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Results

The presence of a pure (neutral) β_1-AR antagonist enhances the inotropic action of endogenous agonists, as shown by Feuerstein and Schlicker [65]. This is only true, however, if negative cooperativity prevails, i.e. if binding of an agonist to the first protomer decreases the affinity of the other agonist molecule for the second one (see methods). Now the β_1-AR antagonist effect comes into play. According to basic principles of receptor theory, a pure antagonist does nothing else than to shift the concentration-response curve of an agonist to the left. Usually, in steadily increasing curves, this means that an antagonist reduces the response. However, in our case of dimer occupations subjected to negative cooperativity, the concentration response curves of models (1) and (2) (see methods and figure 1B) reflect declining parts of the curves with increasing values of q at the abscissa. To shift the concentration-response curve to the left within its declining part means increasing inotropy. This increase in inotropy is also true for the agonist combination of endogenous catecholamines and exogenous dobutamine in the presence of the ultra-short-acting highly selective β_1- AR blocker Landiolol. Landiolol, with a K_B of $10^{-7.045757491}$ M [23], may, dependent on (too high) doses and setting, antagonize positive inotropy and chronotropy [37] or, predominantly, chronotropy [38,42-58]. The contribution of Landiolol to the opposite, the enhancement of inotropy, can be delineated as follows:

The above-mentioned term of fractional agonist receptor occupation (endogenous + exogenous agonist, endogenous agonists NA and A at a normalized concentration of [10^{-7} M], exogenous agonist dobutamine at a normalized concentration of [$10^{-8.0022}$] M (see methods), with a common K_A of 10^{-8} M) is changed by Landiolol with an antagonist dissociation constant of $K_B = 10^{-7.045757491}$ M to

$$q = \frac{[endogenous\ agonist]+[exogenous\ agonist]}{K_A + antagonist\ term + [endogenous\ agonist]+[exogenous\ agonist]}$$

The *antagonist term* is made up according to equation 1 in Mantovani *et al*. [66; see also 67] as follows:

$10^{Lg[landiolol]+Lg[K_A]-Lg[K_B]}$ with $Lg = log_{10}$. Note, that in contrast to the depiction in Feuerstein and Schlicker [65] the dissociation constant of the common agonist is here called K_A, not K_D, and the antagonist dissociation constant is K_B.

To make an example: With the values assumed (see Methods, dobutamine supposed to be a weak, but pure agonist at the β_1-AR), the fractional receptor occupation in the presence of [Landiolol] = $10^{-7.045757491}$ M, i.e. at a concentration equalling its $K_B = 10^{-7.045757491}$M for instance, is calculated to

$$q = \frac{[10^{-6.958607315}]}{10^{-8} + [10^{-7.045757491-8+7.045757491}] + [10^{-6.958607315}]} = 0.846$$

Thus, the presence of the antagonist Landiolol at a concentration equalling its K_B slightly reduces the agonist occupation of the β_1-AR from 0.917 (see Methods) to 0.846. In

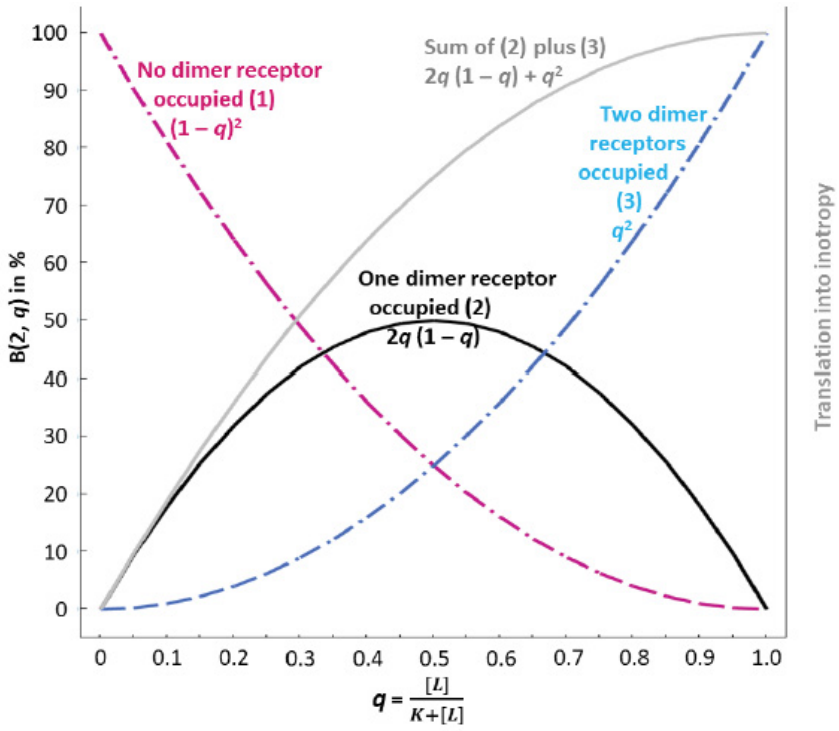

Figure 1A: Binominal distribution and possible translation into inotropy of β_1-adrenoceptor agonists at dimer-receptors without consideration of negative cooperativity.

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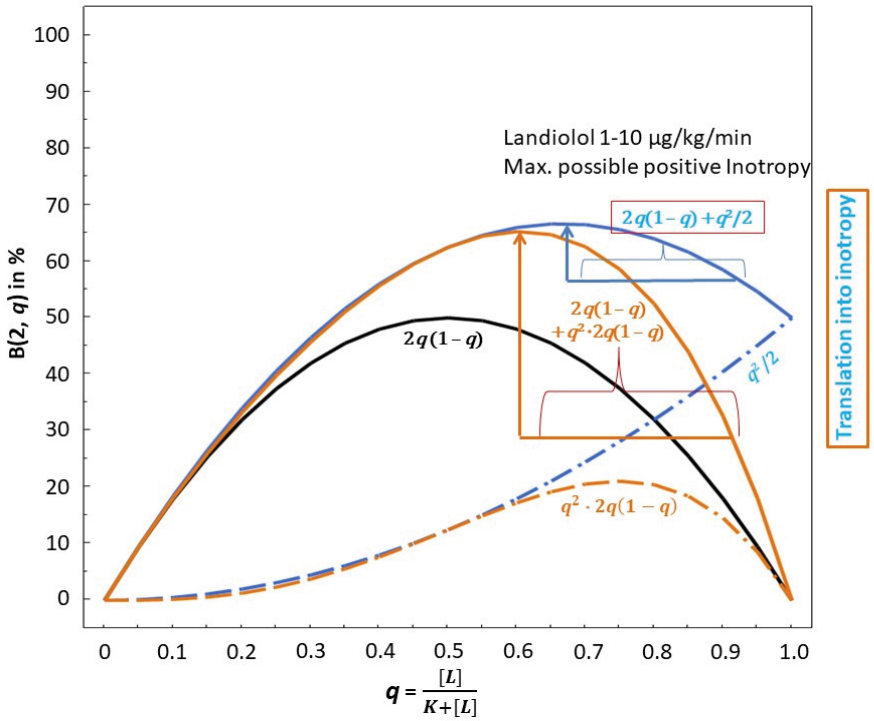

Figure 1B: Binominal distribution and possible translation into inotropy of β_1-adrenoceptor ligands at dimer-receptors with consideration of negative cooperativity according to model 1 and 2. The vertical blue or brown arrows represent the maximum possible gain in inotropy induced by Landiolol in model 1 or 2, respectively. This is achieved in the concentration dose range of 1-10 µg/KG/min.

other words, at this small concentration, Landiolol seemingly doubles K_A and shifts the bell-shaped concentration-response relationship slightly to the left (see FIG. 1B, solid blue upwards directed arrow and solid brown upwards directed arrow). The horizontal blue (Model 1) or brown line (Model 2) below the blue or brown arrow in FIG. 1B shows the extent of this left shift. The probabilities that, at different agonist and antagonist concentrations, no protomer, one of two protomers, or both protomers of the dimers are activated can be calculated. Table 1 displays agonist binding probabilities at the dimer receptors in the absence and presence of Landiolol. Clinically realistic concentrations of the endogenous agonists, of dobutamine and of Landiolol are introduced in the described models of probabilities for agonist activations. According to the above considerations we assume that the agonist binding to at least one dimer receptor is the basis of the translation of agonist occupation into inotropy. The following table shows agonist binding probabilities at the dimer receptors in the absence and presence of the β_1-AR antagonist Landiolol at different concentrations (expressed as *Lg* [Landiolol]) at 1, 7, 28 and 70 K_B scenarios: It is obvious that in both models positive inotropy is achievable with Landiolol in a range between 1-7 K_B whilst 28 K_B in Podel 1 and 70 K_B in both models do not achieve additional inotropy but the contrary, lead to decreased inotropy.

From table 2 it is clear that, according to model 1 in relative terms a double digit percentage inotropic increase (up to +16%) is achievable between 2.9 and 10 µg/KG/min. In model 2 a triple digit percentage increase occurs between 4.3 and 14.3 µg/KG/min (up to +130%). In both models it is however obvious that beyond 4.3 µg/KG/min no substantial further gain in inotropy occurs. At the highest recommended permanent-infusion-dose for patients with normal left ventricular function (40 µg/KG/min which corresponds to 28 K_B) Landiolol starts to worsen the agonist binding probabilities at the dimer receptors, i.e. positive inotropy starts to turn into negative inotropy in model 1 (-24%) whilst model 2 still shows a positive shift (+53%). The Landiolol bolus-dose of 100 µg/KG/min which is applied for 1 min in patients with normal left ventricular function leads to a decrease in inotropy of 58 % and 16 % in both models. It has to be mentioned that the corresponding plasma concentration is calculated for a steady state situation which is not the reality for the bolus as the infusion is applied for 1 min only. However, immediately after application, blood concentration levels may achieve 1500-2600 ng/ml, the range for 50 K_B in table 2. At this blood concentration model 1 shows a -46 % reduction in inotropy and model 2 shows no reduction but also almost no gain (+7%).

Discussion

In view of negative cooperativity, i.e. binding of an agonist to the first protomer decreases the affinity of the agonist for the second one, an extreme example can convincingly explain

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Table 1:

Lg [NA+A+dobutamine] ($K_A = 10^{-8}$ M)	*Lg* [landiolol] ($K_B = 10^{-7.045757491}$ M)		
-6.958607375	-7.045757491 (corresponding to 1 K_B)		
	absent		present
Binding probability according to $2q(1-q)+q^2/2$:	57.29 %	<	61.83 %
Binding probability according to $2q(1-q)+q^2 \cdot 2q(1-q)$:	28.12 %	<	44.68 %
	-6.345501583 (corresponding to 7 K_B)		
	absent		present
Binding probability according to $2q(1-q)+q^2/2$:	57.29 %	<	66.61 %
Binding probability according to $2q(1-q)+q^2 \cdot 2q(1-q)$:	28.12 %	<	64.81 %
	-5.598599460 (corresponding to 28 K_B)		
	absent		present
Binding probability according to $2q(1-q)+q^2/2$:	57.29 %	>	43.66 %
Binding probability according to $2q(1-q)+q^2 \cdot 2q(1-q)$:	28.12 %	<	42.89 %
	-5.200659451 (corresponding to 70 K_B)		
	absent		present
Binding probability according to $2q(1-q)+q^2/2$:	57.29 %	>	24.13 %
Binding probability according to $2q(1-q)+q^2 \cdot 2q(1-q)$:	28.12 %	>	23.65 %

Table 2: Table 2 extends the calculation to further K_B values. In addition, it also relates the responses to the corresponding steady state Landiolol blood concentrations achieved by the administration of the corresponding clinical doses. Furthermore, the percentages in inotropic shifts are indicated in absolute values, delta values (+ abs.%) and relative changes (+ rel.%).

Model 1							
blood conc nmol/l	blood conc ng/ml	multiple K_B	dose µg/KG/min	Inotropy %	Inotropy + %	Inotropy + abs.%	Inotropy + rel. %
64.5	32.9	1.0	1.4	57.29	61.83	4.54	8
129.0	65.7	2.0	2.9	57.29	64.54	7.25	13
193.4	98.6	3.0	4.3	57.29	66	8.71	15
257.9	131.4	4.0	5.7	57.29	66.6	9.31	16
322.4	164.3	5.0	7.1	57.29	66.61	9.32	16
451.3	230.0	7.0	10.0	57.29	66.61	9.32	16
644.8	328.6	10.0	14.3	57.29	62.5	5.21	9
1805.3	920.0	28.0	40.0	57.29	43.66	-13.63	-24
3223.8	1642.9	50.0	71.4	57.29	30.76	-26.53	-46
8059.5	2300.0	70.0	100.0	57.29	24.13	-33.16	-58
Model 2							
blood conc nmol/l	blood conc ng/ml	multiple K_B	dose µg/KG/min	Inotropy %	Inotropy + %	Inotropy + abs.%	Inotropy + rel.%
64.5	32.9	1.0	1.4	28.12	44.68	16.56	59
129.0	65.7	2.0	2.9	28.12	54.46	26.34	94
193.4	98.6	3.0	4.3	28.12	60.14	32.02	114
257.9	131.4	4.0	5.7	28.12	63.28	35.16	125
322.4	164.3	5.0	7.1	28.12	64.8	36.68	130
451.3	230.0	7.0	10.0	28.12	64.81	36.69	130
644.8	328.6	10.0	14.3	28.12	62.6	34.48	123
1805.3	920.0	28.0	40.0	28.12	42.89	14.77	53
3223.8	1642.9	50.0	71.4	28.12	30.11	1.99	7
8059.5	2300.0	70.0	100.0	28.12	23.65	-4.47	-16

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why a pure (neutral) β_1-AR antagonist must enhance inotropy: Let us assume that all dimers are doubly occupied by agonist which may just about be compatible with a basic pumping capacity of the heart, i.e. this most extreme case of negative cooperativity may just about be compatible with survival. Then, the addition of only one β_1-AR antagonist molecule will improve the inotropic condition at one single dimer. This is because the single β_1-AR antagonist molecule ensures that this dimer is no longer double agonistically occupied: the antagonistic molecule displaces one agonistic molecule. The benefit of antagonistic displacement of agonists will prevail as long as antagonist addition produces more singly activated dimers but few doubly antagonistic ones. This benefit can be assessed using the approach of the present paper. The results show that Landiolol, in presence of other inotropes, can, in certain low dose ranges, recruit positive inotropy. In both models the ideal dose and plasma concentration range seems to be between 2.9 and 4.3 µg/KG/min, although doses as low as 1.4 µg/KG/min can already deliver extra positive inotropy. Interestingly according to the European guidelines for the treatment of acute tachycardic atrial fibrillation, Landiolol is the only beta blocker with an indicated dose range for patients with left ventricular dysfunction [40,41]. This dose range (1-10 µg/KG/min) overlaps in a perfect manner with the dose range we have characterized as being able to recruit positive inotropy. Within this dose range it is possible to define the lowest dose which is able to recruit the maximum possible positive inotropy (7.1 and 10 µg/KG/min in model 1 and 2, respectively). In clinical praxis this dose is of course influenced by several factors such as the degree of left ventricular dysfunction, pre- and after load as well as the actual doses of positive inotropic agents in use and the actual heart rate. Thus, it must be emphasized that the ideal positive inotropic dose range varies between individual patients and even within a patient and is always the consequence of a distinct dose finding and dose titration process. It is thus no surprise that Landiolol has already been used successfully in intensive care patients in conjunction with positive inotropic agents [42-53]. The dose range described in these clinical studies was comparable to what we have used as low doses in our model (1-10 µg/KG/min) and was more often between 1-5 µg/KG/min which is the distinct dose range where we observed the lowest possible dose that already achieved substantial possible inotropic response.

Conclusion

This article explains that during co-administration of β_1-receptor agonists and antagonists, the antagonist may, based on the specific behavior of homodimeric β_1-ARs, dose dependently induce a positive inotropic effect in patients with AHF. The approach considers well-established prerequisites, i.e., (i) that the β_1-ARs are spare [54-56], (ii) dimer receptors with activation of one receptor dimer are already leading to the maximum effect [60,61], and (iii) that the concentration of the endogenous agonist at the β_1-AR are higher than their K_A values [K_A – instead of K_D -: agonist dissociation constant, 57-59]. Our calculation, based on the binomial receptor distribution, shows that, due to the negative cooperativity of the receptor dimers [60], negative inotropy is converted into positive inotropy at moderate to rather low concentrations of the β_1-AR antagonist. Both proposed modeling approaches indicate a reduction in positive inotropy again if the concentration of the antagonist becomes too high that it shifts q too far to the left. Then q is in the ascending part of the solid blue or brown curve of Figure 1B. The question can be raised whether this condition with decreasing benefit corresponds to the clinical observation that too high concentrations of β_1-adrenoceptor antagonists can worsen heart failure. We have simulated that and can say that such a phenomenon is also described for the clinical situation [68]. To cope with that, the aspect of a short pharmacokinetic half-life in conjunction with a rapid context sensitive half-life is a big advantage in case of Landiolol [37-39]. Former publications on this topic have raised the question whether increased and possibly harmful concentrations of β_1-adrenoceptor antagonists can be estimated accurately enough on the basis of the proposed modeling approaches to avoid clinical deteriorations in patients with heart failure [65]. A general answer to this question cannot be drawn as head-to-head studies with β_1-blockers in such patients are scarce. Studies have shown that short action duration seems to help when a β_1-blocker induces negative inotropy [37,53,68,69] and higher selectivity seems to be a key element [36-39]. Modelling theories such as the current one and other explanations as mentioned above, deliver a molecular theory and a physiological and pathophysiological explanation basis and provide a rational for a concomitant therapy of β_1-blocker and positive inotropic agents. In case of Landiolol multiple clinical examples as well as specific dose recommendations in the SmPC and the European guidelines and the short half-life of this substance provide support as far as the specific dosing and handling in such situations is concerned. We therefore believe that this publication along with the already existing clinical evidence may help to erase the skeptic attitude towards the use of β_1-AR antagonist in patients with acute left ventricular dysfunction.

Data Availability Statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

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