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INVITED EDITORIAL

Irregular rhythm and atrial metabolism are key for the evolution of proarrhythmic atrial remodeling in atrial fibrillation

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Atrial fibrillation (AF) is the most common clinically relevant arrhythmia [3]. AF is generally considered a progressive disease, with episodes increasing in frequency and/or duration over time, resulting in a transition from paroxysmal (lasting <7 days and spontaneously converting to sinus rhythm) AF (pAF) to persistent AF (lasting >7 days or requiring cardioversion), long-lasting persistent (chronic) AF (cAF), and permanent AF [12, 20]. Although the current AF classification was not developed based on underlying pathophysiological mechanisms, there are important differences in the molecular and cellular electrophysiology of pAF and cAF patients [30, 31]. The AF classification also has important therapeutic implications, with more advanced forms of AF being less amenable to rhythm-control therapy. Nonetheless, the type and time course of AF progression are difficult to predict in an individual patient. A better understanding of the mechanisms of AF progression may help to improve and tailor AF therapy [11, 12].

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Mechanistically, the progressive nature of AF is at least in part due to AF-induced remodeling [12]. Several studies have shown that atrial tachycardia causes a reduction in effective refractory period, calcium-handling abnormalities, structural remodeling and atrial hypocontractility (Fig. 1) [2, 19, 28, 32]. There is a strong non-linear relationship between atrial rate and the extent of atrial electrical remodeling, with rates exceeding 300 beats per minute being required to significantly increase AF duration in vivo [27]. Furthermore, individual components of atrial remodeling develop with distinct time courses [2]. Increased intracellular calcium levels are an early event during atrial tachycardia and play a central role in atrial remodeling [12]. For example, the reduction in depolarizing L-type calcium current ($I_{Ca,L}$), which is an important determinant of the reduced action potential duration (APD) in AF, is calcium dependent and is mediated in part by the calcineurin-A (CnA)/nuclear factor of activated T cell (NFAT) pathway [23]. This pathway also contributes to the increase in inward-rectifier potassium current (I_{K1}), another contributor to the abbreviated APD which causes hyperpolarization of the resting membrane potential in AF, by inhibiting the microRNA-26, thereby de-repressing expression of the Kir2.1 subunit underlying I_{K1} [17]. Rapid pacing of cardiomyocytes can also increase reactive oxygen species [13] and promote atrial structural remodeling by activating apoptotic or hypertrophic signaling pathways within cardiomyocytes, and through paracrine effects on atrial fibroblasts [29, 34]. These effects are at least in part calcium dependent [25] and could play a role in progressive atrial structural remodeling involved in AF chronification (Fig. 1) [12, 15].

In contrast to most experimental studies of the effects of atrial tachycardia, which employ a fixed pacing interval, clinical AF episodes are typically characterized by

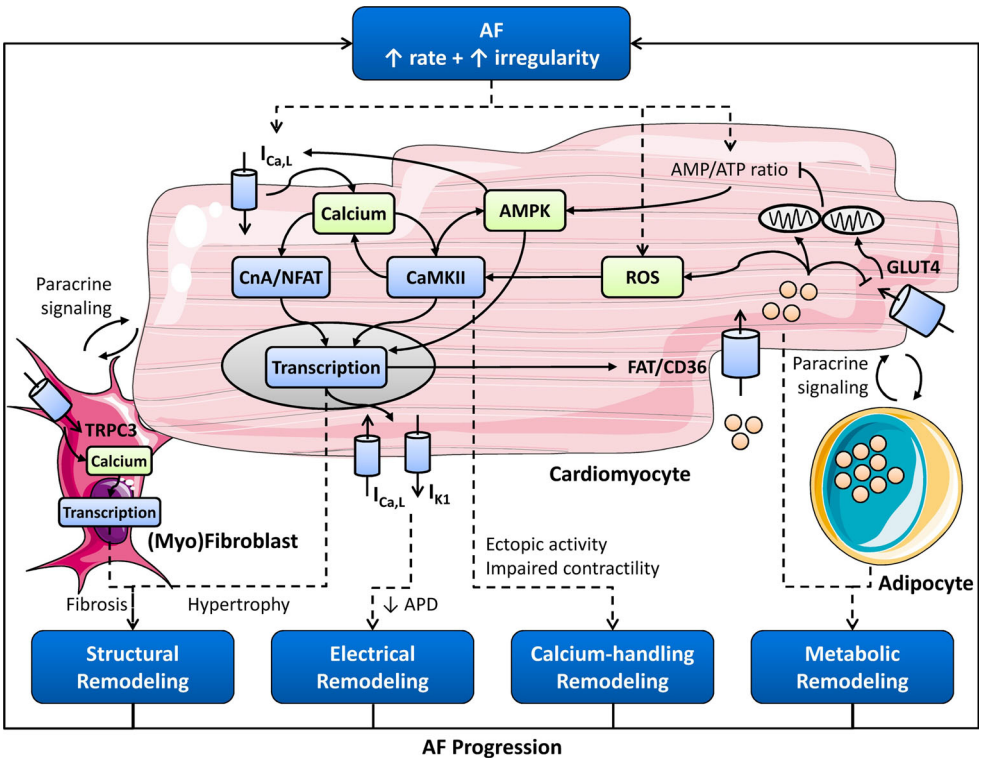

Fig. 1 Schematic representation of the roles of irregular, high-frequent atrial electrical activation in atrial fibrillation progression. Rapid irregular activation activates at least three major interacting signaling pathways through intracellular calcium, reactive oxygen species (ROS), and atrial energy metabolism-sensitive AMP-activated kinase (AMPK), which directly and indirectly (via paracrine signaling) affect multiple components of AF-related remodeling. Altered atrial metabolism might represent a hitherto underappreciated component of atrial remodeling. *TRPC3* transient receptor potential canonical-3 channel. For further abbreviations, see text

irregular electrical activation. In addition to the average rate, the irregularity of electrical activation may have important cardiovascular effects [33]. An irregular pacing interval causes decreased cardiac output, as well as increased pulmonary wedge and right atrial pressure compared to regular pacing at the same rate in patients [7]. In another cohort, greater degrees of irregularity have been associated with increased sympathoexcitation [26]. While it is likely that the effects of irregular activation in vivo are at least partly a macroscopic phenomenon, resulting from restitution properties (i.e., the dependence of electrical and mechanical properties of the heart on the preceding diastolic interval), filling times and baroreflex mechanisms, there is evidence that isolated cardiomyocytes are also modulated by the degree of irregularity of pacing rhythm. For example, irregular pacing of a co-culture of atrial cardiomyocytes and intrinsic cardiac adrenergic cells causes increased expression of catecholamine-synthesizing enzymes compared to regular pacing [24]. This increase can be abrogated by endothelin-A receptor blockade and inhibition of the CnA/NFAT pathway [24], providing a potential calcium-dependent mechanism for the increased sympathoexcitation observed in patients [26]. Furthermore, irregular pacing of neonatal rat ventricular cardiomyocytes (NRVM) results in decreased calcium-transient amplitude compared to regular pacing, possibly due to reduced expression of the sarcoplasmic reticulum (SR) calcium ATPase (SERCA2a) [16]. Nonetheless, the precise role of irregular electrical activation in AF pathophysiology remains incompletely understood.

In the current issue of *Basic Research in Cardiology*, Lenski et al. [14] provide further evidence that cardiomyocytes are intrinsically sensitive to irregular electrical activation. Qualitatively consistent with previous results [16], cultured NRVM paced irregularly with a mean rate of 3 Hz have reduced calcium-transient amplitudes compared to regularly paced NRVM [14]. In addition, Lenski et al. [14] show that irregular pacing increases diastolic calcium levels and reduces APD, resulting in a phenotype consistent with findings in atrial cardiomyocytes from cAF patients [31].

Atrial tachycardia also increases atrial energy consumption and altered atrial metabolism may play an important role in AF pathophysiology [8, 18]. Genes involved in metabolism are among the most strongly regulated genes in pAF patients compared to sinus rhythm patients [5]. Moreover, there is increasing evidence for a role of epicardial adipose tissue and changes in atrial adipocyte-related gene expression in atrial tachycardia-induced remodeling [6]. The work by Lenski et al., for the first time, links irregular pacing, calcium-handling abnormalities and alterations in atrial metabolism. The adenosine monophosphate-activated protein kinase (AMPK) is a critical sensor of cellular energy balance that is activated by increased AMP/ATP ratios and can increase energy availability through downstream signaling pathways [9]. Lenski

et al. show that irregular pacing activates AMPK, resulting in increased membrane expression of fatty acid translocase (FAT/CD36) and lipid accumulation, while membrane expression of glucose transporter-4 (GLUT-4) and glucose uptake are decreased [14]. Inhibition of AMPK normalizes lipid accumulation and glucose uptake, suggesting a causal role for AMPK activation in atrial metabolic remodeling. In addition, the authors show that mice overexpressing the Rac1-GTPase, which develop spontaneous AF with aging, as well as left atrial tissue from AF patients, both show increased AMPK phosphorylation (and thus activation) and higher FAT expression, suggesting a potential clinical relevance for this in vitro model.

The present study raises a number of intriguing questions for future research. The complex interplay between the various signaling pathways within an atrial cardiomyocyte (Fig. 1) makes it difficult to assess the hierarchy of events that ultimately lead to atrial metabolic remodeling. For example, Lenski et al. show that inhibition of calcium/calmodulin-dependent protein kinase type-II (CaMKII) reduces AMPK phosphorylation and normalizes GLUT-4 expression [14], placing AMPK downstream of CaMKII. CaMKII autophosphorylation (and thus activation) increases with irregular, but not regular pacing, which is consistent with the increased expression/activation of CaMKII in AF patients in the present and previous studies [4, 14, 22, 31]. However, since activation of AMPK has positive effects on atrial cardiomyocyte calcium handling [10], AMPK may also indirectly promote CaMKII activation, suggesting a bidirectional interaction between both pathways. Likewise, the observed changes in cardiomyocyte calcium handling might occur downstream of CaMKII activation (e.g., resulting from increased SR calcium leak), or might be upstream, with increased diastolic calcium levels promoting CaMKII activation. Of note, the first step of the cascade (i.e., through which mechanisms irregular pacing promotes calcium-handling alterations and/or CaMKII activation compared to regular pacing) remains largely unknown, although it appears likely that restitution properties of cardiomyocyte calcium handling and activation/deactivation kinetics of CaMKII play a role.

The clinical relevance of AMPK activation in AF is unclear. The data from the present paper suggest that AF-induced hyperactivation of AMPK could lead to lipid accumulation and reduced glucose uptake. These findings were associated with activation of pro-apoptotic signaling pathways in Rac1-GTPase mice in AF compared to littermates in sinus rhythm, as well as in AF patients [14]. Increased apoptosis could contribute to AF progression. However, increased AMPK is traditionally considered a protective factor, improving metabolic disturbances and cellular dysfunction [9]. In agreement, recent work showed that knock-out of liver kinase B1, an activator of AMPK, reduces AMPK activation and results in an age-dependent development of spontaneous AF in mice [21]. Since the present work did not validate whether AMPK inhibition reduces apoptosis under these experimental conditions, AMPK activation might be an adaptive response to AF, with the apoptosis resulting from other pathways activated during AF. On the other hand, AMPK activation can also stimulate ubiquitination of connexin-43, producing conduction heterogeneities that could promote AF maintenance/progression [1]. Taken together, these data suggest that both increased and decreased AMPK activation may have multiple pro- and antiarrhythmic roles. Since fractional AMPK phosphorylation is upregulated in pAF but not in cAF patients [10], this points to complex dynamics in the activation of AMPK during the progression of AF to more persistent forms.

Finally, there are important differences in heart rate, metabolism, electrophysiology, and calcium handling between rodents and humans. To the best of our knowledge, all in vitro studies assessing the effects of irregular pacing to date have been performed with NRVM. Whether human atrial cardiomyocytes are similarly sensitive to irregular pacing rhythms is unknown. Furthermore, the in vivo activation rates during AF are much faster than the 3 Hz employed in the cellular experiments. Whether the AF-induced remodeling is dominated by the frequency at these high rates or whether irregularity also contributes, remains to be determined. Development of more specific approaches to target AMPK and downstream signaling components in experiments in human atrial samples will be required to delineate the role of irregular-rhythm-mediated alterations in atrial metabolism and their consequences for AF pathophysiology.

In summary, the study by Lenski et al. [14] highlights the integrated structure of various components of atrial remodeling and indicates that cardiomyocytes are able to detect both changes in average rate as well as in rhythm regularity. Although important questions remain, these findings enhance our understanding of AF pathophysiology and could have important consequences for AF therapy, for instances with respect to the issue of rate versus rhythm control.

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References

1. Alesutan I, Voelkl J, Stockigt F, Mia S, Feger M, Primessnig U, Sopjani M, Munoz C, Borst O, Gawaz M, Pieske B, Metzler B, Heinzel F, Schrickel JW, Lang F (2015) AMP-activated protein

kinase alpha1 regulates cardiac gap junction protein connexin 43 and electrical remodeling following pressure overload. Cell Physiol Biochem 35:406–418. doi:10.1159/000369706
2. Allessie M, Ausma J, Schotten U (2002) Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc Res 54:230–246
3. Andrade J, Khairy P, Dobrev D, Nattel S (2014) The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. Circ Res 114:1453–1468. doi:10.1161/CIRCRESAHA.114.303211
4. Chelu MG, Sarma S, Sood S, Wang S, van Oort RJ, Skapura DG, Li N, Santonastasi M, Muller FU, Schmitz W, Schotten U, Anderson ME, Valderrabano M, Dobrev D, Wehrens XH (2009) Calmodulin kinase II-mediated sarcoplasmic reticulum Ca^{2+} leak promotes atrial fibrillation in mice. J Clin Invest 119:1940–1951
5. Chiang DY, Zhang M, Voigt N, Alsina KM, Jakob H, Martin JF, Dobrev D, Wehrens XH, Li N (2015) Identification of microRNA-mRNA dysregulations in paroxysmal atrial fibrillation. Int J Cardiol 184:190–197. doi:10.1016/j.ijcard.2015.01.075
6. Chilukoti RK, Giese A, Malenke W, Homuth G, Bukowska A, Goette A, Felix SB, Kanaan J, Wollert HG, Evert K, Verheule S, Jais P, Hatem SN, Lendeckel U, Wolke C (2015) Atrial fibrillation and rapid acute pacing regulate adipocyte/adipositas-related gene expression in the atria. Int J Cardiol 187:604–613. doi:10.1016/j.ijcard.2015.03.072
7. Clark DM, Plumb VJ, Epstein AE, Kay GN (1997) Hemodynamic effects of an irregular sequence of ventricular cycle lengths during atrial fibrillation. J Am Coll Cardiol 30:1039–1045
8. Ghezelbash S, Molina CE, Dobrev D (2015) Altered atrial metabolism: an underappreciated contributor to the initiation and progression of atrial fibrillation. J Am Heart Assoc 4:e001808. doi:10.1161/JAHA.115.001808
9. Harada M, Nattel SN, Nattel S (2012) AMP-activated protein kinase: potential role in cardiac electrophysiology and arrhythmias. Circ Arrhythm Electrophysiol 5:860–867. doi:10.1161/CIRCEP.112.972265
10. Harada M, Tadevosyan A, Qi XY, Xiao J, Liu T, Voigt N, Karck M, Kamler M, Kodama I, Murohara T, Dobrev D, Nattel S (2015) AMP-activated protein kinase-dependent regulation of calcium handling in canine atrial cardiomyocytes and atrial fibrillation. J Am Coll Cardiol. doi:10.1016/j.jacc.2015.04.056
11. Heijman J, Voigt N, Ghezelbash S, Schirmer I, Dobrev D (2015) Calcium handling abnormalities as a target for atrial fibrillation therapeutics: how close to clinical implementation? J Cardiovasc Pharmacol. doi:10.1097/FJC.0000000000000253
12. Heijman J, Voigt N, Nattel S, Dobrev D (2014) Cellular and molecular electrophysiology of atrial fibrillation initiation, maintenance, and progression. Circ Res 114:1483–1499. doi:10.1161/CIRCRESAHA.114.302226
13. Heinzel FR, Luo Y, Dodoni G, Boengler K, Petrat F, Di Lisa F, de Groot H, Schulz R, Heusch G (2006) Formation of reactive oxygen species at increased contraction frequency in rat cardiomyocytes. Cardiovasc Res 71:374–382. doi:10.1016/j.cardiores.2006.05.014
14. Lenski M, Schleider G, Kohlhaas M, Adrian L, Adam O, Tian Q, Kaestner L, Lipp P, Lehrke M, Maack C, Böhm M, Laufs U (2015) Arrhythmia causes lipid accumulation and reduced glucose uptake. Basic Res Cardiol. doi:10.1007/s00395-015-0497-2
15. Li N, Chiang DY, Wang S, Wang Q, Sun L, Voigt N, Respress JL, Ather S, Skapura DG, Jordan VK, Horrigan FT, Schmitz W, Muller FU, Valderrabano M, Nattel S, Dobrev D, Wehrens XH (2014) Ryanodine receptor-mediated calcium leak drives progressive development of an atrial fibrillation substrate in a transgenic mouse model. Circulation 129:1276–1285. doi:10.1161/CIRCULATIONAHA.113.006611
16. Ling LH, Khammy O, Byrne M, Amirahmadi F, Foster A, Li G, Zhang L, dos Remedios C, Chen C, Kaye DM (2012) Irregular rhythm adversely influences calcium handling in ventricular myocardium: implications for the interaction between heart failure and atrial fibrillation. Circ Heart Fail 5:786–793. doi:10.1161/CIRCHEARTFAILURE.112.968321
17. Luo X, Pan Z, Shan H, Xiao J, Sun X, Wang N, Lin H, Xiao L, Maguy A, Qi XY, Li Y, Gao X, Dong D, Zhang Y, Bai Y, Ai J, Sun L, Lu H, Luo XY, Wang Z, Lu Y, Yang B, Nattel S (2013) MicroRNA-26 governs profibrillatory inward-rectifier potassium current changes in atrial fibrillation. J Clin Invest 123:1939–1951. doi:10.1172/JCI62185
18. Mayr M, Yusuf S, Weir G, Chung YL, Mayr U, Yin X, Ladroue C, Madhu B, Roberts N, De Souza A, Fredericks S, Stubbs M, Griffiths JR, Jahangiri M, Xu Q, Camm AJ (2008) Combined metabolomic and proteomic analysis of human atrial fibrillation. J Am Coll Cardiol 51:585–594. doi:10.1016/j.jacc.2007.09.055
19. Morillo CA, Klein GJ, Jones DL, Guiraudon CM (1995) Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation 91:1588–1595
20. Nattel S, Guasch E, Savelieva I, Cosio FG, Valverde I, Halperin JL, Conroy JM, Al-Khatib SM, Hess PL, Kirchhof P, De Bono J, Lip GY, Banerjee A, Ruskin J, Blendea D, Camm AJ (2014) Early management of atrial fibrillation to prevent cardiovascular complications. Eur Heart J 35:1448–1456. doi:10.1093/eurheartj/ehu028
21. Ozcan C, Battaglia E, Young R, Suzuki G (2015) LKB1 knockout mouse develops spontaneous atrial fibrillation and provides mechanistic insights into human disease process. J Am Heart Assoc 4:e001733. doi:10.1161/JAHA.114.001733
22. Purohit A, Rokita AG, Guan X, Chen B, Koval OM, Voigt N, Neef S, Sowa T, Gao Z, Luczak ED, Stefansdottir H, Behunin AC, Li N, El-Accaoui RN, Yang B, Swaminathan PD, Weiss RM, Wehrens XH, Song LS, Dobrev D, Maier LS, Anderson ME (2013) Oxidized Ca^{2+}/calmodulin-dependent protein kinase II triggers atrial fibrillation. Circulation 128:1748–1757. doi:10.1161/CIRCULATIONAHA.113.003313
23. Qi XY, Yeh YH, Xiao L, Burstein B, Maguy A, Chartier D, Villeneuve LR, Brundel BJ, Dobrev D, Nattel S (2008) Cellular signaling underlying atrial tachycardia remodeling of L-type calcium current. Circ Res 103:845–854. doi:10.1161/CIRCRESAHA.108.175463
24. Saygili E, Gunzel C, Noor-Ebad F, Schwinger RH, Mischke K, Marx N, Schauerte P, Rana OR (2011) Irregular electrical activation of intrinsic cardiac adrenergic cells increases catecholamine-synthesizing enzymes. Biochem Biophys Res Commun 413:432–435. doi:10.1016/j.bbrc.2011.08.113
25. Schild L, Bukowska A, Gardemann A, Polczyk P, Keilhoff G, Tager M, Dudley SC, Klein HU, Goette A, Lendeckel U (2006) Rapid pacing of embryoid bodies impairs mitochondrial ATP synthesis by a calcium-dependent mechanism—a model of in vitro differentiated cardiomyocytes to study molecular effects of tachycardia. Biochim Biophys Acta 1762:608–615. doi:10.1016/j.bbadis.2006.03.005
26. Segerson NM, Sharma N, Smith ML, Wasmund SL, Kowal RC, Abedin M, Macgregor JF, Pai RK, Freedman RA, Klein RC, Wall TS, Stoddard G, Hamdan MH (2007) The effects of rate and irregularity on sympathetic nerve activity in human subjects. Heart Rhythm 4:20–26. doi:10.1016/j.hrthm.2006.09.017
27. Shiroshita-Takeshita A, Mitamura H, Ogawa S, Nattel S (2009) Rate-dependence of atrial tachycardia effects on atrial refractoriness and atrial fibrillation maintenance. Cardiovasc Res 81:90–97. doi:10.1093/cvr/cvn249
28. Sun H, Chartier D, Leblanc N, Nattel S (2001) Intracellular calcium changes and tachycardia-induced contractile dysfunction in canine atrial myocytes. Cardiovasc Res 49:751–761
29. Tsai CT, Tseng CD, Hwang JJ, Wu CK, Yu CC, Wang YC, Chen WP, Lai LP, Chiang FT, Lin JL (2011) Tachycardia of atrial

myocytes induces collagen expression in atrial fibroblasts through transforming growth factor β1. Cardiovasc Res 89:805–815. doi:10.1093/cvr/cvq322

30. Voigt N, Heijman J, Wang Q, Chiang DY, Li N, Karck M, Wehrens XH, Nattel S, Dobrev D (2014) Cellular and molecular mechanisms of atrial arrhythmogenesis in patients with paroxysmal atrial fibrillation. Circulation 129:145–156. doi:10.1161/CIRCULATIONAHA.113.006641
31. Voigt N, Li N, Wang Q, Wang W, Trafford AW, Abu-Taha I, Sun Q, Wieland T, Ravens U, Nattel S, Wehrens XH, Dobrev D (2012) Enhanced sarcoplasmic reticulum Ca^{2+} leak and increased Na^{+}–Ca^{2+} exchanger function underlie delayed after depolarizations in patients with chronic atrial fibrillation. Circulation 125:2059–2070. doi:10.1161/CIRCULATIONAHA.111.067306
32. Wakili R, Yeh YH, Yan Qi X, Greiser M, Chartier D, Nishida K, Maguy A, Villeneuve LR, Boknik P, Voigt N, Krysiak J, Kaab S, Ravens U, Linke WA, Stienen GJ, Shi Y, Tardif JC, Schotten U, Dobrev D, Nattel S (2010) Multiple potential molecular contributors to atrial hypocontractility caused by atrial tachycardia remodeling in dogs. Circ Arrhythm Electrophysiol 3:530–541. doi:10.1161/CIRCEP.109.933036
33. Wijesurendra RS, Casadei B (2015) Atrial fibrillation: effects beyond the atrium? Cardiovasc Res 105:238–247. doi:10.1093/cvr/cvv001
34. Yeh YH, Kuo CT, Chan TH, Chang GJ, Qi XY, Tsai F, Nattel S, Chen WJ (2011) Transforming growth factor-β and oxidative stress mediate tachycardia-induced cellular remodelling in cultured atrial-derived myocytes. Cardiovasc Res 91:62–70. doi:10.1093/cvr/cvr041