractory hypertension was defined. Requiring use of chlorthalidone and spironolactone before considering a patient to be failing antihypertensive treatment, clearly substantially reduces the occurrence of refractory hypertension.

Apparent versus True

Resistant hypertension

The estimates of prevalence rates of resistant hypertension discussed above are based solely on clinic blood pressure levels and the number of prescribed antihypertensive medications. The estimates do not account for common causes of so-called pseudo-treatment resistance including white coat effects, poor medication adherence, or under treatment. Accordingly, estimates of prevalence rates of resistant hypertension based solely on the number of prescribed medications without having corrected for causes of pseudo-resistance are described as reporting the prevalence of "apparent" resistant hypertension. Correcting for these factors results in lower estimated rates and better approximate the prevalence of "true" resistant hypertension.

A number of recent studies have attempted to quantify the role that these different causes of pseudo-resistance play in falsely elevating the rate of apparent versus true resistant hypertension. The studies have generally looked at the possible factors individually as opposed to collectively. For example, in the de la Serra et al.[11] discussed above that was based on individuals included in the Spanish Ambulatory Blood Pressure Monitoring Registry, it was reported that almost 38% of the patients with apparent resistant hypertension had white coat resistant hypertension (i.e., blood pressure elevated in clinic but controlled outside of clinic) meaning the prevalence of true resistant hypertension was only 62.5% of individuals having apparent resistant hypertension based solely on clinic blood pressure levels.

Studies assessing medication adherence suggest that poor adherence with prescribed antihypertensive medications is a very common cause of apparent versus true resistant hypertension. For example, Jung et al.[13] recently reported that of 76 patients referred to a hypertension specialty clinic for resistant hypertension, 53% were non-adherent with their antihypertensive medications based on toxicological testing of the patients' urine for the prescribed medications or their corresponding metabolites. Of those non-adherent, 30% were taking none of their medications according to the toxicological results.

Under treatment is likewise a common cause of apparently but not truly resistant hypertension. In an evaluation of >200 community-based clinics in the Southeast United States based on data collected through an electronic medical record network, Egan et al.[14] identified 44684 patients whose blood pressure remained uncontrolled while being prescribed 3 or more antihypertensive agents. Of these, only 15% were considered to have been prescribed an optimal regimen based on use of a diuretic and all agents being prescribed at least 50% of the maximum recommended dose for treatment of hypertension.

Unlike studies that attempted to quantify causes of pseudo-treatment resistance individually, Grigoryan et al.[15] looked all three factors in systematically quantifying the prevalence of white coat resistant hypertension, poor medication adherence, and under treatment in a cohort of patients with apparent resistant hypertension. The authors did a post-hoc evaluation of patients who had completed a randomized, multi-center study designed to assess clinical inertia and blood pressure control. Overall, 69 patients with resistant hypertension based on office blood pressure levels, who had undergone 24-hr ambulatory blood pressure monitoring and whose adherence with prescribed antihypertensive

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agents had been monitored by an electronic pill bottle monitoring system, were included in the evaluation. Of these subjects, 22% had controlled ambulatory blood pressure levels and so had white coat resistant hypertension and 29% were non-adherent with their prescribed medications. The remaining 49% of patients were confirmed to have true resistant hypertension based on having elevated ambulatory blood pressure levels and having been adequately adherent with their medications.

However, Grigoryan et al.[15] further reported that most of the patients with seemingly true resistant hypertension were not receiving what would be considered effective antihypertensive regimens. While 91% of the patients were receiving a diuretic (either HCTZ or furosemide), none were receiving chlorthalidone, and even worse, none of the subjects were receiving an MRA. Further, use of the maximum doses of calcium channel blockers and angiotensin converting enzyme inhibitors or angiotensin receptor antagonists, which have a relatively small dose range and are generally well tolerated even at high doses, was only 15 to 40%, respectively. Overall, the findings of Grigoryan et al.[15] and other recent studies indicate that the prevalence of true resistant hypertension is likely less than 50% of the estimates of the prevalence of apparent resistant hypertension.

Refractory hypertension

Determinations of apparent versus true refractory hypertension have not yet been systematically done. Rigorous determinations of adherence based on measurement of serum or urinary drug levels are absent. Likely, the prevalence medication non-adherence among patients with refractory hypertension will be high as with resistant hypertension, but the actual rate awaits determination. Two of the published studies on refractory did report white coat effects based on having done 24-hr ambulatory monitoring.[8][9] Modolo et al.[8] reported that patients with refractory hypertension were more likely to have a prominent white effect (≥20/10 mmHg ambulatory versus office blood pressure levels) than patients with controlled or uncontrolled resistant hypertension, but without having specified the number or percentage of patients with white coat refractory hypertension. Dudenbostel et al.,[9] in their study, reported that 24-hr ambulatory blood pressure levels were significantly higher in patients with refractory versus controlled resistant hypertension, but without reporting the degree or white coat effect or prevalence of white coat refractory hypertension. Accordingly, while multiple studies indicate that causes of pseudo-resistance are common in patients with resistant hypertension, the degree to which these same factors are present in patients with refractory hypertension has not yet been quantified.

Patient Characteristics and Associated Comorbidities

Resistant hypertension

A number of observational studies have characterized patients with resistant from variety of different cohorts. The largest analysis is likely the evaluation by Sim et al.[10] of over 470000 individuals with hypertension enrolled in the Kaiser Permanente Southern California health care system between January 1, 2006 and December 31, 2007. Overall, 60327 hypertensive individuals met the criteria for resistant hypertension. This accounted for 12.8% of all hypertensive individuals and 15.3% of those taking medications.

Compared to individuals with non-resistant hypertension, that is, controlled blood pressure with 1 or 2 medications, individuals with resistant hypertension were older, more likely obese, and more likely African American. In addition, individuals with resistant hypertension had a greater prevalence of comorbid conditions, including diabetes, ischemic heart disease, cerebrovascular disease, and CKD. These findings are consistent with multiple other studies demonstrating that African American race, older age, and being overweight or obese are common risk factors for having resistant hypertension.[11][12][16][17] The same studies also indicate that patients with resistant hypertension are more likely to have been diagnosed with diabetes, CKD, left ventricular hypertrophy (LVH), and prior stroke compared to patients with more easily controlled hypertension.

Refractory hypertension

In the cross-sectional analysis of the REGARDS cohort discussed above, the strongest predictor of having refractory hypertension was being of African American race with a prevalence ratio of 4.88 (95% confidence interval, 2.79-8.72).[7] Being of African origin was also a strong independent risk factor for having refractory hypertension in study by Modolo et al.[8] In both of the studies from the University of Alabama, refractory hypertension was more common in African Americans than in Caucasian patients.[5][9] In the REGARDS analysis, being overweight or obese also significantly increased risk of having refractory hypertension compared to all hypertensive participants.[7]

The REGARDS analysis further indicated that patients with refractory hypertension were more likely to have a history of diabetes, CKD, known coronary heart disease, and prior stroke compared to all hypertensive participants.[7] Modolo et al.[8] reported a higher prevalence of LVH quantified by echocardiogram compared to patients with resistant hypertension. Acelajado et al.[5] in their retrospective study and Dudenbostel et al.[9] in their prospective analysis found that patients with refractory hypertension were

much more likely to have been hospitalized for congestive heart failure (CHF) than patients with controlled resistant hypertension. Overall, these studies indicate, like resistant hypertension, strong independent risk factors for developing refractory hypertension include obesity and being of African origin. Also similar to resistant hypertension, comorbidities commonly associated with refractory hypertension include diabetes, CKD, heart disease, and prior stroke.

Prognosis

Resistant hypertension

An increasing number of longitudinal and prospective studies clearly demonstrate that patients with resistant hypertension have an increased risk of cardiovascular and renal complications and all-cause mortality compared to patients with more easily controlled hypertension. For example, investigators evaluated the risk of incident stroke and coronary heart disease (CHD) and all-cause mortality among 2043 REGARDS participants with resistant hypertension relative to 12279 REGARDS participants with controlled hypertension being treated <4 antihypertensive medication classes or uncontrolled hypertension treated with 1 or 2 antihypertensive medication classes.[18][19] Resistant hypertension was stratified into two subgroups, including participants with controlled hypertension on ≥4 antihypertensive medication classes (i.e., controlled resistant hypertension) and uncontrolled hypertension on ≥3 antihypertensive medication classes (i.e., uncontrolled resistant hypertension). During a median follow-up of 5.9 years and after multivariable adjustment, the risk of incident stroke was increased by 25% (hazard ratio, 1.25; 95% confidence interval, 0.94-1.65) compared to participants without resistant hypertension.[18] During a median follow-up of 4.4 years, incident CHD was increased by 69% (1.69; 1.27-2.24) and all-cause mortality by 29% (1.29; 1.14-1.46) during a median follow-up of 6.0 years. Compared with controlled resistant hypertension, uncontrolled resistant hypertension was associated with increased risk of CHD (2.33; 1.21-4.48), but not stroke or mortality. Having resistant hypertension that was controlled did not increase risk of stroke, CHD, or mortality compared to participants without resistant hypertension.

In an analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, investigators determined the risk of incident stroke, CHD, peripheral artery disease (PAD), end-stage renal disease (ESRD), and all-cause mortality in participants with controlled or uncontrolled resistant hypertension (n=1870) versus participants without resistant hypertension (n=12814) defined as controlled blood on ≤3 antihypertensive medications.[20] The average follow-up was 4.9 years. Incidence of all outcomes as well as all-cause mortality was increased in participants with resistant hypertension. Increased risk was highest for development of ESRD (95%), CHF (88%), and stroke (57%). Risk of incident CHD and PAD was increased by 44% and 23%, respectively. All-cause mortality was increased by 30% compared to participants without resistant hypertension. Interestingly, the crude incidence rates for CHD, CHF, PAD and ESRD were each higher among participants with controlled resistant hypertension compared to participants without resistant hypertension, suggesting a residual risk for incident cardiovascular and renal disease even after blood is controlled but with use of 4 or more medications. These two studies, as well as other prospective studies, clearly indicate that hypertension that requires 4 or more medications substantially increases risk of cardiovascular and renal complications and as well as death compared to hypertension that is controlled with use of 3 or less medications.[18][20-23]

Refractory hypertension

Outcomes, including mortality, have not yet been assessed in patients with refractory hypertension. Given the history of long-standing, uncontrolled and often severe hypertension as well as the greater risk of prior cardiovascular complications including stroke and CHF, it seems intuitive that patients with refractory hypertension suffer a higher incidence of CV complications and death than patients with controlled hypertension. However, demonstration of such higher risk is current absent.

Mechanisms of Resistant versus Refractory Hypertension

A large body of literature implicates persistent intravascular fluid retention as a common underlying cause of resistant hypertension. For example, Taler et al.[24] demonstrated that patients with true resistant hypertension were characterized by increased intravascular expansion as estimated by thoracic fluid content. In turn, multiple studies have linked this persistent fluid retention to hyperaldosteronism, both classical primary aldosteronism and lesser degrees of aldosterone excess.[25-28] Additional factors likewise contributing to the inappropriate fluid retention that characterizes resistant hypertension include factors common to resistant hypertension known to increase salt sensitivity, including African American race, older age, CKD, and diabetes. Separately, a high salt diet, typical now of most countries worldwide, has been shown to contribute directly to excess fluid retention and development of resistant hypertension, although excess fluid retention has

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not always been observed in association high dietary salt intake in animal models of hypertension and generalized hypertensive cohorts.[29)30)]

The underlying role that inappropriate fluid retention plays in causing resistant hypertension is further supported by the importance of effective diuretic use in overcoming treatment resistance, including especially, use of an MRA. The importance of effective diuretic use in treating resistant hypertension is underscored by the fact that the diagnosis of resistant hypertension has generally required use of a multi-drug regimen that includes a diuretic, and more recently, it has been suggested that the definition should be updated to include failure of a combined regimen that includes both a long-acting thiazide-like diuretic, specifically chlorthalidone, and an MRA, such as spironolactone.

In contrast to resistant hypertension, refractory hypertension may represent a different phenotype in terms of etiology in not being volume dependent. The retrospective analysis by Acelajado et al.[5)] indicated that persistent intravascular fluid retention is unlikely to explain the observed antihypertensive failure as all individuals with refractory hypertension were failing combined use of chlorthalidone and spironolactone, along with most other classes of agents. Further, in spite of considerably higher baseline blood pressure levels, the antihypertensive response to adding spironolactone was considerably less in individuals with refractory hypertension compared to individuals whose blood pressure could be controlled (<140/90 mmHg). This lesser effect was observed even with use of higher doses of spironolactone than used in the control group. Failing this more intensive diuretic use, including higher doses of spironolactone, would suggest a mechanism of treatment failure separate from inappropriate fluid retention. If true, such a distinction would have important clinical implications, as further intensification of diuretic therapy would be unlikely to provide any better blood pressure control while increasing risk of diuretic-related adverse events.

The Acelajado et al.[5)] analysis provided preliminary evidence that antihypertensive failure may be more neurogenic in etiology, i.e., heightened sympathetic tone, as opposed to being volume dependent. This evidence was based on an observation of consistently higher resting heart rates in individuals with refractory hypertension compared to individuals with controlled resistant hypertension. The higher heart rates persisted even after increased use of beta blockers in the former group. The retrospective analysis by Modolo et al.[8)] also provided findings consistent with heightened sympathetic tone as an underlying cause of antihypertensive treatment failure. Although 24-hr ambulatory heart rate levels were not different, patients with refractory hypertension did manifest a larger white coat effect, a phenomenon that the authors interpreted as potentially reflecting increased sympathetic nervous system activity.

The Dudenbostel et al.[9)] study represents the first prospective characterization of refractory hypertension as a unique phenotype. In this study, the higher office heart rate reported by Acelajdo et al.[5)] in patients with refractory hypertension was again observed. In addition, higher heart rate levels were confirmed by ambulatory blood pressure monitoring, with the biggest difference being at night (72.7±9.0 vs. 65.6±9.0 beats/min, refractory vs. controlled resistant hypertension). Evidence of heightened sympathetic stone was further supported by patients with refractory hypertension having significantly higher levels of norepinephrine excretion measured from 24-hr urine collections.[9)] Also reported, was a higher pulse wave velocity in patients with refractory hypertension.

The prospective evaluation also confirmed important negatives in terms of underlying mechanisms of refractory hypertension. Patients with refractory hypertension were not older, were not more obese, did not have higher aldosterone levels, and were not ingesting higher levels of dietary sodium compared to patients with controlled resistant hypertension.[9)] In addition, thoracic fluid content, as measure by thoracic impedance, was not different between the two groups, suggesting that were not differences in intravascular fluid retention. In total, these negative findings argue against excessive fluid retention as being an important mediator of antihypertensive treatment failure compared to patients with resistant but controlled hypertension.

Conclusion

Refractory hypertension is being proposed as a novel phenotype of antihypertensive treatment failure. While evolving, the definition of the phenotype has most recently been defined as the inability to control blood pressure with use of five or more different antihypertensive classes, including a long-acting thiazide diuretic and a MRA. Initial studies suggest that risk factors for the phenotype include obesity, CKD, being of African origin, and possibly, female gender. Patients with refractory hypertension, like the larger subgroup of patients with resistant hypertension, have evidence of more advanced target organ damage compared to patients whose blood pressure can be controlled, include higher rates of CKD, LVH, CHF, and prior stroke. Given its history of uncontrolled and often severe hypertension, having refractory hypertension likely portends a poor prognosis, but outcome studies specific for the phenotype are currently lacking.

Preliminary findings suggest that refractory and resistant hypertension may different importantly in terms of their underlying

etiology. Resistant hypertension has been largely attributed to persistent intravascular fluid retention, necessitating intensive diuretic therapy for effective management. In contrast, patients with refractory hypertension are by definition, failing intensive diuretic therapy as well as all other classes of agents, suggesting underlying mechanisms of antihypertensive treatment failure distinct from excessive fluid retention. Higher office and ambulatory heart rate values and greater excretion rates of norepinephrine provide preliminary evidence of heightened sympathetic tone as a potentially important cause of antihypertensive treatment failure. Additional studies are clearly needed to better define and characterize the phenotype in order to identify more effective treatment strategies for this rare for extremely high-risk subgroup of hypertensive patients.

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