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Funny and Late: Targeting Currents Governing Heart Rate in Atrial Fibrillation

James D. Daniels, MD¹ and Joseph A. Hill, MD, PhD^{1,2}

¹Department of Internal Medicine (Cardiology), UT Southwestern Medical Center, Dallas, TX

²Department of Molecular Biology, UT Southwestern Medical Center, Dallas, TX

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, contributing significantly to cardiac morbidity and mortality. Currently available agents for pharmacologic management of AF are limited by suboptimal efficacy and proarrhythmic risk. Therapeutic strategies are broadly categorized as rhythm control, where therapy is directed at minimizing AF burden, and rate control, in which the ventricular response is targeted.

Medical and interventional treatments focusing on rhythm control for patients with paroxysmal and persistent AF have improved significantly over the past two decades with the introduction of new antiarrhythmic agents and advances in ablation therapy. However, over the same time period, little progress has emerged in available options to control ventricular rate in patients with AF.

Most medications used for rate control slow conduction through the AV node by increasing refractoriness. Beta-blockers remain the most commonly prescribed agents for rate control, followed by calcium channel blockers and digoxin.¹ Each of these agents slows AV nodal conduction.

A second mechanism by which the ventricular rate is reduced in AF may be by altering the dominant frequency within the fibrillating atria. Some have postulated that decreasing the dominant AF frequency, with fewer impulses engaging the AV node, will reduce ventricular rate.² In a report in this issue of the *Journal*, new rate control strategies are tested that combine these two mechanisms using drugs that were developed to treat angina: ivabradine and ranolazine.²

Funny and late currents

The pacemaking function of the sino-atrial node (SAN) is governed in large part by a special current termed the “funny” current.³ This current (I_f) is a mixed sodium-potassium current that activates with membrane hyperpolarization, as opposed to the more common activation with depolarization (hence “funny”). It is also activated by increased intracellular levels of

Correspondence: Joseph A. Hill, MD, PhD, Division of Cardiology, UT Southwestern Medical Center, NB11.200, 6000 Harry Hines Blvd, Dallas, TX 75390-8573, Tel: 214.648.1400, Fax: 214.648.1450 joseph.hill@utsouthwestern.edu.

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cAMP.⁴ Elevated adrenergic tone results in an increase in heart rate through cAMP-mediated activation of I_f in SAN cells.⁵

Initially discovered in Purkinje cells, I_f is found only in the heart, making it a potential target for rate-lowering medications.³ Furthermore, I_f was originally thought to be present only in the SAN. However, more recent data have shown functional expression in the AV node as well, suggesting that drugs that block this current may be a novel means of modulating AV nodal conduction.⁶

Twenty years ago, the compound S 16257, now known as ivabradine, was first demonstrated to reduce heart rate by selectively modulating I_f in isolated rabbit and guinea pig preparations.⁷ Subsequent investigation in both animals and humans has shown that ivabradine decreases heart rate to an extent similar to that seen with clinical doses of beta blockers but without suppressing cardiac index or LV function.^{8, 9}

Based on these effects, ivabradine was initially developed as an antianginal agent. A double-blind, placebo-controlled trial reported improvements in exercise tolerance in patients with chronic stable angina.¹⁰ Subsequently, ivabradine was studied in three large clinical trials, two of which evaluated the drug in chronic stable angina: BEAUTIFUL¹¹ and SIGNIFY¹². The BEAUTIFUL trial enrolled patients with stable coronary artery disease (CAD) and left ventricular ejection fraction (LVEF) $\geq 40\%$, randomizing patients to ivabradine or placebo on top of baseline therapy. Event rates of the composite primary endpoint did not meet statistical significance between the ivabradine and placebo groups.¹¹ The SIGNIFY trial was published this year and also showed no benefit of ivabradine in patients with chronic stable angina.¹² Ivabradine has been available in the European Union since 2006 for the treatment of chronic stable angina, but it has yet to gain FDA approval in the United States.

A third trial, SHIFT¹³, evaluated ivabradine as a treatment for heart failure with reduced ejection fraction (HFrEF) in patients with elevated resting heart rates despite beta blocker therapy. This trial, which enrolled patients with chronic HFrEF (LVEF $\leq 35\%$), recent heart failure hospitalization, and in sinus rhythm with a resting heart rate >70 beats per minute, randomized patients to up to 7.5 mg twice daily or placebo. This trial reported a 5% absolute risk reduction (HR 0.82, 95% CI 0.75–0.9, $p<0.0001$) in the composite endpoint of heart failure hospitalization and cardiovascular death. The SHIFT trial also reported increased incidence of symptomatic bradycardia and visual side effects in the ivabradine group.¹³

Whereas the rate-limiting effects of ivabradine were expected, the antiarrhythmic effects of ranolazine were not a main focus of development. Ranolazine was first evaluated and approved as an adjunct antianginal therapy for refractory chronic stable angina. Several trials and meta-analyses have reported reduction in anginal frequency and exercise duration when ranolazine is added to conventional anti-anginal therapy.¹⁴ Ranolazine has a chemical structure similar to lidocaine,¹⁵ and it was noted early in development that ranolazine also possesses significant antiarrhythmic properties. Several studies have shown that at clinical doses, ranolazine blocks the peak sodium current (I_{Na}), the late sodium current (I_{NaL}), the inward rectifier potassium current (I_{Kr}), and sarcolemmal calcium current (I_{Ca}).¹⁵ Furthermore, there appears to be synergism when ranolazine is used in combination with

amiodarone or dronedarone to maintain sinus rhythm.^{15–17} Ranolazine has been reported to decrease the dominant frequency in AF, which leads to enhanced success of cardioversion.¹⁸

Rate control in AF

In this issue of the *Journal*, Verrier et al assessed the electrophysiological effects of combined therapy with ivabradine and ranolazine in preclinical models of AF.² Their hypothesis was that, acting via distinct mechanisms, ivabradine (by reducing I_f in the AV node), and ranolazine (by decreasing the dominant frequency of AF) would result in a significant decrease in the ventricular response during AF without affecting contractility. Measurements were obtained in anesthetized male Yorkshire pigs and in an isolated guinea pig heart preparation. The investigators reported that addition of ranolazine to ivabradine resulted in increases in the PR and A–H intervals that were greater than the predicted additive effects of the two drugs. More relevant clinically is the finding that the combination of the two drugs reduced the ventricular rate in AF by 23%. Importantly, there were no changes in contractility (dP/dt) or mean arterial pressure.

These results suggest that the combination of ivabradine and ranolazine may be a useful method of controlling rapid AF acutely. As noted, current treatment options include beta-blockers, calcium channel antagonists, and digoxin. However, in a recently-published retrospective cohort study, incident digoxin use was found to be associated with 71% higher risk of death and 63% higher risk of hospitalization.¹⁹ Furthermore, use of beta-blockers and calcium channel blockers is often limited clinically by hypotension or concern for exacerbating heart failure. In the various clinical trials assessing ivabradine and ranolazine, there has been a noticeable lack of hypotension or heart failure exacerbation,^{13, 20, 21} adding support to the hypothesis that AF patients will also tolerate these drugs. This suggests that, unlike beta-blockers and calcium channel blockers, the combination of ivabradine and ranolazine is likely to be well tolerated by patients with rapid AF and acute decompensated HFrEF and/or low normal blood pressure.

If a clinically meaningful decrease in the ventricular response to AF can be accomplished with these agents, then they may become clinically useful for rate control. In this study, heart rate decreased by 23% after coadministration of the two drugs. Clinically, this would be equivalent to decreasing the ventricular rate from 160 to 120, or 120 to 90, which is often adequate to stabilize the patient until more definitive therapy, such as electrical cardioversion, can be administered electively. Ivabradine exhibits use-dependent inhibition of I_f , as it targets the channel open state; thus, it is conceivable that ivabradine would be most effective during rapid cycles of channel opening and closing (i.e., tachycardia).

In a recent retrospective emergency department study, beta-blockers (metoprolol) and calcium channel blockers (diltiazem and verapamil) were found to lower heart rate by 41 (~31%) and 37 bpm (29%), respectively. Patients in this study received both oral and IV agents over the 5 hours, on average, that they spent in the ED. Of note, 4% risk of hypotension was reported.²² In another short duration study of patients with chronic AF, diltiazem 240 mg daily lowered the baseline heart rate of 96 bpm by an average of 20 bpm (~21%), while verapamil 360 mg daily, metoprolol 100 mg daily and carvedilol 25 mg twice

daily lowered heart rate 12–15 bpm (~13–16%).²³ The acute heart rate reduction reported by Verrier and colleagues in preclinical models was of similar magnitude. That said, it remains unclear whether this would translate to the same reduction in average heart rate over 24 hours or if oral plus IV agents were combined.

While this study suggests that the combination of ivabradine and ranolazine may be a viable method of rate control in AF, there are significant caveats to bear in mind. The authors note that the ivabradine doses used in this study result in plasma levels that are 3–6 times the usual serum levels observed with chronic clinical oral doses.² Whether these results can be replicated in humans at usual doses for ranolazine and ivabradine is unclear. Also, the mechanism of the synergism between the two drugs is not completely defined. The authors postulate that the reduction in dominant frequency of AF by ranolazine combined with the inhibition of I_f by ivabradine may result in a lower-than-expected ventricular rate. However, whether a decrease in dominant frequency results in a change in the ventricular response is unproven. One could similarly postulate that such a decrease in dominant frequency could, in fact, increase the ventricular rate, much like flecainide administration can result in increased ventricular rate by converting AF to atrial flutter. The “rapidity of impulses bombarding the AV” in atrial flutter is, by definition, less than that in AF, yet the ventricular rate can increase if the flutter is conducted more rapidly through the AV node (so-called class Ic atrial flutter).

In addition, there may be potentially undiscovered interactions between the two drugs. Both medications are hepatically metabolized, mostly by the CYP3A4 isoform of the cytochrome P450 system, and if they compete for metabolism, then plasma levels may emerge higher than predicted. Although drug levels remained stable 30 minutes after administration of the other drug in the present study, this is not likely long enough to assess potential interactions in metabolic elimination. Furthermore, ranolazine has been reported to increase the QT interval due to its action on I_{Kr} . While this increase has not translated into increased risk of *torsades de pointes* with ranolazine (possibly due to concomitant inhibition of I_{NaL}), there is potential for increased risk of *torsades* when administered with a drug that causes bradycardia (e.g., ivabradine). Lastly, measurements in this study were obtained over a short time period, so conclusions regarding long-term use of these drugs for chronic rate control cannot be inferred at this time.

Despite these limitations, Verrier’s study provides solid preclinical evidence that ivabradine and ranolazine, alone or in combination, have roles in AF rate control. Both short-term and long-term clinical trials in patients with AF will need to be conducted to determine appropriate doses and to measure changes in heart rate. Close monitoring for potential drug-drug interactions, as well as risk of QT prolongation and *torsades*, are required. However, thanks to the insights gleaned in the present study, novel approaches to controlling heart rate in AF may be in the offing.

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References

1. Vaughan-Sarrazin MS, Mazur A, Chrischilles E, Cram P. Trends in the pharmacologic management of atrial fibrillation: Data from the veterans affairs health system. *Am Heart J*. 2014; 168:53–59. e51. [PubMed: 24952860]
2. Verrier RL, Silva AF, Bonatti R, Batatinha JA, Nearing BD, Liu G, Rajamani S, Zeng D, Belardinelli L. Combined actions of ivabradine and ranolazine reduce ventricular rate during atrial fibrillation. *J Cardiovasc Electrophysiol*. 2014;10.1111/jce.12569
3. DiFrancesco D. Funny channel-based pacemaking. *Heart Rhythm*. 2010; 7:276–279. [PubMed: 20022815]
4. Baruscotti M, Bucchi A, DiFrancesco D. Physiology and pharmacology of the cardiac pacemaker (“funny”) current. *Pharmacol Ther*. 2005; 107:59–79. [PubMed: 15963351]
5. DiFrancesco D, Tortora P. Direct activation of cardiac pacemaker channels by intracellular cyclic amp. *Nature*. 1991; 351:145–147. [PubMed: 1709448]
6. Liu J, Noble PJ, Xiao G, Abdelrahman M, Dobrzynski H, Boyett MR, Lei M, Noble D. Role of pacemaking current in cardiac nodes: Insights from a comparative study of sinoatrial node and atrioventricular node. *Prog Biophys Mol Biol*. 2008; 96:294–304. [PubMed: 17905415]
7. Thollon C, Cambarrat C, Vian J, Prost JF, Peglion JL, Vilaine JP. Electrophysiological effects of s 16257, a novel sino-atrial node modulator, on rabbit and guinea-pig cardiac preparations: Comparison with ul-fs 49. *Br J Pharmacol*. 1994; 112:37–42. [PubMed: 8032660]
8. Manz M, Reuter M, Lauck G, Omran H, Jung W. A single intravenous dose of ivabradine, a novel i(f) inhibitor, lowers heart rate but does not depress left ventricular function in patients with left ventricular dysfunction. *Cardiology*. 2003; 100:149–155. [PubMed: 14631136]
9. Joannides R, Moore N, Iacob M, Compagnon P, Lerebours G, Menard JF, Thuillez C. Comparative effects of ivabradine, a selective heart rate-lowering agent, and propranolol on systemic and cardiac haemodynamics at rest and during exercise. *Br J Clin Pharmacol*. 2006; 61:127–137. [PubMed: 16433867]
10. Borer JS, Fox K, Jaillon P, Lerebours G. Antianginal and antiischemic effects of ivabradine, an i(f) inhibitor, in stable angina: A randomized, double-blind, multicentered, placebo-controlled trial. *Circulation*. 2003; 107:817–823. [PubMed: 12591750]
11. Fox K, Ford I, Steg PG, Tendera M, Ferrari R. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (beautiful): A randomised, double-blind, placebo-controlled trial. *Lancet*. 2008; 372:807–816. [PubMed: 18757088]
12. Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R. Ivabradine in stable coronary artery disease without clinical heart failure. *N Engl J Med*. 2014; 371:1091–1099. [PubMed: 25176136]
13. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. Ivabradine and outcomes in chronic heart failure (shift): A randomised placebo-controlled study. *Lancet*. 2010; 376:875–885. [PubMed: 20801500]
14. Savarese G, Rosano G, D’Amore C, Musella F, Della Ratta GL, Pellegrino AM, Formisano T, Vitagliano A, Cirillo A, Cice G, Fimiani L, del Guercio L, Trimarco B, Perrone-Filardi P. Effects of ranolazine in symptomatic patients with stable coronary artery disease. A systematic review and meta-analysis. *Int J Cardiol*. 2013; 169:262–270. [PubMed: 24063912]
15. Fragakis N, Koskinas KC, Vassilikos V. Ranolazine as a promising treatment option for atrial fibrillation: Electrophysiologic mechanisms, experimental evidence, and clinical implications. *Pacing Clin Electrophysiol*. 2014; 37:1412–1420. [PubMed: 25138058]
16. Fragakis N, Koskinas KC, Katritsis DG, Pagourelas ED, Zografos T, Geleris P. Comparison of effectiveness of ranolazine plus amiodarone versus amiodarone alone for conversion of recent-onset atrial fibrillation. *Am J Cardiol*. 2012; 110:673–677. [PubMed: 22621799]
17. Verrier RL, Pagotto VP, Kanas AF, Sobrado MF, Nearing BD, Zeng D, Belardinelli L. Low doses of ranolazine and dronedarone in combination exert potent protection against atrial fibrillation and vulnerability to ventricular arrhythmias during acute myocardial ischemia. *Heart Rhythm*. 2013; 10:121–127. [PubMed: 22985658]

18. Murdock DK, Kaliebe J, Larrain G. The use of ranolazine to facilitate electrical cardioversion in cardioversion-resistant patients: A case series. *Pacing Clin Electrophysiol.* 2012; 35:302–307. [PubMed: 22229482]
19. Freeman JV, Reynolds K, Fang M, Udaltsova N, Steimle A, Pomernacki NK, Borowsky LH, Harrison TN, Singer DE, Go AS. Digoxin and risk of death in adults with atrial fibrillation: The atria-cvrrn study. *Circ Arrhythm Electrophysiol.* 2014
20. Borer JS, Bohm M, Ford I, Robertson M, Komajda M, Tavazzi L, Swedberg K. Efficacy and safety of ivabradine in patients with severe chronic systolic heart failure (from the shift study). *Am J Cardiol.* 2014; 113:497–503. [PubMed: 24332674]
21. Chaitman BR, Pepine CJ, Parker JO, Skopal J, Chumakova G, Kuch J, Wang W, Skettino SL, Wolff AA. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: A randomized controlled trial. *JAMA.* 2004; 291:309–316. [PubMed: 14734593]
22. Scheuermeyer FX, Grafstein E, Stenstrom R, Christenson J, Heslop C, Heilbron B, McGrath L, Innes G. Safety and efficiency of calcium channel blockers versus beta-blockers for rate control in patients with atrial fibrillation and no acute underlying medical illness. *Acad Emerg Med.* 2013; 20:222–230. [PubMed: 23517253]
23. Ulimoen SR, Enger S, Carlson J, Platonov PG, Pripp AH, Abdelnoor M, Arnesen H, Gjesdal K, Tveit A. Comparison of four single-drug regimens on ventricular rate and arrhythmia-related symptoms in patients with permanent atrial fibrillation. *Am J Cardiol.* 2013; 111:225–230. [PubMed: 23111138]