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Letter to Editor

How and when do β-Adrenoceptor Ligands Enhance Inotropy in Acute Heart Failure?

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In a recent paper, we highlighted that the super-selective, short-acting β_1-adrenoceptor antagonist Landiolol (Feuerstein and Krumpl 2022, [1]), which is administered to patients experiencing acute left ventricular decompensation, did not worsen but, in fact, improved the cardiovascular status of these patients. The mechanisms previously proposed to explain the beneficial effects of β-blockers, such as Landiolol, in acute heart failure (AHF) are detailed in [1]. For example, β-blockers may mitigate the negative impacts of endogenous catecholamines, including tachycardia and tachyarrhythmias.

However, the mechanism we proposed for the beneficial effects of β_1-blockers in acute AHF, particularly Landiolol, significantly diverges from conventional explanations. In the context of AHF, where there are highly elevated levels of endogenous agonists—noradrenaline and adrenaline—, their binding to β_1-adrenoceptor dimers does not produce the expected negative inotropic effects typically associated with β-blockers. On the contrary, negative inotropy is transformed into positive inotropy at moderate to low concentrations of a β_1-adrenoceptor antagonist. This conversion occurs only when negative cooperativity is a dominant factor (see, for example, [2]).

Negative cooperativity, an important phenomenon observed in β_1-adrenergic receptors in the heart, influences how dimeric receptors respond to their agonists. This phenomenon has significant implications for understanding cardiac function and drug interactions. Negative cooperativity in β_1-adrenergic receptors refers to a decrease in the binding affinity of a subsequent agonist after the initial binding of a first agonist to one receptor in a dimer. This effect arises from allosteric interactions between the two receptor protomers of this dimer.

We discovered that in AHF, the negative cooperativity of the β_1-receptor dimers was reduced by the β_1-blocker Landiolol, leading to its unexpected positive inotropic effect [1]. To better understand this observation, we developed receptor binding model calculations based on the binomial distribution, which shed light on the intriguing phenomenon where β_1-blockers, typically associated with negative inotropic effects, can instead induce positive inotropy. Note that, in the failing heart, the proportion of β_1 and β_2 receptors reaches a balanced 50/50 ratio (see [1] for citations). However, the shift from negative to positive inotropy is attributed exclusively to β_1-adrenoceptor antagonism (see below).

When publishing the aforementioned paper [1], we were mindful of the need to address any reservations regarding the use of Landiolol to treat AHF. Our approach, which utilized a discrete probability distribution to describe the interactions between the two identical protomers of the β_1-adrenoceptor dimers, was not easily comprehensible. However, we believed that understanding this rather unconventional approach was essential for cardiologists treating AHF with β-blockers.

The following issue arose: As is common in AHF, a putative β-adrenergic stimulant such as dobutamine is often co-administered in these patients, alongside Landiolol in our case. We justified the additional use of dobutamine as standard practice, assuming it acted as a pure, low-affinity agonist at the protomers of the β_1-dimers (see [1]). This perspective suggested that dobutamine would contribute minimally to the agonist occupation of the β_1-adrenoceptor dimers, given the significantly higher affinity of the endogenous catecholamines.

So far, textbook knowledge categorizes the racemic mixture of dobutamine as a β-adrenoceptor agonist. It is understood that the (+)-enantiomer activates both β_1- and β_2-receptors, whereas the (–)-enantiomer is responsible for agonism at the α_1 receptor. Consequently, the effects at α_1 and β_2 receptors counterbalance each other, leading to what appears to be selective β_1-agonism.

In addition, one of the reasons why the co-administration of Landiolol and dobutamine may be advantageous lies in the ability of a selective β_1-receptor blocker to effectively antagonize the agonistic effects of dobutamine on the β_1-receptors in the sinus node, as well as its positive inotropic effects via the β_1-receptors in the myocardium. However, it does not inhibit dobutamine's positive inotropic effects mediated through the upregulated myocardial β_2-receptors or its activation of α_1 receptors.

It is important to note that the combination of selective β_1-receptor ligands, such as Landiolol, with inotropes that act downstream of the β-receptors, such as milrinone [3] or levosimendan [e.g. 4, 5], also constitutes a logical approach.

However, research has effectively shown dobutamine to be a partial agonist, shedding light on the complex interactions between agonists and antagonists at the β_1-adrenoceptors: In 2011, a comprehensive preclinical

study elucidated the structural basis for both agonist and partial agonist actions on β_1-receptors, classifying dobutamine as partial β_1-receptor agonist [6]. Generally, noteworthy differences have been described in the β_1-catecholamine binding pocket when full agonists are bound compared to when an antagonist or partial antagonist is bound.

Moreover, an earlier significant paper, published in 1998, explored the (ant)agonism of dobutamine at β-adrenoceptors, successfully integrating both preclinical and clinical perspectives [7]. Preclinically, dobutamine activated β_2-adrenoceptors as partial agonist compared to the full agonist adrenaline. Clinically, dobutamine's partial agonism and adrenaline's full agonism may have targeted both β_1- and β_2-adrenoceptors in the patients investigated following aortocoronary bypass surgery [7]. Regarding the previously mentioned negative cooperativity, it should not be assumed that dimeric β_2-receptors play a role in this phenomenon. Recent studies have demonstrated that the only confirmed function of dimeric β_2-receptors is their constitutive activity, supported by molecular insights into this activity in living cells [8].

β_1-Receptors most probably represented the majority of heart β-receptors in the patients without heart failure [7].

Regarding the three ligands (an endogenous catecholamine, dobutamine, and Landiolol) present at the β-adrenoceptors in AHF, as described in [1], the agonist component of dobutamine, which has low affinity, cannot influence the effects of the highly elevated, high-affinity endogenous agonists. These endogenous agonists occupy nearly all protomers of the existing dimers, resulting in negative cooperativity among the dimers.

In the absence of β-antagonists such as Landiolol, the β_1-antagonistic component of dobutamine has the potential to protect one protomer of a dimer with two agonistically occupied protomers from being further occupied by an endogenous agonist. This allows dobutamine to counteract the negative cooperativity of this dimer, thereby producing a positive inotropic effect. It is implausible to attribute this positive inotropy solely to dobutamine's low-affinity β-agonism, since high-affinity endogenous catecholamines almost fully occupy the β-receptors in acute AHF.

However, in the presence of the high-affinity β_1-blocker Landiolol, this inotropic enhancement due to dobutamine's antagonistic effect may be diminished.

We intentionally chose not to address the partial (ant)agonism of dobutamine at β-adrenoceptors, as our goal was to streamline our message in [1] and avoid overwhelming the reader with complexities regarding dobutamine's pharmacological profile. We aimed to enhance the comprehensibility and acceptance of our paper by keeping [1] straightforward, refraining from overcrowding it with additional information about dobutamine not being a pure β-agonist.

Nevertheless, randomized double-blind clinical studies have convincingly demonstrated dobutamine's partial (ant)agonist action. This is evidenced by the attenuation of dobutamine's effects in the presence of β-blockers observed in the LIDO study [4, 5]. This finding was further supported by a subpopulation analysis of the SURVIVE trial [9], which highlighted a reduced inotropic effect of dobutamine when co-administered with β-blockers. In this analysis, β-blockers were more frequently used (88% of the subpopulation in Finland) compared to other countries (52% of the rest of the SURVIVE trial).

In summary, the clinical studies detailing the interactions between dobutamine and genuine β-blockers in AHF suggest that the presence of β-blockers diminishes dobutamine's positive inotropic effects. Only in its role as a β-adrenoceptor antagonist can dobutamine lose its positive inotropic effect in the presence of other pure β-antagonists.

With regard to Landiolol and other selective, short-acting β_1-adrenoceptor antagonists for use in AHF, it seems essential to further elucidate the interaction between pure β_1-adrenoceptor antagonists and dobutamine. I propose conducting a well-powered comparative clinical study to determine whether dobutamine affects the anticipated positive inotropic effects of pure β_1-adrenoceptor antagonists in AHF patients. Such a study could provide a definitive answer on whether, in the presence of high endogenous catecholamine concentrations, dobutamine reduces, has no effect on, or even enhances the positive inotropic effects of these antagonists.

In this study, all AHF patients would receive an intriguing β_1-adrenoceptor antagonist, such as Landiolol, with half of these patients also receiving dobutamine. If the dobutamine-treated patients show lower or unchanged inotropic effects in the presence of the pure β_1-receptor antagonist, future use of dobutamine alongside a true β_1-antagonist could be reconsidered. Conversely, if a beneficial effect of dobutamine is observed, further investigation would be required to understand this effect, particularly given dobutamine's low affinity for β-adrenoceptors [4, 9]. Any previously unrecognized properties of dobutamine should be thoroughly explored.

If confirmed, this proposed study could prompt a reevaluation of the combined use of dobutamine and selective β_1-receptor antagonists in clinical practice for AHF treatment.

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