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Choosing among β-blockers in heart failure patients according to β-receptors' location and functions in the cardiopulmonary system.

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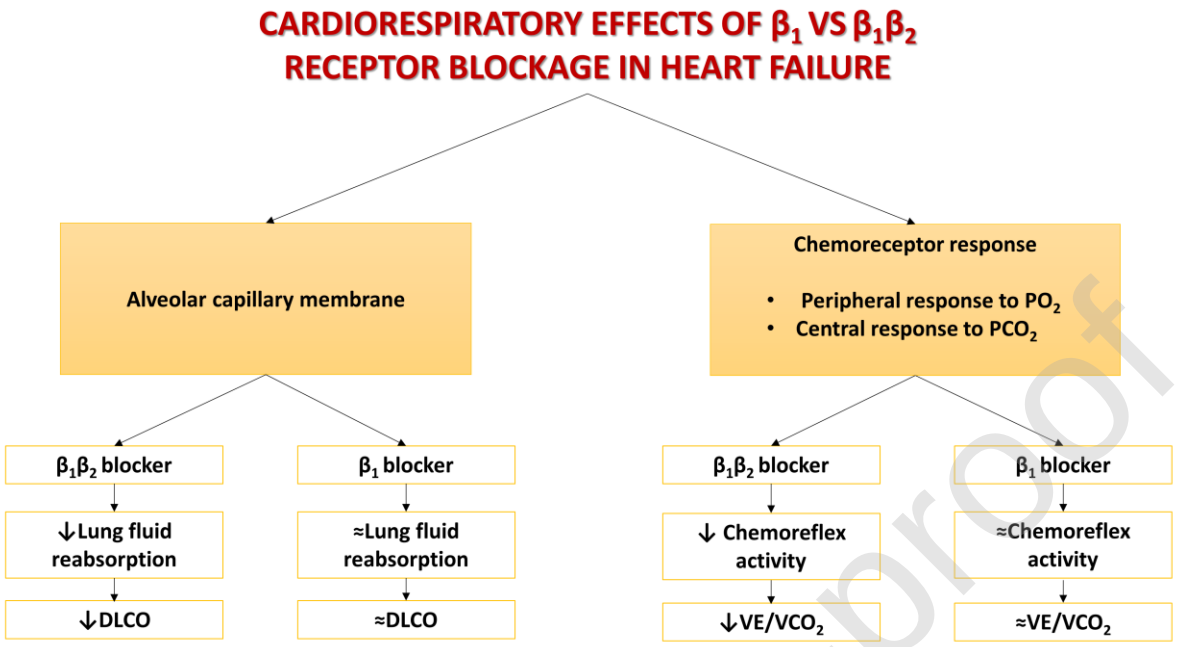
Graphical abstract



ABSTRACT

Several large clinical trials showed a favorable effect of β-blocker treatment in patients with chronic heart failure (HF) as regards overall mortality, cardiovascular mortality, and hospitalizations. Indeed, the use of β-blockers is strongly recommended by current international guidelines, and it remains a cornerstone in the pharmacological treatment of HF.

Although different types of β-blockers are currently approved for HF therapy, possible criteria to choose the best β-blocking agent according to HF patients' characteristics and to β-receptors' location and functions in the cardiopulmonary system are still lacking. In such a context, a growing body of literature shows remarkable differences between β-blocker types (β1-selective blockers versus β1-β2 blockers) with respect to alveolar-capillary gas diffusion and chemoreceptor response in HF patients, both factors able to impact on quality of life and, most likely, on prognosis.

This review suggests an original algorithm for choosing among the currently available β-blocking agents based on the knowledge of cardiopulmonary pathophysiology. Particularly, starting from lung physiology and from some experimental models, it focuses on the mechanisms underlying lung mechanics, chemoreceptors, and alveolar-capillary unit impairment in HF. This paper also remarks the significant benefit deriving from the correct use of the different β-blockers in HF patients through a brief overview of the most important clinical trials.

ABBREVIATION LIST

- atrial fibrillation (AF)
- capillary volume (VCap)
- carbon dioxide (CO_2)
- cardiac output (CO)
- chronic obstructive pulmonary disease (COPD)
- dead space/tidal volume (VD/VT)
- diffusing capacity (DLCO)
- forced expiratory volume (FEV1)
- forced vital capacity (FVC)
- functional residual capacity (FRC)
- heart failure (HF)
- maximal oxygen uptake (peak VO_2)
- membrane diffusion (DM)

- sinus rhythm (SR)
- ventilation/CO_2 output relationship (VE/VCO_2)

Key words: heart failure; β-blocker; β-receptor; lung; prognosis; cardiopulmonary interaction.

Chemical compounds

Bisoprolol, CID: 2405

Carvedilol, CID: 2585

Nebivolol, CID: 189562

Metoprolol, CID: 441308

Sotalol, CID: 66245

The use of β-blockers is a mainstay in the pharmacological treatment of patients with chronic heart failure (HF) [1]. The β-blockers currently indicated in HF differ in adrenergic receptor selectivity and effects on lung mechanics and lung diffusion, as well as on maximal oxygen uptake (peak VO_2) and ventilatory response during exercise. The aim of this review is to show the current use of the different β-blockers approved for HF and the criteria for their choice in the clinical practice, which are presently limited. The choice can only be based on a precise notion of β-receptors' location and functions in normal and HF subjects.

Efficacy of β-blockers in heart failure

- **Prognostic impact**

Large clinical trials showed the favorable prognostic impact of β-blocker use in HF (Table 1). Indeed, HF patients on β-blocker treatment had more favorable outcomes as regards overall mortality, cardiovascular mortality, and hospitalizations [2, 3]. Before 1996, two short-term trials, the CIBIS-I and the US-Carvedilol Trial, showed beneficial effects both on mortality and hospitalizations of patients on Bisoprolol and Carvedilol compared to placebo [4, 5]. These data were then confirmed in larger clinical trials using different β-blocking agents, the CIBIS-II (Bisoprolol), the MERIT-HF (Metoprolol), and the COPERNICUS (Carvedilol) trials, which demonstrated that β-blocker treatment was more effective than placebo (-34% mortality for Bisoprolol and Metoprolol and -35% for Carvedilol compared to placebo) [6-8]. Similarly, both all-cause hospitalisations and HF hospitalizations were significantly reduced by β-blockers (-20% all-cause hospitalizations for Bisoprolol and Carvedilol and -18% for Metoprolol; -32% HF hospitalizations for Bisoprolol and Carvedilol and -35% for Metoprolol). In patients with non-ischemic HF, in the MDC trial, Metoprolol

prevented clinical deterioration and reduced both all-cause mortality and hospitalizations for HF [9]. Even a large network meta-analysis, including a total of 21 trials, reaffirmed the protective role of the blockade of sympathetic activity in patients with HF, showing that β-blocker administration is significantly associated with a reduction in mortality by ~30% (odds ratio 0.71, 95% Confidence Interval 0.64-0.80; p<0.001) [10], with a more pronounced effect in HF patients with ejection fraction (EF) <40%. [10]. Moreover, a recent meta-analysis [11] showed that, in HF patients in sinus rhythm with reduced, mid-range, and preserved EF, β-blockers reduced cardiovascular mortality as compared to placebo, an effect that was consistent across EF strata, except for the small subgroup with EF ≥ 50%. These data confirmed that β-blocker benefit is more robust for EF <40%, and, whereas the efficacy may still be observed in the subgroup of patients with EF 40-49%, there is no evidence of mortality reduction through β-blocker therapy in patients with EF>40%. Specifically a randomized study assessing the effects of carvedilol in patients with HF (based on modified Framingham criteria) in the range of EF >40% had found no benefit of carvedilol compared to placebo on the combined endpoint of hospitalization and survival in either the EF 40-50% or EF >50% range [12]. Accordingly most recent ESC guidelines defined the evidence about β-blocker treatment in middle range HF patients as class IIb [13] Finally, besides demonstrating the overall favorable class effect of β-blocker treatment on HF prognosis, some trials also addressed specific topics. The CIBIS-III trial demonstrated that Bisoprolol is as safe as Enalapril to initiate HF treatment, thus reducing the initial reluctance to start β-blocker treatment at the time of HF diagnosis [14]. Another β-blocker, namely Nebivolol, albeit less effective in reducing hard endpoints, has proven particularly indicated in HF patients aged over 75 in the SENIOR trial [15]. Conversely, the neutral effect of Bucindolol in patients with HF has been attributed to a possible impact of genomic differences in predicting β-blocker response [15, 16]. Overall, the effect of β-blockers appears to be class mediated. However, in the COMET trial, non-selective β-blockade with Carvedilol extended survival benefits over Metoprolol [17], although some

methodological aspects of the COMET trial might be at least in part responsible for the observed difference. Unfortunately, besides the COMET trial, no direct comparison has been made among β-blocking agents, and putative conclusions might be found in meta-analyses, where Carvedilol does not seem to be superior to Metoprolol in reducing all-cause mortality [18, 19]. In summary, a number of major trials have demonstrated a survival benefit with Metoprolol, Carvedilol, and Bisoprolol. Conversely, β-blockers with intrinsic sympathomimetic activity (ISA) (such as Alprenolol, Oxprenolol, Practolol, Pindolol, Xamoterol) seem to have a reduced clinical benefit in post-myocardial infarction patients, as the presence of an ISA effect predicts a nearly significant reduction in benefits [12]. Moreover, a possible explanation for the lack of overall mortality benefit with Bucindolol [12] may include differences in the pharmacological properties of Bucindolol, which displays substantially higher intrinsic activity than Metoprolol and Carvedilol in human ventricular myocardium [20]. The difference in intrinsic activity may contribute to differences in β-adrenoceptor regulation and possibly to differences in outcomes [20].

- **Antiarrhythmic effect**

β-blockers are also useful for reducing the overall arrhythmic burden in HF patients. Their use inhibits the adrenergic-associated increase of Na^+, K^+, and Ca^{2+} currents, and it reduces the occurrence of after-depolarization phenomena [21]. Bisoprolol and Metoprolol are useful in patients with atrial fibrillation (AF) together with Sotalol, which exerts specific type-III antiarrhythmic action [22]. However, the use of Sotalol must be considered with caution in HF, since it is associated with a higher rate of sudden death in patients with previous myocardial infarction [23]. Although AF guidelines recommend β-blockers to reduce symptoms but not to improve prognosis, these drugs remain the standard of care for patients with HF and concomitant AF [24], even if their effects in this category are less clearly defined than in HF patients in sinus rhythm (SR) and opposite results have been reported [24, 25]. Indeed, the results of an individual-patient data meta-analysis did not support β-blocker therapy over other rate-

control medications for improving prognosis [26]; these results were confirmed in a more recent meta-analysis, where β-blockers had no effect on mortality in patients with AF and the achievement of a lower heart rate was associated with better prognosis only in patients in SR[27]. However, in a recent propensity-matched analysis, β-blockers were associated with a significantly lower mortality in HF patients with reduced ejection fraction and AF, irrespective of the pattern (i.e., paroxysmal or persistent) or burden of AF [28]. Moreover, β-blocker therapy has been associated with reduced mortality in AF, with a particular benefit for patients with heart rate >100 beats per minute compared to a heart rate ≤60 beats per minute [29]. Further larger dedicated studies are needed to assess the prognostic usefulness of β-blockers in HF patients with AF. Indeed, in patients with HF and AF, heart rate, hemodynamics, and VO_2 kinetics show a different behavior during exercise compared to HF patients with SR [30, 31]. Moreover, β-blockers are less effective in reducing heart rate, acting mainly on the atrioventricular node instead of the sinus node in patients in SR [24]. Furthermore, hemodynamic changes in patients with HF are both cause and effect of a more severe underlying condition [24]. However, heart rate is an important target in the treatment of HF. As a matter of fact, the introduction of Ivabradine, which selectively lowers heart rate, led to an improvement of cardiovascular outcomes [32]. It seems that it is the magnitude of heart rate reduction by β-blockers plus Ivabradine, rather than the background β-blocker dose, that primarily determines the subsequent effect on outcomes [33].

- **Safety in prevalent HF comorbidities**

Comorbidities are common in patients with HF, and they significantly affect prognosis and sometimes complicate the therapeutic management. In case of chronic obstructive pulmonary disease (COPD), the use of β-blockers is recommended and quite safe in improving long-term prognosis.

The prevalence of COPD in HF ranges from 8% to 52%. COPD is characterized by persistent airflow limitation, which usually requires bronchodilator therapy. β-blockers used to be considered – and are

frequently still considered – contraindicated in patients with asthma and, to a lesser extent, in patients with COPD [34]. More recently, highly cardioselective β-blockers have proven to be safe both in asthma and COPD patients, while some concern still exists on the use of non-selective compounds, especially in asthma patients [35-37]. In particular, as regards asthma, ESC HF guidelines [1] report that β-blockers are only relatively contraindicated in asthma, apart from true severe asthma, however they should only be used under close medical supervision with consideration of the risk/benefit ratio. In clinical practice, cardioselective β-blockers in these patients should be started at low doses, up-titrated, and combined with close monitoring for signs and symptoms of airway obstruction [1]. However, no clear indications are available on this specific topic. As regards COPD, some recent studies showed a higher tolerability and a better outcome in patients with HF and COPD with the use of cardioselective β-blockers than with Carvedilol [38, 39]. Moreover, a meta-analysis by Salpeter et al. [40] reported that the use of selective β-blockers is not related to clinically significant adverse respiratory effects in patients with mild-to-moderate reactive airway disease nor in patients with concomitant chronic airway obstruction. Indeed, although β-blockers might induce bronchoconstriction in case of COPD and HF, the European HF guidelines [41] recommend cardioselective β-blockers (i.e. Bisoprolol, Metoprolol succinate, or Nebivolol), starting with low doses, combined with close monitoring for signs of airway obstruction, especially in HF elderly, in whom asthma is common [41].

β-receptors and heart-lung interaction

The combined use of β-blockers and β-stimulating agents in HF patients with concomitant COPD is only one of the cases where the heart-lung interaction comes into play in HF pathophysiology, affecting the clinical course of the disease. As a matter of fact, bronchodilation via β_2-receptor stimulation and reduction of overall sympathetic stimulation – clinically evident in terms of tachycardia, vasoconstriction, enhanced metaboreflex and chemoreflex activity – via β_1-receptor blockade are both

desirable but apparently opposite actions. Heart and lungs are located in the thorax, so that the heart is nested in the "cardiac fossa", being surrounded by the lungs [42]. Both heart and lung function imply dynamic volume changes, so that, during systole and diastole, the heart has to "push and pull" the lungs. Similarly, during inspiration and expiration, the pressure around the heart changes, affecting cardiac performance [43]. Clearly, a stiff lung, such as in emphysema and COPD, increases cardiac work, and an enlarged heart compromises lung function.

In HF, and particularly in severe HF, restrictive lung disease and alveolar-capillary gas diffusion impairment are both frequently observed [44, 45]. The former is defined by a similar reduction in forced expiratory volume (FEV1) and forced vital capacity (FVC), and it is associated with a reduction of alveolar volume and gas exchange surface [44, 45]. Alveolar-capillary gas diffusion impairment, as measured by carbon monoxide (CO) diffusing capacity (DLCO), is characterized by a reduction of both its components, membrane diffusion (DM) and capillary volume (VCap), which is the amount of hemoglobin participating to gas exchange [44]. β-receptors exert several effects in the respiratory system. The respiratory system is provided with predominantly β_2-type (70%) receptors, mostly located on the alveolar cells (nearly 90%) [46], where they regulate alveolar fluid clearance, with consequent effects on lung diffusing capacity. The remaining β_2-receptors are located in the small and large airways, and they regulate smooth muscular tone. Moreover, the stimulation or blockade of β-receptors modulates pulmonary function and diffusing capacity, ventilatory response to exercise, and chemoreceptor response.

- **Alveolar-capillary gas diffusion impairment in HF**

The reduction of alveolar-capillary gas diffusion in HF has several components: a) reduction in lung capillary network and increase in intrapulmonary shunt. Both, combined with a non-uniform increase in pulmonary arteriolar vascular resistance, are the main factors responsible for the ventilation-

perfusion mismatch; b) anatomical changes of the alveolar-capillary membrane due to fibrosis, interstitium thickening, and capillary thrombosis and rupture; c) the weight of the enlarged heart that squeezes some portion of the lung depending on the subject's position; d) the effects of drug treatment on the active mechanisms regulating the alveolar-capillary gas diffusion [47].

In HF patients, the reduction of membrane diffusion during active exercise is counteracted by an increase in capillary volume, so that the total gas diffusion is usually preserved [48-50]. Differently, in the recovery phase, alveolar-capillary diffusion decreases, particularly in severe HF [50].

- **Ventilation impairment and lung mechanics in HF**

In HF, ventilation may be highly inefficient, as shown by the increase of the slope of the ventilation vs. carbon dioxide production (VCO_2). Consequently, a HF patient needs to ventilate more than a normal subject for the same VO_2. Wasserman et al [45] showed that, in severe HF, ventilation for a given VCO_2 is twice as much as that observed in healthy individuals, and it is characterized by a low tidal volume and a high respiratory rate during exercise [45]. Ventilation increase has several causes, including increased CO_2 output at the muscular level for a given VO_2 due to early anaerobiosis, ventilation/perfusion mismatch with lung zones ventilated but under-perfused, and zones perfused but under-ventilated, increase in dead space/tidal volume (VD/VT), alveolar-capillary diffusion abnormalities, and increased sympathetic activity, specifically increased chemoreflex and metaboreflex activity on ventilation. Notably, all the above-reported causes of ventilation inefficiency are controlled and regulated by β-receptors. Moreover, in HF, lung compliance is reduced, and functional residual capacity (FRC) must increase progressively to increase tidal volume and ventilation during exercise up to the occurrence of the expiratory flow limitation, which impedes a further ventilation increase [51]. The increase in FRC also implies the presence of gas trapping in the lung and a further increase in lung stiffness and pulmonary vascular resistance [51]. The increased lung stiffness may contribute to cardiac

restriction, which is evidenced by the parallel and equal increase of right and left atrial pressures observed during exercise in case of severe HF [52]. This phenomenon can be counteracted by a reduction of lung fluids and by the consequent increase in lung compliance. Differently from what happens in normal subjects, even a small amount of saline infusion is associated with a further reduction in lung compliance, as evidenced by a further increase of the ventilation/CO_2 production relationship (VE/VCO_2) slope, and by a reduction of the alveolar-capillary membrane diffusion. The improvement of cardiac function and the consequent reduction of excessive lung fluids lead to an improvement of lung mechanics but not of alveolar-capillary gas diffusion [53]. These findings have been demonstrated in several clinical conditions, such as ultrafiltration treatment of HF and heart transplant, showing that the alveolar-capillary membrane diffusion is altered mainly because of anatomical membrane changes [53, 54]. An improvement of DLCO in HF has been observed only with chronic treatments directly affecting alveolar-capillary membrane function [55, 56].

- **Alveolar fluid clearance in HF**

In healthy subjects, the alveolar surfaces and the lung interstitium are kept dry both by the lymphatic system and by the intravascular oncotic pressure. Otherwise, in the pathological settings characterized by alveolar edema, fluid removal is guaranteed by the alveolar epithelium, a semipermeable membrane able to move fluid toward upper airways via cilia movement and, most importantly, to regulate active and passive fluid/ion interchange between the alveolar space, the lung interstitium, and the bloodstream [57, 58].

Several factors regulate alveolar fluid clearance (figure 1), and the so-called “catecholamine-dependent” mechanism is the most intriguing. Indeed, as previously reported, the respiratory system is provided with a number of β-receptors that are predominantly β_2 type (70%) and mostly located on the alveolar cells (nearly 90%) [46]. Their stimulation is thought to facilitate the alveolar fluid removal by

increasing the intracellular Na+ transport through an augmented synthesis of epithelial sodium (Na+) channel (ENaC) and Na+/K+-ATPase pumps, as well as through their recruitment from intracellular pools to the cell membrane [59, 60]. Interestingly, experimental studies [61] suggest that β_2-receptor stimulation is needed in case of airspace fluid overload, whereas it has a marginal role in the physiological lung fluid balance; this supports the key role of β_2-receptors in the resolution of alveolar edema. Finally, the effects of β_2-receptor stimulation in the alveolar epithelium have been shown to exert a number of other protective effects on the alveolar-capillary barrier function, which could most likely preserve gas exchange as well as the lung defensive properties [62-67].

- **β_1/β_2-receptor modulation in normal subjects and in experimental conditions**

Several animal and ex-vivo human lung studies documented an increase in alveolar fluid clearance upon stimulation of the β_2-alveolar receptors by non-specific and specific β_2-adrenergic receptor agonists [68-70]. Recently, Taylor et al. studied the effect of β_2-receptor stimulation in humans [71]. Diffusing capacity of the lungs, cardiac output, and pulmonary function were analyzed at baseline and 30 and 60 minutes after the administration of nebulized albuterol, as compared with nebulized saline. Albuterol was responsible for an increase in cardiac output and for an improvement in pulmonary function (FEV_1 and forced expiratory flow at 50% of FVC) compared to saline. Post-albuterol DLCO changes are complex and inconclusive, with a reported decrease in DLCO at 60 minutes driven by a drop in VCap with no changes in DM. However, DM was significantly higher than at baseline when accounting for changes in VCap, since DM/VCap is considered an index of alveolar-capillary unit diffusing capacity.

On the other side, β_2-receptor blockade through β-blockers affects lung diffusing capacity in healthy subjects, with some differences between selective and non-selective β-blockers. Paolillo et al. [72] demonstrated, in 22 healthy males randomly treated with the non-selective Carvedilol or with the β_1-

selective Bisoprolol, that Carvedilol, but not Bisoprolol, decreased DM (-13±7%, p= 0.001) and increased VCap (+20±22%, p= 0.016), and that it worsened ventilatory efficiency (VE/VCO_2 slope, +12±8%, p< 0.01). These observations were presumably related with the β_2-blockade that was able to downregulate the active pumps located on the alveolar surface needed to pump fluid out of the alveolar compartment, supporting the hypothesis that β_2-alveolar receptors contribute to alveolar fluid control in humans. To further support the role of β_2-receptors in lung fluid clearance, the evaluation of effects of Carvedilol and Bisoprolol on lung diffusion and exercise capacity was also repeated after rapid 25 ml/kg saline infusion to over-hydrate the lung and determine interstitial edema [72]. The saline infusion additionally affected the previously reported changes when combined with Carvedilol treatment, with a further reduction in DM (-18±13% p< 0.01) and a further increase in VCap (+44±28% p< 0.001) and in VE/VCO_2 slope (+20±10% p< 0.001) (Figure 2). As a consequence, these data seem to support the concept that selective β_1-blockers should be preferred in case of clinical and/or radiological signs of lung fluid accumulation.

The physiological role of β-receptors has also been studied after acute high-altitude exposure, a condition characterized by hypobaric hypoxia. In particular, acute high-altitude exposure in healthy subjects is responsible for extravascular lung fluid increase with a reduction in DLCO and DM [73]. Differently, with prolonged high-altitude exposure, lung diffusing capacity goes back to values even higher than at sea level, due to an increase of hemoglobin, alveolar volume, and membrane diffusion [74]; the increase of membrane diffusion is likely related with high-altitude-induced sympathetic stimulation. It has also been reported, in 37 healthy mountaineers prone to high-altitude pulmonary edema, that the prophylactic inhalation of Salmeterol decreased the incidence of pulmonary edema by more than 50 percent (from 74% with placebo to 33%) [75]. In a normoxic environment, treatment with β-blockers may decrease exercise capacity in healthy subjects due to a reduction in peak heart rate,

cardiac output, and peripheral blood flow distribution [76]. Moreover, non-selective β-blockers, such as Carvedilol, also affect exercise-induced hyperventilation by reducing peripheral chemoreflex sensitivity [77] and attenuating mitochondrial adaptation to exercise [78]. At high altitude, two main factors influence exercise performance: the alveolar-capillary gas diffusion and the chemoreflex-mediated ventilatory response to hypoxia. As a matter of fact, the exercise capacity of healthy subjects at high altitude is influenced by the type of β-blocker used. At very high altitude, Valentini et al. [79] showed lower peak VO_2 values in healthy subjects treated with Carvedilol than in Nebivolol-treated subjects (-37.6 vs. -22.5%; $p< 0.01$), together with lower peak heart rate values (–43.9±11.9 beats/min vs. 24.8±13.6 beats/min; $p< 0.05$). Peak ventilation decreased with Carvedilol (–9.3%) and increased with Nebivolol (+15.2%) ($p= 0.053$), and it was the only variable that predicted peak VO_2 decrease. In brief, stimulation or blockade of β_2-receptors may interfere with ventilation, alveolar-capillary gas diffusion, and exercise capacity at high altitude, but different β-blockers act differently, suggesting a specific role of β_1- vs. β_2-receptors. Thus, the consequences of β-receptor stimulation or blockade in healthy subjects and in experimental models underline their pathophysiological importance, and they support the notion of a physiology-based therapeutic approach in pathological conditions.

- **Respiratory effects of β_1/β_2-receptor modulation in HF**

The pharmacological effects of β-blockers in HF, including lowering of heart rate and blood pressure, are mainly related to the blockade of β_1- and β_2-receptors located on myocardium and vessels, even though further mechanisms could be invoked for β-blockers with direct vasodilatory activity. Even though β-blockade acutely induces a reduction in myocardial inotropism, in HF, chronic β-blockade leads to an increase in myocardial contractility, mainly thanks to the counteracting effect on the downregulation of β_1-receptors. However, due to the heart-lung interaction, the net effect of β-blockers in HF does not only depend on their direct action on the cardiovascular system, but the effect on the

pulmonary system could also play an important role, since β-receptors, mainly β_2, are widely represented both in the airways and in the alveolar cells [58, 60].

a) Effect of β-blockade on lung mechanics in HF

Only few data are available regarding the effects of β-blockers with different degrees of cardioselectivity on lung mechanics in HF in the absence of significant COPD [47, 77, 80, 81]. In this context, most studies show no or negligible effects of β-blockers on FVC or FEV_1, without any significant difference between tested compounds [47, 77, 80, 81]. However, with Bisoprolol (β_1-selective), a bronchodilation response to inhaled β-agonists slightly higher than with Carvedilol (non-selective) has been described [80]. The effect of Bisoprolol on lung mechanics and symptoms/quality of life was tested in 27 HF patients suffering from moderate-to-severe COPD, without asthma. In comparison with placebo, Bisoprolol caused a significant albeit small reduction in FEV_1 after 4 months of treatment (-70 ml); however, reversibility following β-agonist was preserved, and no significant change was observed in arterial blood gases and in measures of health status (quality of life scores and number of exacerbations of COPD) [82].

b) Effect of β-blockade on lung diffusion in HF

The effects of the blockade of alveolar β_2-receptors, which mediate fluid reabsorption from alveolar surface to lung interstitium [58], have been extensively addressed in several studies on small HF populations. Carvedilol administered for a six-month period significantly reduced DLCO in 15 stable HF patients with reduced ejection fraction in a crossover, double-blind, placebo-controlled study [77]. The reduction in DLCO was entirely due to a reduction in DM, without any significant change in VCap. In 53 HF patients treated sequentially with a cardioselective (Bisoprolol) and a non-selective (Carvedilol) β-blocker, lung diffusion appeared significantly lower with Carvedilol than with Bisoprolol [80], strongly suggesting a detrimental effect of alveolar β_2-receptor blockade on lung

diffusion. This result was confirmed in a study with a similar design (crossover, single blind) comparing Carvedilol, Bisoprolol, and Nebivolol (CARNEBI Trial [47]), in a population of 60 HF patients. Once again, DLCO and particularly DM resulted significantly lower during treatment with Carvedilol than with Bisoprolol or Nebivolol (Figure 3). Since Bisoprolol and Nebivol are highly β_1-selective, the hypothesis that the impairment of lung diffusion could be exclusively induced by β_2-receptor blockade appears even more attractive. Notably, in both the last cited studies, DLCO impairment after Carvedilol treatment was associated with a reduction in peak VO_2, underlining the close relationship between the functional integrity of the alveolar-capillary membrane and the efficiency of O_2 delivery during exercise. Moreover, the above-reported observations suggest that alveolar β_2-receptors could even be considered as a therapeutic target in HF. Indeed, some very exploratory data showed a reduction in lung water content and an improvement in lung diffusion after albuterol nebulization in stable HF patients [61] and in normal subjects [71], respectively.

c) Effects of β-blockade on the ventilatory response to exercise

An inappropriate ventilatory response to exercise (increased VE/VCO_2 slope) is a hallmark of HF, and it correlates with the severity of the disease and with outcomes [83, 84]. The etiology of elevated VE/VCO_2 slope is multifactorial and still not completely elucidated. Several mechanisms have been proposed, including abnormalities in chemoreceptor sensitivity and ergoreceptor activity and increase in pulmonary dead space [45, 85-87]. Interestingly, all these mechanisms are influenced by adrenergic activity, and, indeed, treatment with β-blockers has been associated with an improvement in ventilatory efficiency [88], i.e. a reduction in VE/VCO_2 slope, more evident in patients with the highest pretreatment values, which likely explains symptom amelioration [81]. Consistently, Carvedilol, in comparison with placebo, reduced ventilation during a constant workload exercise test as well as

throughout a maximal exercise test (Figure 4) in 15 stable HF patients, with a concurrent reduction in VE/VCO_2 slope [77]. This behavior was observed both in normoxic conditions and during exposure to a simulated altitude (hypoxic conditions, ~2000 meters). However, PaO_2, measured in the plateau phase of a constant workload exercise test, was significantly lower with Carvedilol than with placebo [77]. This suggests that increased ventilation is a pivotal compensatory mechanism of hypoxia, whose impediment by Carvedilol could be detrimental in specific settings of HF patients. Notably, the damping effect on exercise hyperpnoea does not seem to be a class effect of β-blockers, since it has not been described with β-blockers other than Carvedilol. For example, in a retrospective study on 572 HF patients with reduced EF, it was observed that VE/VCO_2 slope was significantly reduced by Carvedilol in comparison to no β-blocker treatment, but not by Bisoprolol [89]. In the CARNEBI trial [47], exercise ventilation and VE/VCO_2 slope appeared to be significantly lower with Carvedilol than with Bisoprolol or Nebivolol. Moreover, central and peripheral chemosensitivity to CO_2 and to O_2 concentrations where investigated, observing the lowest degree of sensitivity with Carvedilol and the highest with Bisoprolol, with Nebivolol in an intermediate position [47]. As chemoreceptor function is highly influenced by adrenergic stimuli and NO concentration, this finding is consistent with the observation that Carvedilol induces a more complete adrenergic blockade than Bisoprolol, and that Nebivolol can increase NO bioavailability.

Conclusions

There is clear consensus that HF should be treated with β-blockers also in the presence of respiratory comorbidities, with the only important exception of true severe asthma, uncommon in older people. Regardless in the real life setting there is evidence of undertreatment with β-blockers of HF patients with concomitant COPD [90]. What is still unclear is whether there is a practical utility in choosing the type of β-blocker according to patients' characteristics. Indeed, when β-blockers are chosen randomly,

no prognostic difference is observed [91]. However, a few reports showed a remarkable difference in alveolar-capillary gas diffusion and chemoreceptor response according to the β-blocker used. Moreover, it should be underlined that some of the cited studies suffer from a study design (e.g. retrospective analysis, use of non-equivalent doses of β-blockers, non-adjustment for potential confounders, and so on) that might limit the interpretation and the applicability of data in the clinical practice. The reported flowchart (Figure 5) suggests a new practical way to optimize β-blocker treatment considering two categories of β-blockers: β_1-selective blockers and β_1-β_2 blockers. Particularly, in case of low DLCO, a β_1-selective blocker should be preferred. Similarly, a β_1-selective blocker could be chosen in case of HF patients with preserved DLCO but with concomitant severe COPD, hypoxia due to any cause or programmed exposure to hypoxia (i.e. high altitude, flight on commercial airplanes). In all other HF patients with a normal DLCO, age and the VE/VCO_2 slope value, an index of chemoreceptor activity, should drive the β-blocker choice. Indeed, in case of a pronounced ventilatory inefficiency (high VE/VCO_2 slope), a β_1-β_2 non-selective blocker should be preferred, while the choice will remain "free" in HF patients with a preserved DLCO and low VE/VCO_2 slope values. It is clearly recognized, however, that the proposed diagram is based only on physiological studies, that it has never been applied in the clinical setting, and that it does not take into account a lot of other factors differently affected by the various β-blockers such as cardiac and renal function, glucose tolerance, blood pressure, heart rate at rest and peak exercise, pulmonary function including airway hyperactivity, as it does not considers that the various β-blockers have different actions on the several comorbidity frequently present in chronic HF patients. All the above reported conditions must be taken into account when deciding about β-blocker treatment and choosing among different β-blockers. However, the flowchart proposed in figure 5 is a new fascinating working hypothesis which utility needs to be assessed. Moreover, we should underline that the proposed progression of the flowchart, i.e. starting with DLCO and then moving on to VE/VCO_2 slope, is

arbitrary, as are the proposed DLCO and VE/VCO_2 cut-off values. Finally, no clinical trials comparing β-blockers, chosen with this new approach, on hard endpoints (e.g. survival) are currently available, but they would be strongly needed to support the accuracy of the flowchart we proposed.

Conflict of interests: none

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Figure legend

Figure 1: Alveolar fluid clearance in the lung

Because of the gradient created by Na+/K+-ATPase, water passively follows Na+ into the alveolar cells through ENaC and also through the water channels, called aquaporins (AQPs), as well as through other paracellular pathways. Chloride (Cl-) transport through the cystic fibrosis transmembrane conductance regulator (CFTR) may support fluid transport across the alveolar space.

Figure 2: Effect of Carvedilol and Bisoprolol on lung function, lung diffusing capacity, and exercise performance in healthy subjects after saline infusion

FVC = Forced vital capacity; FEV1 = Forced expiratory volume in 1 second; DLCO = Lung diffusion for carbon monoxide; DM = Membrane diffusion; VCap = Capillary volume; VA = Alveolar volume; HR = Heart rate; VO_2peak = Oxygen uptake at peak exercise; VE/VCO_2slope = slope of the linear regression analysis of VE plotted vs. VCO_2 from the beginning of loaded pedaling to the end of the isocapnic buffering period. Reproduced from ref. 64 with permission.

Symbols denote statistical significance (** = $p< 0.01$; *** = $p< 0.001$).

Figure 3: Lung diffusion according to β-blocker type

DLCO, DM, and Vcap with Carvedilol (C), Bisoprolol (B), or Nebivol (N) in 60 patients with heart failure and reduced ejection fraction. Reproduced from ref. 38 with permission. ** $p< 0.001$, *** $p< 0.0001$.

Figure 4: Ventilation in normoxia and hypoxia

Mean (±SD) ventilation at several steps of a maximal exercise test in normoxic and hypoxic conditions during treatment with Carvedilol and placebo in 15 patients with heart failure and reduced ejection fraction. Data from ref 69. * $p< 0.05$ (comparison between Carvedilol and placebo in normoxia and hypoxia).

Figure 5: Flowchart of optimized β-blocker treatment

Suggestion on ß-blocker treatment strategies, based on physiological data. In orange the first choice, in blue the second choice, and in red non-suggested β-blockers.

HR = heart rate; SBP = systolic blood pressure

Fig1

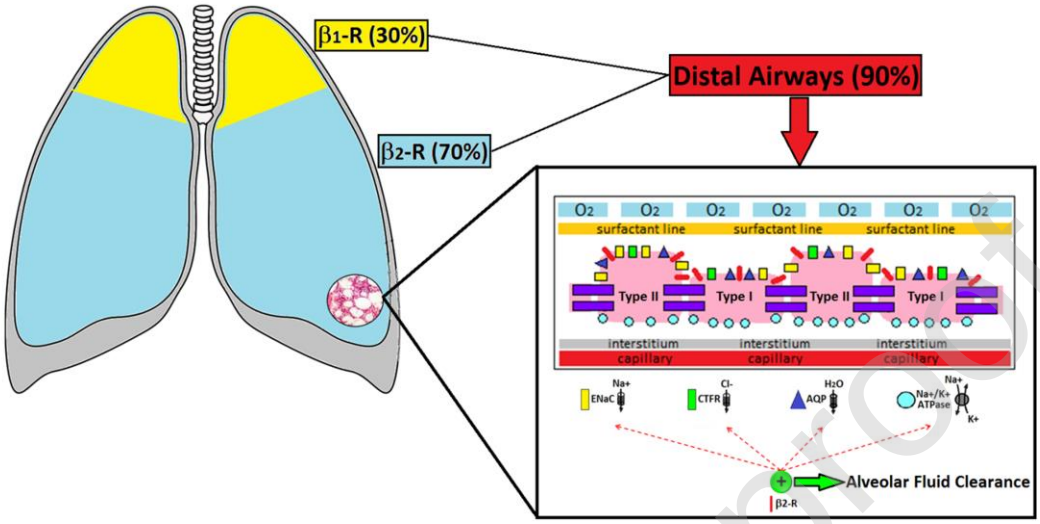

Fig 2

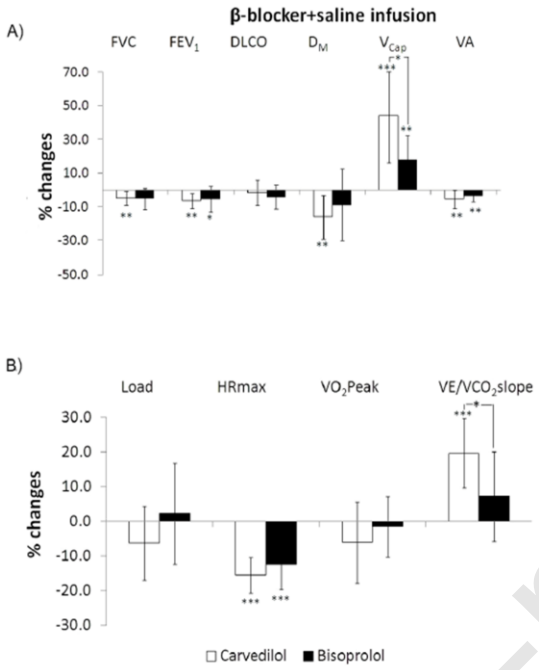

Fig 3

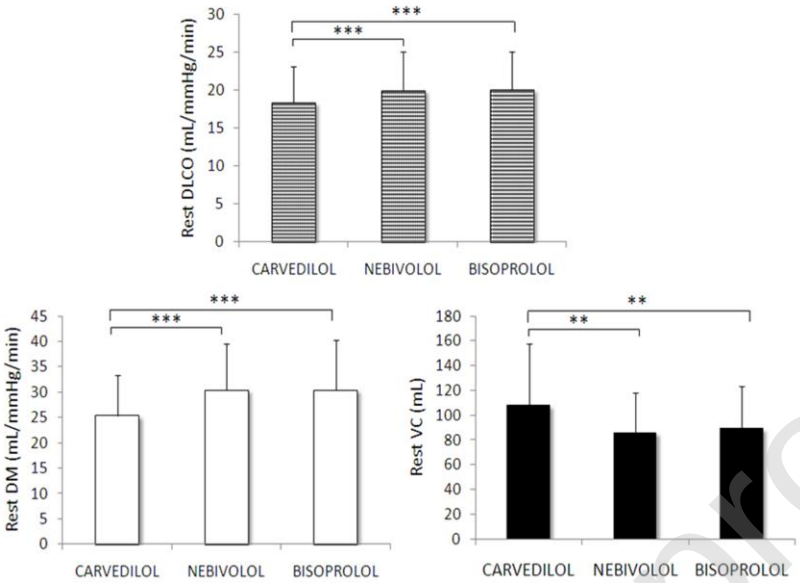

Fig 4

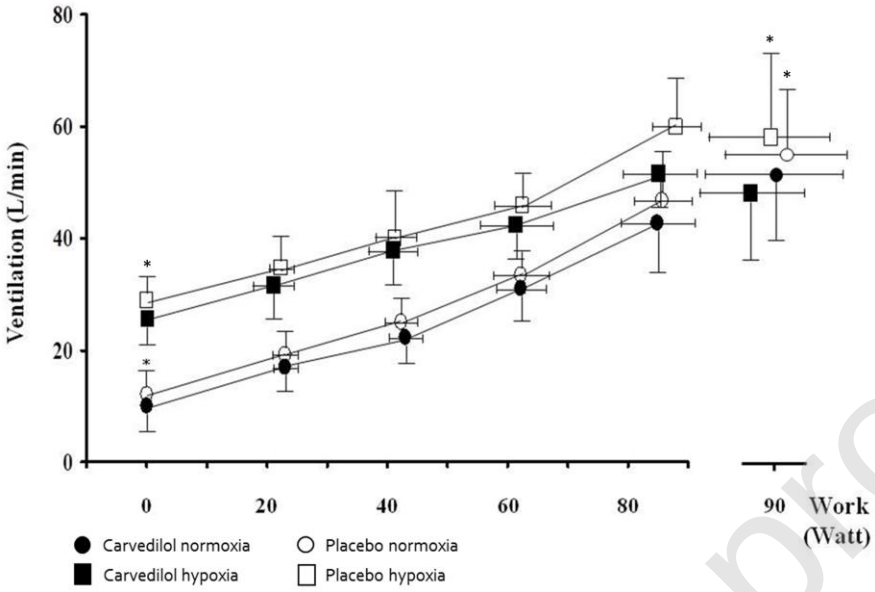

Fig 5