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Current controversies in determining the main mechanisms of atrial fibrillation

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Abstract. Schotten U, Dobrev D, Platonov PG, Kottkamp H, Hindricks G (Cardiovascular Research Institute Maastricht, Maastricht Centre of Systems Biology, Maastricht University, Maastricht, The Netherlands; Institute of Pharmacology, West German Heart and Vascular Center, School of Medicine, University Duisburg-Essen, Essen, Germany; Center for Integrative Electrocardiology at Lund University (CIEL) and Arrhythmia Clinic, Skåne University Hospital, Lund, Sweden; Klinik Hirslanden, Zürich, Switzerland; and Department of Cardiac Electrophysiology, Heart Center, University of Leipzig, Leipzig, Germany). Current controversies in determining the main mechanisms of atrial fibrillation (Review Symposium). J Intern Med 2016; 279: 428–438.

Despite considerable basic research into the mechanisms of atrial fibrillation (AF), not much progress has been made in the prognosis of patients with AF. With the exception of anticoagulant therapy, current treatments for AF still do not improve major cardiovascular outcomes. This may be due partly to the diverse aetiology of AF with increasingly more factors found to contribute to the arrhythmia. In addition, a strong increase has been seen in the technological complexity of the methods used to quantify the main pathophysiological alterations underlying the initiation and progression of AF. Because of the lack of standardization of the technological approaches currently used, the perception of basic mechanisms of AF varies widely in the scientific community. Areas of debate include the role of Ca2+-handling alterations associated with AF, the contribution and noninvasive assessment of the degree of atrial fibrosis, and the best techniques to identify electrophysiological drivers of AF. In this review, we will summarize the state of the art of these controversial topics and describe the diverse approaches to investigating and the scientific opinions on leading AF mechanisms. Finally, we will highlight the need for transparency in scientific reporting and standardization of terminology, assumptions, algorithms and experimental conditions used for the development of better AF therapies.

Keywords: atrial fibrillation, Ca2+-handling, fibrosis, multiple wavelet hypothesis, rotors.

Introduction

Since the 1990s there has been a tremendous increase in basic research to investigate the mechanisms of atrial fibrillation (AF) with increasing attention from the scientific community in terms of both allocated resources and scientific output. While the resulting understanding of the pathomechanisms of AF has grown steadily, the major clinical outcomes of AF patients have improved only marginally. Antiarrhythmic drug treatment can often not prevent recurrences of AF. Catheter ablation, originally developed for treatment of paroxysmal AF, has a limited efficacy in patients with persistent AF and anticoagulation therapy, even since the introduction of the novel oral anticoagulants, is still associated with potentially harmful side effects.

The lack of improvement in clinical outcomes in AF may partially reflect our inability to detect individual disease mechanisms underlying the arrhythmia in individual patients. The multifactorial aetiology of AF has been recognized for many
years but so far individual disease mechanisms cannot be reliably identified by easily accessible clinical signs and symptoms [1]. Closing this ‘translational gap’ by linking the diverse pathomechanisms to sets of phenotypic features in patients is among the most important challenges in cardiac research in general and in the field of AF in particular [2].

Another reason for the slow improvement of current AF therapies may be related to the complexity of the basic research related to this field. Very different and increasingly more sophisticated technological approaches are being used to unravel basic AF mechanisms. Definitions, assumptions and algorithms used in these technical approaches vary widely and have resulted in fundamentally different perceptions even of very basic mechanisms of AF.

Here, we will provide a brief overview of some of these controversial areas of AF research. Specifically, we will discuss the contribution of Ca$^{2+}$-handling alterations and the role of atrial fibrosis in AF as well as the still debated issue of the prevailing conduction patterns during AF.

**Ca$^{2+}$-handling instability versus Ca$^{2+}$-signalling silencing**

It is likely that the limited efficacy of current pharmacological treatment options result from an incomplete understanding of AF pathophysiology. Focal ectopic firing is required for the initiation of AF in a vulnerable substrate, but can also maintain AF when it occurs repetitively at a high frequency. While reentry is a well-accepted mechanism of AF, the contribution of ectopic (triggered) activity caused by delayed afterdepolarizations (DADs), which depend on abnormalities of Ca$^{2+}$ handling, is less clear and somewhat controversial [3].

Recent studies in small and large animal models of AF have provided evidence for and insights into the potential molecular basis of DAD-mediated triggered activity. Important roles for ryanodine receptor (RyR2) dysfunction, increased sarcoplasmic reticulum (SR) Ca$^{2+}$ leak and spontaneous Ca$^{2+}$-release events in pacing-induced AF have been suggested by the results of experimental studies in mice lacking the RyR2-stabilizing subunit FKBP12.6, carrying an E169K mutation in junctophilin-2 or with gain-of-function mutations predisposing to catecholaminergic polymorphic ventricular tachycardia (CPVT) [4–7]. Pharmacological inhibition of Ca$^{2+}$/calmodulin-dependent protein kinase type-II (CaMKII), genetic inhibition of CaMKII-dependent RyR2-Ser2814 phosphorylation and the RyR2-stabilizing compound S107 prevent AF initiation in FKBP12.6 knock-out mice, also supporting a critical role for RyR2 dysfunction in AF vulnerability [6–8].

Findings from large animal models of AF also indicated a role of Ca$^{2+}$-handling abnormalities in AF pathophysiology. Dogs with persistent AF show hyperphosphorylated RyR2 and increased RyR2 open probability [9]. Experimental heart failure increases SR Ca$^{2+}$ load and promotes cellular triggered activity, which involves increased CaMKII but reduced RyR2 expression with unaltered phosphorylation [10]. In goats with persistent AF, SR Ca$^{2+}$ uptake is reduced, whereas CaMKII-dependent RyR2 phosphorylation is increased, which is likely to increase SR Ca$^{2+}$ leak [11]. Ca$^{2+}$-handling abnormalities along with a higher incidence of DADs also occur in right atrial cardiomyocytes from patients with persistent AF, suggesting Ca$^{2+}$-handling instability in AF patients [12–14]. Increased CaMKII function with subsequent CaMKII-dependent RyR2 hyperphosphorylation appears to play a key role in diastolic SR Ca$^{2+}$ leak and cellular triggered activity in patients with persistent AF [7, 13, 14]. Taken together there is now compelling evidence in animal models and in patients for a role of DAD-mediated cellular triggered activity in patients with persistent AF. However, despite the occurrence of DADs and cellular triggered activity in human atrial cardiomyocytes from patients with persistent AF in vitro, it is not clear whether DADs can also occur during AF in vivo and, if so, how they contribute to the fibrillatory process maintaining AF (Fig. 1).

There is evidence from a rabbit model that sustained high atrial activation rates per se do not increase SR Ca$^{2+}$ leak despite hyperphosphorylation of the RyR2 [15]. Computational analysis suggested that the strongly reduced RyR2 expression in this model may offset the effects RyR2 hyperphosphorylation on SR Ca$^{2+}$ leak. Ca$^{2+}$-wave propagation to the myocyte centre was impaired in both rabbits and patients with persistent AF, which is likely to be due to an increase in Ca$^{2+}$-buffering strength along with a reduction in intracellular Na$^{+}$ concentration following rapid atrial pacing. Atrial tachycardia remodelling in dogs also induces impaired Ca$^{2+}$-wave propagation to the cell centre [16]. Together, these data suggest that sustained high atrial rates per se may not produce Ca$^{2+}$-handling instability and...
indicate the possibility that these Ca\textsuperscript{2+}-handling abnormalities including increased SR Ca\textsuperscript{2+} leak in patients with persistent AF might result from the accompanying cardiovascular diseases rather than from AF itself. In addition, it appears that once AF persists the high atrial rate may cause Ca\textsuperscript{2+}-handling silencing to counteract the potentially cytotoxic effects of chronically elevated intracellular Ca\textsuperscript{2+} levels. Therefore, it could be speculated that depending on the underlying cardiovascular conditions, either proarrhythmic Ca\textsuperscript{2+}-handling abnormalities or arrhythmia-suppressing Ca\textsuperscript{2+}-handling silencing might prevail, highlighting the need for appropriate substrate classification and tailored Ca\textsuperscript{2+}-handling targeting in an individual AF patient.

Na\textsuperscript{+} homeostasis has a very important impact on the function of various ion channels and transporters [17]. Findings from experimental models suggest that atrial tachycardia and AF reduce Na\textsuperscript{+} load [15] which, if also the case in human AF, paradoxically may contribute to Ca\textsuperscript{2+} depletion and prolongation of the action potential.

Another inconsistency in the field is the discrepancy between results from experiments in isolated human atrial cardiomyocytes and in human atrial trabecular tissue. Although Ca\textsuperscript{2+}-handling instability has been reported in human atrial myocytes [14, 18], in human atrial trabeculae spontaneous activity defined as abnormal aftercontractions is less common in tissue from patients with AF as compared to those in sinus rhythm [19]. These results may be due to the fact that the Na\textsuperscript{+} concentration in isolated myocytes is altered by the concentration of the ion in the patch pipette, which is not the case in atrial trabeculae. Further work is needed to specifically address this important but underinvestigated area.

It could be speculated that during AF instead of contributing to DAD development the persistent SR Ca\textsuperscript{2+} leak may initiate Ca\textsuperscript{2+}-dependent pathways, thereby contributing to the remodelling process that promotes the transition of AF to more persistent forms of AF. Evidence supporting such a concept was provided by Li et al. [20] in studies in mice with cardiac-restricted overexpression of a repressor form of the cAMP response element modulator (CREM-TG mice), which exhibit atrial dilatation, abnormal cardiomyocyte growth, mild atrial fibrosis, reduced expression of connexin-40 and Ca\textsuperscript{2+}-handling abnormalities including increased SR Ca\textsuperscript{2+} leak. CaMKII-dependent hyperphosphorylation of the RyR2 and SR Ca\textsuperscript{2+} leak are likely to be early events in the spontaneous development of AF in CREM-TG mice, because spontaneous AF is eliminated when these animals are crossed with RyR2-S2814A-TG mice resistant to CaMKII-dependent

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**Fig. 1** Molecular determinants of the generation of delayed after depolarization (DAD) and cellular triggered activity in patients with paroxysmal and chronic atrial fibrillation (AF). Red upward and downward arrows indicate factors that are increased or decreased in AF patients, respectively. Question marks indicate areas of uncertainty that need to be further studied. JNC-2, junctophilin-2; RyR2, ryanodine receptor; CaMKII, Ca\textsuperscript{2+}/calmodulin-dependent protein kinase type-II; NCX, Na\textsuperscript{+}/Ca\textsuperscript{2+}-exchanger; SERCA2a, SR Ca\textsuperscript{2+}-ATPase. See main text for further details.
RyR2 hyperphosphorylation. In addition, these authors demonstrated that the development of AF substrate was directly linked to excess RyR2-mediated SR Ca\(^{2+}\) leak and that excess RyR2-mediated SR Ca\(^{2+}\) leak in CREM-TG mice stimulated the calcineurin–NFAT pathway associated with atrial dilatation and decreased connexin-40 expression associated with decreased conduction velocity [20]. Mice with a RyR2 CPVT mutation causing increased SR Ca\(^{2+}\) leak and mouse hearts with acutely elevated intracellular Ca\(^{2+}\) levels also showed decreased atrial conduction velocity [21]. The underlying mechanisms appear to involve both acute Ca\(^{2+}\)-dependent inhibition of Na\(^{+}\) channels and chronic downregulation of Nav1.5 expression [22]. Most importantly, normalization of the RyR2-mediated Ca\(^{2+}\) leak in CREM-TG mice prevented the development of both atrial dilatation and conduction velocity reduction [20]. This suggests that RyR2-mediated SR Ca\(^{2+}\) leak may drive AF progression via these and possibly other remodelling pathways, thereby potentially contributing to AF maintenance by structural remodelling and reentry.

Finally, right atrial cardiomyocytes from patients with paroxysmal AF, who had been in sinus rhythm at the time of tissue procurement for several weeks, also exhibited an increased incidence of DADs and cellular triggered activity [18]. The underlying molecular substrate involves increased SR Ca\(^{2+}\) load and RyR2 dysregulation, with the latter resulting from increased protein expression and higher single-channel open probability. A relative deficiency of the RyR2-stabilizing protein junctophilin-2, due to increased RyR2 but unaltered junctophilin-2 expression, might explain the RyR2 dysfunction, although the precise mechanisms of SR Ca\(^{2+}\) leak in patients with paroxysmal AF are still incompletely understood. Further work is needed to delineate the molecular mechanisms of increased cellular triggered activity in patients with paroxysmal AF and to determine whether these cellular events contribute to initiation and recurrence of AF episodes in these patients.

AF-induced structural remodelling versus primary atrial cardiomyopathy

Despite years of research and advances in catheter-based therapies for AF, we are still striving to understand the reasons for the development of AF and the mechanisms underlying the structural abnormalities in atrial walls observed in patients with the arrhythmia. The common perception that AF is the result of interplay between the structural changes in the atrial myocardium induced by the well-described cardiovascular disease risk factors and structural remodelling induced by the arrhythmia itself has recently been challenged by observations of progressive structural abnormalities in the atrial walls that occur independently from the cardiovascular comorbidities and persistency of AF [23]. However, to what extent this fibrotic atrial cardiomyopathy represents a ‘common cause’ of AF or a mechanism responsible for arrhythmia development in a subgroup of patients with AF phenotype remains uncertain.

One of the first observations that challenged the causative relationship between AF and development of atrial fibrosis came from an experimental study demonstrating that atrial pacing-induced AF per se did not result in any detectable fibrosis development, whereas induction of congestive heart failure was associated with AF inducibility and led to significant fibrotic transformation of atrial myocardium [24]. In humans, an indirect indication of the link between cardiovascular comorbidities and AF comes from epidemiological studies, in which potentially fibrosis-causing conditions such as hypertension, ischaemic heart disease and diabetes are highly predictive of incident AF [25]. An age-related increase in the prevalence of AF has also been well-documented [26] and explained by growing cardiovascular disease burden in the elderly as well as an age-related increase in the extent of atrial fibrosis [27]. However, attempts to provide a quantitative assessment of atrial structural abnormalities associated with AF have demonstrated a more complex picture. Even though catheter-based techniques of endocardial voltage mapping and emerging noninvasive MRI have been valuable for visualization of atrial structural abnormalities, histological evaluation of atrial tissue samples remains the gold standard for tissue characterization. This approach, however, is often limited to a small volume of tissue samples that can be collected in patients undergoing atrial biopsy or confined to right or left atrial appendages in patients undergoing open-chest heart surgery, thus imposing a significant bias on patient selection and leaving large portions of atrial walls, in which AF perpetuates, unattainable.

In a postmortem study that included atrial tissue samples collected from multiple locations in the right and left atria in patients with paroxysmal AF, permanent AF or no history of AF in a 1:1:1
fashion according to prespecified inclusion criteria [28], the extent of fibrosis and fatty tissue in the atrial myocardium showed strong and significant correlation with the presence of AF at all tissue sampling locations in the left and right atria (see examples in Fig. 2). Notably, patients with and without AF did not differ in regard to cardiovascular comorbidities and no age-related increase in the extent of atrial fibrosis was evident. Similar observations were made in patients with persistent or long-standing AF referred for surgical ablation [29], thus suggesting that development of structural abnormalities in the atria is not a result of concomitant diseases but rather a phenomenon associated with AF. Indirect assessment of atrial fibrosis using MRI in a large cohort has further supported this theory as no significant differences in the estimated extent of fibrosis between AF patients with and without comorbidities were found [30]. To our knowledge, however, no histological studies have been conducted to specifically address the issue of causal relationships between the burden of concomitant cardiovascular diseases and atrial fibrosis in patients with AF.

However, whether or not structural abnormalities observed in the atria are the cause or consequence of AF remains unclear. Indeed, the presence of a relationship between the extent of fibrosis and AF burden could be explained in one of two ways: extensive fibrosis in the atria may promote persistent AF or may be a consequence of the long-standing fibrillatory process. The lack of this relationship, however, would favour the concept that the primary fibrotic atrial cardiomyopathy underlies AF development. Available data suggest that the extent of fibrosis tends to be higher in patients with permanent AF compared with those with paroxysmal AF [28] but the relationship between the extent of structural abnormalities and duration of AF seems to disappear in patients with persistent AF [29]. In another study in which the expression of extracellular matrix proteins in atrial tissue samples collected during heart surgery was quantified, no systematic differences between patients with paroxysmal and permanent AF were observed [31]. Even though this does not address the unresolved causality issue, it could be speculated that the extent of fibrosis in the atrial walls may be linked to AF burden and clinical manifestations of the arrhythmia at the early stages of the disease but upon reaching a certain level would no longer affect AF phenotype in patients who develop persistent AF.

Long-term observational studies would be able to resolve this controversy if they were able to show that successful rhythm-control intervention slows or abolishes progression of the atrial structural changes; however, direct histological evidence of this cause–effect relationship is lacking at present. By contrast, the first proof of progressive atrial...
remodelling after successful catheter ablation was reported from a small cohort study of patients who demonstrated a further decrease in atrial electrogram voltage and further slowing of atrial conduction velocity 1 year after pulmonary vein isolation [32]. To what extent these findings can be generalized to a larger population of patients with AF remains to be investigated.

Table 1 provides an overview of the most relevant pathophysiological alterations associated with or predisposing to AF.

Multiple wavelet hypothesis versus rotors

Another central topic of debate is the analysis and interpretation of electrograms during AF. Defining the sequence of activation during AF is fundamental to the understanding of the pathophysiology of AF. The current diversity in the perception of different mechanisms sustaining AF is partly due to the fact that no consensus has been achieved so far with regards to minimal requirements for electrogram recordings and analysis or the interpretation of electrograms during AF.
Traditionally, AF was thought to be sustained by multiple wavelets, as proposed by Moe in the late 1950s [33]. According to this hypothesis, continuous wavefront–wavetail interactions lead to wavebreak and generation of new wavefronts while the number of fibrillation waves tends to be reduced by collision and fusion. As long as the number of fibrillation waves stays above a critical number, multiple wavelets are able to sustain AF. The multiple wavelet hypothesis is supported by much experimental evidence ranging from the initial observation of numerous independent wavefronts in canine atria exposed to acetylcholine [34] to the finding of multiple wavelets in patients with AF based on ECG imaging [35] and epicardial high-density mapping in patients undergoing open chest surgery [36, 37].

Spiral wave reentry or rotors were identified in the atria more than 90 years ago [38]. In the 1970s Allessie et al. [39] demonstrated in rabbit atria that rotating reentry does not require an anatomical obstacle. More recently, Mandapati et al. [40] identified rotors driving AF in isolated sheep atria exposed to acetylcholine. A comparison of mechanisms underlying spiral wave reentry and multiple wavelets is shown in Fig. 3.

Recently, several groups have demonstrated rotors driving AF in humans. Using phase analysis of endocardial atrial electrograms recorded with a basket catheter, Narayan et al. [41] demonstrated rotors in both the right and left atria. Many of these rotors are detectable for many seconds up to minutes at the same location [42]. Ablation of the core of these rotors and focal sources [focal impulse and rotor modulation (FIRM)] led to termination of AF in 86% of the patients (72% with persistent AF and 28% with paroxysmal AF) [41]. In a more recently published report from a multicentre FIRM registry, single-procedure freedom from AF after a follow-up of 1 year was approximately 80% and similar in patients with paroxysmal or persistent AF [43].

Using a completely different approach, Haissaguerre et al. [44] have also detected rotors. They used ECG imaging, a technique which allows the reconstruction of conduction patterns in the heart based on an array of body surface electrograms and the individual anatomy of the thorax from thoracic CT or MRI. This technique shows driver regions consisting of rotors (80%) and focal breakthroughs (20%). The driver regions were not spatially stable but occurred at preferential sites visualized by an automatically calculated cumulative source density map. Overall, 70% of the drivers occurred in the left atrium. Ablation of the drivers resulted in termination of AF in 75% of patients with persistent AF; 85% of patients with persistent AF were still in sinus rhythm after 1 year (comparable to the control group undergoing stepwise ablation) but the radiofrequency delivery
time was shortened to less than 50% as compared to the control group suggesting that targeting rotors identified by ECG imaging is a very effective intervention to destabilize AF.

Despite the very promising results presented from studies targeting rotors for ablation of AF, many questions essential to the understanding of the role of rotors in AF and of the mechanisms of AF in general remain unanswered. First, it is clear that detection of rotors using basket mapping data and FIRM provides fundamentally different results regarding the spatial behaviour of rotors as compared to ECG imaging. Whereas FIRM demonstrates spatially stable rotors with hundreds of revolutions taking place at one specific site, ECG imaging as conducted by Haisssaguerre et al. shows that the reentrant circuits are not spatially stable but migrate throughout the atrium. Nevertheless, they occur preferentially at specific sites that may provide a target for ablation. The reason for this significant discrepancy between the spatial behaviour of rotors identified by these different techniques is currently unclear.

A very striking distinction between the new mapping techniques and direct contact mapping is the huge difference in complexity. While ECG imaging can detect between two and 10 simultaneous fibrillation waves in patients with persistent AF [35], the number of simultaneous waves identified by direct contact mapping is 0.5 per cm² which is equivalent to at least 100 simultaneous waves in total [37]. It is possible that the considerable difference in AF complexity between FIRM and ECG imaging on the one hand and direct contact mapping on the other is related to preprocessing of the electrogroms. Both ECG imaging and basket mapping use phase analysis to determine rotational conduction behaviour during AF. A repetitive phenomenon is described by phase analysis not as its actual state as a function of time but by its phase within a repetitive cycle. A classical example is time, commonly measured as time after midnight. Phase analysis can be performed on signals that show a high degree of periodicity and a monophasic shape. Phase analysis has been used for monophasic or optical action potential data or for ventricular electrogroms which show a more regular and monophasic shape. Atrial electrogroms show a high degree of fractionation and therefore need to be preprocessed to allow for a meaningful analysis of phase [45]. This preprocessing must contain a strong element of spatial or temporal filtering and smoothing so that fractionalization is fully removed from the signals. It is currently unclear how far this massive prefiltering step affects the conduction pattern determined by these techniques but it is reasonable to assume that any smoothing and major filtering will reduce the detected complexity of AF.

Finally, the relation between the identified conduction patterns and the anatomy of the atrium has not been addressed in detail in studies using FIRM. The use of high-density direct contact mapping has provided evidence that the anatomy of endocardial atrial trabeculae and muscle bundles as well as the fibre orientation in the epicardial layer constitute important determinants of direction and preferentiality of fibrillation waves [46], however, no such data have been provided using FIRM. The spatial distribution of the identified sources of AF has been described but the location of important anatomical structures such as the pulmonary veins is often not included in the graphical depictions or movies showing stable rotors identified by basket mapping. Thus, relevant issues remain to be addressed, such as whether the stability of some of the reported rotors is related to reentry around the pulmonary veins.

Unfortunately, many details of the algorithms used for the analysis of ECG imaging and for FIRM have not been disclosed. Investigators studying AF conduction patterns by direct contact mapping have provided detailed information on assumptions, definitions and algorithms of the quantitative parameters used [36, 37, 45, 47], but such description is largely lacking in the case of ECG imaging and FIRM. It is clear that in these cases the economic interests of the intellectual property holders of these techniques compete with the principle of transparency of scientific research and the culture of sharing methods and results within the scientific community.

A plea for transparency in translational electrophysiology

The translation of data from basic science and animal studies into clinical practice is one of the most important goals of medical research and the foundation of intense research interest. The considerable expense associated with basic and experimental research and the required extensive funding may at last receive social justification if this research finally leads to a transfer of knowledge to clinical medicine and, thereby, to a recognizable improvement of patient care. Extensive exchange and cooperation between basic research
scientists and clinicians is essential for the promotion of this translational process. Subsequently, rapid translation is crucial to achieve wider application and thus easier confirmation and reproduction of results derived from implementation of novel methods and technologies. An open approach with extensive disclosure of research data and of technical details is not only undoubtedly an ethically superior approach, but is also beneficial for clinical scientists as this is the fastest way for wide acceptance of novel ideas and ultimately for scientific recognition of research work. Financial considerations of possible benefits deriving for example from patented algorithms or techniques may impose barriers to such an open approach. However, the current practice of very successful large corporations exhibiting astonishing openness in this context may serve as an example that this openness is not necessarily disadvantageous. We believe that it is essential that all stakeholders in the field, including scientists and business developers as well the editors of major scientific journals, recognize their particular responsibility to promote open and reliable access to scientific data for the successful future of basic and clinical science.

Conflict of interest statement
None of the authors have any conflicts of interest to declare.

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