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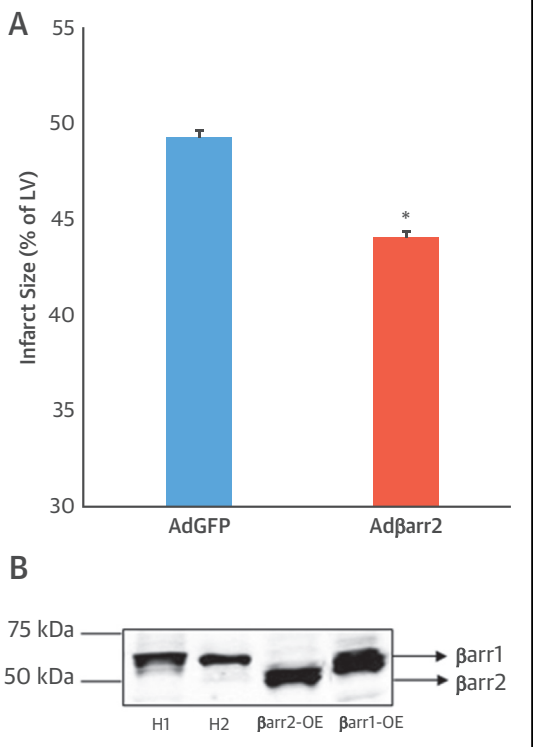
Cardiac βarrestin2 Improves Contractility and Adverse Remodeling in Heart Failure, But Is Underexpressed in Humans

The 2 βarrestin isoforms, βarrestin1 and βarrestin2, normally decrease cardiac function and exacerbate post-myocardial infarction (MI) heart failure (HF) by desensitizing the procontractile G protein–dependent signaling of cardiac β_1-adrenergic receptors (1). Although βarrestin1 exacerbates post-MI cardiac function and remodeling by diminishing cardiac adrenergic and inotropic reserves and by promoting apoptosis and inflammation, the βarrestin2 isoform may actually be beneficial post-MI (1).

Cardiac-specific βarrestin2 gene delivery at the time of MI improves cardiac function 3 weeks later (2). Additionally, post-MI adverse remodeling parameters (i.e., apoptosis, inflammation, and fibrosis) are all ameliorated (2), resulting in infarct size reduction (Figure 1A). The signaling mechanism for the direct increase in positive inotropy afforded by cardiac βarrestin2 is stimulation of SUMOylation of Sarco(Endo)plasmic Reticulum Ca^{2+}-ATPase (SERCA2a), leading to enhanced levels and activity of this calcium pump (2,3). Notably, βarrestin1 lacks this effect on SERCA2a (2). Thus, cardiac-specific βarrestin2 gene transfer might be safely used for treatment of both acute and chronic HF, because it seems to act as a positive inotrope with beneficial, reverse remodeling effects in the failing heart.

Of note, however, βarrestin2 is virtually undetectable in human heart biopsies (Figure 1B); thus, βarrestin1, which mediates negative inotropy and adverse remodeling post-MI, is essentially the only βarrestin expressed in adult human hearts (1). This has 2 important implications. First, it may explain why the initially promising SERCA2a gene therapy failed in a recent large human HF trial (CUPID-2, NCT01643330). Apart from dosing and other design issues, the negative results of this trial may reflect the fact that simply restoring the levels of down-regulated SERCA2a in the hearts of patients with HF is insufficient to confer clinical benefit; proper function of this calcium pump in the recipient hearts must also be ensured. In fact, SUMOylation of cardiac SERCA2a, necessary for its proper activity/function, is also deficient in patients with HF (3). Because βarrestin2 (but not βarrestin1) is a crucial inducer of cardiac SERCA2a SUMOylation (2) and the human heart almost exclusively expresses βarrestin1 (Figure 1B), it is entirely plausible that the virally delivered SERCA2a in the CUPID-2 trial was insufficiently SUMOylated and thus had subpar activity in the hearts of the recipient patients. In other words, human SERCA2a gene therapy must be coupled with cardiac βarrestin2 gene delivery (and probably also with SUMO1 gene delivery) to ensure proper SUMOylation and function of the delivered SERCA2a, thereby realizing its full therapeutic potential for human HF. Of course, given its virtual absence in

FIGURE 1 Cardiac βarrestin2-Dependent Reverse Remodeling in Experimental Post-MI Heart Failure and its Endogenous Levels in Humans



(A) Average LV infarct size at 3 weeks post-MI measured from triphenyltetrazolium chloride–stained cross-sections. *$p < 0.05$; $n = 3$ hearts/group. No difference between the groups at 24 h post-MI, indicating similar extent of surgical MI-induced lesion (2). **(B)** Immunoblotting for endogenous βarrestins in human LV extracts (H1, H2). HEK293 cell extracts (separately) overexpressing βarrestin2 (βarr2-OE) or βarrestin1 (βarr1-OE) are shown as positive controls. Only βarrestin1 (~57 kDa) is robustly expressed in human LV extracts. βarrestin2 protein (~50 kDa) is undetectable. Adβarr2 = mice receiving adenovirus encoding βarrestin2; AdGFP = mice receiving adenovirus encoding GFP; LV = left ventricular; MI = myocardial infarction.

normal healthy hearts and the likelihood of extracardiac side effects, rigorous clinical studies of βarrestin2 gene delivery alone are warranted to gauge the true risk-to-benefit ratio of human βarrestin2 gene therapy.

The other key clinical implication of our present findings pertains to the newly developed βarrestin-biased agonist drugs that target the angiotensin II type 1 receptor (AT_1R), which also recently failed to show any benefit for acute HF treatment (BLAST-AHF, NCT01966601). Again, because the human heart mainly expresses βarrestin1, with very little (if any) βarrestin2 protein (**Figure 1B**), it follows then that these drugs actually stimulate βarrestin1, instead of βarrestin2, in patients with HF, which would have detrimental effects on cardiac inotropy in the acute HF setting (1). Therefore, these drugs might also need to be combined with cardiac βarrestin2 gene therapy to attain therapeutic benefit for human HF.

In summary, our present study aims to bring the attention of clinicians and pharmacologists to the remarkable functional divergence of the 2 βarrestins in the heart, which, coupled with the virtual absence of the "good" cardiac βarrestin2 protein in humans, highlights potential causes of 2 recent clinical failures of novel, otherwise promising therapies for human HF. Importantly, it points to a "missing link" (boosting endogenous cardiac βarrestin2 levels) for these therapeutics that is necessary to attain efficacy for human HF treatment.

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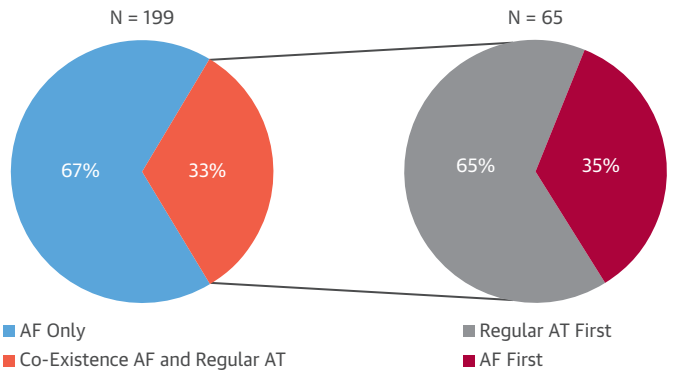
Atrial Fibrillation

The Next Epidemic for Patients With Congenital Heart Disease

We have read with interest the recent paper by Labombarda et al. (1), which describes the development of different types of atrial tachyarrhythmias (ATs) in patients with congenital heart disease (CHD). Although previous studies reported that regular ATs are an increasing health burden in patients with CHD, the current study showed that atrial fibrillation (AF) might be the next major health issue in the aging CHD population. Their observation is in line with our report on AF development in 199 patients with CHD, in whom AF developed at a relatively young age of 49 years (2). We also reported frequent co-existence of regular AT and AF (**Figure 1**) and rapid progression from paroxysmal to (long-standing) persistent and/or permanent AF.

In the current study, the investigators included a considerable number of patients (37.3%) who received pacemaker therapy. Unfortunately, information on

FIGURE 1 AF in Patients With CHD



(Left) All patients with congenital heart disease (CHD) with development of atrial fibrillation (AF) either without **(blue)** or with co-existence of regular atrial tachyarrhythmia (AT) **(orange)**. **(Right)** Co-existence of AT, including first development of regular AT and subsequent AF **(grey)** or vice versa **(red)**.