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VIEW POINT

Beta-blockers in atrial fibrillation—trying to make sense of unsettling results

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Abstract Atrial fibrillation is closely associated with heart failure and adversely affects outcomes. Beta-blockers are strongly recommended to avoid rapid ventricular conduction and tachycardia-induced cardiomyopathy. In this Viewpoint article, we discuss an emerging body of evidence that questions beta-blockers as a preferred rate-control therapy in patients with atrial fibrillation.

Keywords Heart failure with preserved ejection fraction • Atrial fibrillation • Beta-blockers • Diastolic dysfunction

What's new?

- Observational studies and secondary analysis suggested that beta-blockers may be superior to other rate-control medications in atrial fibrillation.
- Randomized studies provided contrary results that are discussed in this Viewpoint article.

Introduction

Atrial fibrillation co-exists with heart failure and adversely affects morbidity and mortality. Rapid conduction of atrial fibrillation to the ventricles is a common cause of heart failure with a reduced ejection fraction. It is for this reason that the use of atrioventricular node suppressing medications, chief among them beta-blockers, is strongly recommended.[1,2] Without substantiating evidence, it is generally assumed that beta-blockers are beneficial and safe in patients with atrial fibrillation. Herein, we discuss emerging data from randomized studies that should prompt a reappraisal of beta-blockers as a preferred therapy for rate control in atrial fibrillation.

Beta-blockers may be Inferior to other rate limiting medications

In addition to their suppressive effects on heart rate, contractility and relaxation, beta-blockers slow conduction through the atrioventricular node. It is for this dromotropic effect that beta-blockers are strongly recommended in the treatment of atrial fibrillation to 'improve quality of life and reduce the risk of tachycardia-induced cardiomyopathy'.[2] However, this recommendation is not based on large randomized outcome trials. In addition, it was never established that beta-blockers reduce the risk of atrial fibrillation in patients in sinus rhythm. What has been demonstrated is that lenient rate control of atrial fibrillation that allowed heart rates up to 110 b.p.m. was non-inferior to strict rate control with a target heart rate below 80 b.p.m.[3] Although several observational and secondary analyses suggested that beta-blockers were associated with a survival benefit when compared with digoxin, recent results from small randomized studies that directly compared beta-blockers to digoxin or non-dihydropyridine calcium-channel blockers revealed unfavourable effects of beta-blockers such as an impaired functional capacity and higher NT-proBNP levels.[4,5] The RATE-AF trial that compared digoxin vs. bisoprolol even raised safety concerns as patients in the beta-blocker arm had twice as many serious adverse events, e.g. heart failure hospitalizations and about five times more office visits for atrial fibrillation.[5]

To get a better understanding of the overall effect of beta-blockers on clinical outcomes, it is valuable to take a close look at historic and contemporary heart failure outcomes studies.

The effectiveness of beta-blockers depend on ejection fraction and rhythm

Heart failure with a *reduced* ejection fraction is the only condition in which selective beta-adrenergic receptor blockade provides unequivocal benefits that result in higher ejection fractions and a longer life. The modest benefits of beta-blockers after myocardial infarction were only apparent in the pre-revascularization era where patients had larger myocardial infarctions and reduced ejection fractions. A first clue that

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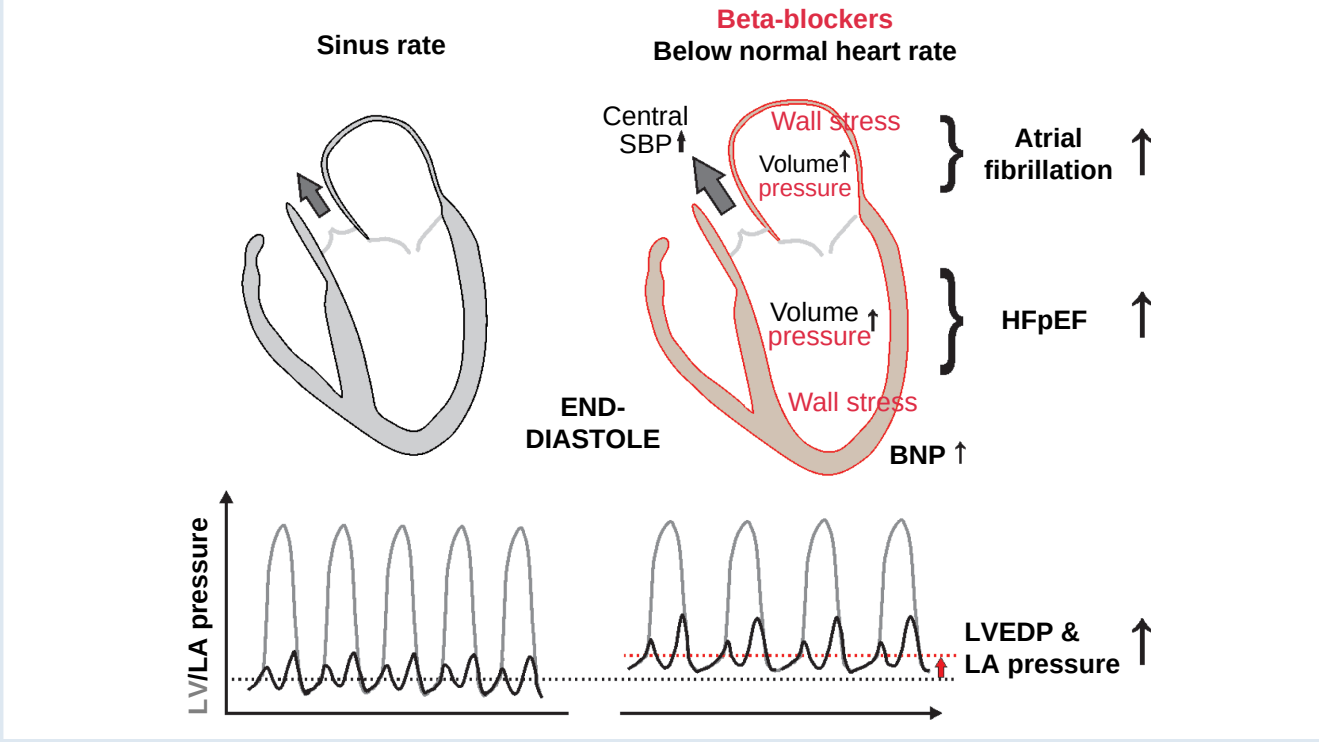

Figure 1 Illustration of the haemodynamic effects of heart rate reductions with beta-blockers on left atrial and ventricular volumes and pressure. BNP, B-type natriuretic peptide; HFpEF, heart failure with a preserved ejection fraction; LA, left atrial; LVEDP, left ventricular end-diastolic pressure; SBP, systolic blood pressure.

the effects of beta-blockers are ejection fraction dependent came from randomized studies of beta-blockers in the era of rapid reperfusion therapies that revealed an unexpected *increase in heart failure hospitalizations* with beta-blockers.[6]

That the underlying rhythm plays an important role in the effectiveness of beta-blockers was apparent in a pooled patient-level analysis of 11 large randomized beta-blocker heart failure trials.[7] This analysis uncovered two large subgroups of heart failure patients that did not derive a benefit from beta-blockers. One was the group of patients with an ejection fraction of 50% or higher and the other group were patients with atrial fibrillation at baseline. In other words, only the patients in sinus rhythm and a reduced ejection fraction derived a benefit from beta-blockers in the large heart failure outcomes trials. This finding also suggests that the reduction in sinus rate by beta-blockers, typically by about 5–10 b.p.m., is the main mechanism by which beta-blockers normalize ejection fraction and improve outcomes. The importance of sinus rhythm is also corroborated in the SHIFT heart failure trial of ivabradine, which selectively lowers sinus rates, and the salutary effects of atrial fibrillation ablation therapy in heart failure with a reduced ejection fraction.[8,9]

In the historic heart failure trials of beta-blockers, atrial fibrillation was not assessed as a major clinical outcome. However, some large randomized hypertension trials provide an insight on the effect of beta-blockers on the risk of developing atrial fibrillation.

Sinus rate lowering in patients with a normal ejection fraction increases the risk for atrial fibrillation

Two large, randomized hypertension trials provided a better understanding of the effects of beta-blockers on the incidence of atrial fibrillation in patients with predominantly normal ejection fractions. In the LIFE hypertension trial, a large outcomes study that compared atenolol with losartan, beta-blocker use resulted in a >30% higher risk of subsequent atrial fibrillation.[10] An adverse effect of beta-blockers on incident atrial fibrillation was also identified in an abstract of the ASCOT hypertension trial of amlodipine vs. atenolol.[11] Because these trials revealed other detrimental effects of beta-blockers, e.g. an increase in stroke risk, beta-blockers were down-graded from preferred to second-line antihypertensive agents.

That the suppression of the sinus rate plays a key role in these unexpected outcomes was evident in the SIGNIFY trial that tested the sinus node inhibitor ivabradine vs. placebo in patients with coronary artery disease without heart failure at baseline.[12] When compared with placebo, ivabradine reduced the heart rate by about 10 b.p.m. and increased the relative risk for heart failure *and* atrial fibrillation by ~20 and 40%, respectively.

But why should a modest suppression of the sinus rate be associated with more heart failure and atrial fibrillation? The answer may lie in the haemodynamic effects of heart rate lowering in patients with normal cardiac dimensions.

Adverse haemodynamic effects of below normal heart rates

By lowering the heart rate, beta-blockers and ivabradine prolong diastolic filling time. As documented in historic studies prolonged diastolic filling with beta-blocker leads to higher filling pressures as the additional blood volume must overcome the increasing resistance of the expanding ventricle.[13] Higher filling pressures in turn raise left atrial and ventricular wall stress as shown in *Figure 1*. Increased atrial afterload impairs atrial function and triggers atrial remodelling and dilation.

Thus, by reducing the heart rate below normal, beta-blockers create a reversible state of intracardiac congestion reflected in attendant increases in natriuretic peptide levels, a biomarker of wall stress that predicts both heart failure and atrial fibrillation. This mechanism is further compounded by the load-induced activation of the Frank–Starling mechanism to increase stroke volumes and central arterial pressures which are further augmented by superimposed reflected peripheral pressure waves. These mechanisms combine to raise the risk for atrial fibrillation and heart failure with a preserved ejection fraction.

What is the best rate-control strategy in atrial fibrillation?

As discussed, some studies of rate control for atrial fibrillation suggest that beta-blockers are inferior to non-dihydropyridine calcium-channel blockers[4,14] and digoxin,[5] and lenient rate control up to 110 b.p.m. is non-inferior to stricter rate control.[3] In consideration of the lack of evidence from large outcomes studies and the availability of alternative agents, we contend that beta-blockers are overused in atrial fibrillation. The available data suggest that the adverse effect of beta-blockers is most pronounced in patients with a normal ejection fraction and low heart rates, typified by patients with paroxysmal atrial fibrillation on high maintenance doses of beta-blockers that markedly suppress the sinus rate.

Lastly, it is generally overlooked that non-dihydropyridine calcium-channel blockers, such as diltiazem or verapamil, have a pharmacological advantage over beta-blockers. They preferentially bind to activated calcium channels making their effect on heart rate use dependent. In other words, they have little effect at lower heart rates, while exerting a robust dromotropic effect at rates encountered with fast conducting atrial fibrillation and thus provide protection from tachycardia-induced cardiomyopathy when it is most needed.[15] By extension, non-dihydropyridine calcium-channel blockers have little effect on sinus rate, filling pressures, and wall stress to explain why the progression towards permanent atrial fibrillation may be slower and why they are better tolerated than beta-blockers.[4,14]

Conclusion

There are no long-term safety and efficacy data for beta-blockers in the treatment of atrial fibrillation and there are several emerging concerns regarding their use. Considering the uncertain evidence basis, the known unfavourable side-effect profile, and the availability of alternative medications we avoid beta-blockers in patients with atrial fibrillation in the absence of a clear and specific indication. When considering the high prevalence of atrial fibrillation, there is an urgent need for larger randomized outcomes trials that compare rate-control strategies.

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Data availability

No original data presented—data sharing policy does not apply.

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