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Certainties fading away: β-blockers do not worsen chronic obstructive pulmonary disease

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For many years, β-blockers have been considered contraindicated in patients with heart failure (HF) and in those with bronchial asthma or even chronic obstructive pulmonary disease (COPD) although without clear evidence of asthma. Today, despite overwhelming evidence of the usefulness of β-blockers, especially in HF with reduced left ventricular ejection fraction (HFrEF), and in ischaemic heart disease, some reluctance persists in using these drugs when COPD coexists. Such resistance is due to the fear that a possible worsening of bronchospasm induced by β-blockers could induce negative effects greater than the benefits. The Guidelines of the European Society of Cardiology clearly suggest that: (i) implantation of a cardiac defibrillator (ICD) are not contraindicated in COPD without clear evidence of bronchial asthma; (ii) β-blockers are only 'relatively' contraindicated when there is certainty of bronchial asthma with a documented bronchodilator response to the β2 stimulant. Therefore, bronchial asthma is not an absolute contraindication to β-blockers. The cardiologist should not limit the diagnosis of COPD to clinical suspicion, but should rely on a spirometry examination associated with any bronchodilation tests. In any case, selective β1 blockers are preferred, starting at a basic dose, which ensure a better dilator response to bronchodilators and in any case cause less bronchospasm than non-selective β-blockers. Unfortunately, there is still some reluctance to the use of β-blockers in patients with COPD associated with HF, which should be eliminated.

The older ones among us will remember how decisively and confidently it was necessary to answer 'Heart failure (HF), bronchial asthma, chronic obstructive pulmonary disease (COPD)', under penalty of immediate rejection, to the question by the Professor about what were the contraindications to treatment with β-blockers. Indeed, the simple prescription of a β-blocker in a patient with HF was a reason for criminal complaint.[1]

Now the times have changed and overwhelming evidence accrued on the usefulness of β-blockers, especially in HF with reduced ejection fraction (HFrEF) and in ischaemic heart disease.

Despite these evidences, a certain 'reluctance' to use these drugs persisted for several years and, as Prof. Ferrari pointed out,[1] it was necessary to organize a specific National Project (BRING-UP)[2] to promote this practice in patients with HF.

Unfortunately, this reluctance has continued in the therapeutic approach to patients suffering not only from HF, but also from other conditions with indications for

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β-blockers, such as ischaemic heart disease, when bronchial asthma coexists, or even COPD without clear evidence of bronchial asthma.

Coexistence of HF and COPD

HF and COPD coexist more frequently than one may imagine. Out of 100 patients with HF, about 30 also have COPD and, conversely, out of 100 patients with COPD, about 30 have HF.[3,4]

According to various surveys, COPD increases the risk of developing HF, ischaemic heart disease, or cardiovascular disease in general by 2–5 times.[5,6] In addition, patients with COPD more frequently have subclinical coronary events characterized by occasional elevations in troponin and, sometimes, from sudden cardiac death.[7]

It is very likely that at the basis of the coexistence of cardiovascular diseases (notably HF) and COPD in many patients there are various common pathogenic factors including cigarette smoking, air pollution, advanced age, a chronic inflammatory state, and possibly overweight/obesity.[3,8,9] As we will see later, a reduced use of β-blockers in patients with HF associated with COPD could represent a further reason for the adverse prognosis linked to the coexistence of the two conditions.

Unfortunately, the coexistence of HF and COPD in the same patient exerts an important adverse prognostic effect, increasing, in the long term, the risk of hospitalization and mortality by at least 30% compared to their non-coexistence.[3,4,10] The risk of developing atrial flutter or fibrillation increases by ∼50% when HF and COPD coexist, compared to when they are alone.[11]

The coexistence of COPD and cardiovascular diseases assumes particular importance in the pathophysiology of COPD exacerbations, which often represent the cause of death of these patients.[12] In fact, the coexistence of cardiovascular diseases in patients with COPD not only increases the *probability of COPD exacerbation* itself but also increases *the severity of exacerbations, the likelihood of acute cardiovascular complications*, and the associated mortality.[13] Specifically, COPD exacerbation increases the risk of acute myocardial infarction by 2 times, the risk of HF by 6 times, and the risk death of 4 times.[14]

Also from a pathogenetic point of view, if on the one hand, the chronic inflammatory state associated with COPD could favour the progression of atherosclerotic lesions, the exacerbation of COPD could determine a further inflammatory effect on the plaque with consequent fissuring, rupture, and possibly thrombosis.[3,8]

Problems of diagnosis

Since many symptoms and signs are shared by HF and COPD (dyspnoea, asthenia, exercise intolerance, etc.), it is not always easy to interpret them correctly in the individual patient.[3] It would be very important to be supported by instrumental investigations, which, however, are not used very frequently. Spirometry, however, formally required by the Guidelines for diagnosing COPD, is performed only in about 30% of patients with HF in whom the cardiologist has already made a presumptive clinical diagnosis of COPD.[15] Therefore, it is not uncommon to make mistakes both in one sense and the other. In fact, out of 100 patients with HF, at least 30 would be misdiagnosed as having COPD, and at least another 30 would have true COPD which, however, went unnoticed.[16]

Figure 1, modified from a Review by Canepa *et al.*, shows broadly how the cardiologist should interpret the spirometric examination in patients with cardiovascular disease and suspicion of COPD and/or bronchial asthma. First of all, the FEV1/FVC ratio should be analysed, which, if <0.70 ('low'), defines an 'obstructive pattern' and if ≥ 0.70 ('normal') a non-obstructive pattern. In case of obstructive pattern, the FVC value will be evaluated which, if $<80\%$ of the predicted one, will confirm the obstructive pattern which will then be stratified into mild, moderate, severe, or very severe on the basis of the absolute value of FEV1 (always compared to the predicted). In case of a non-obstructive pattern, an FVC $<80\%$ predicted will define a restrictive pattern.

In case of obstructive but also restrictive pattern, further pulmonary tests (diffusion capacity, etc.) of pneumologist competence may be necessary. In particular, a reversibility of FEV1 $> 12\%$ 10–15 min after inhalation of 200–400 μg of albuterol or equivalent bronchodilator will lead to the diagnosis of asthma.

Three important points must be carefully considered: (i) The interpretation of spirometry is substantially identical in the presence of HFrEF and HF with preserved ejection fraction (HFpEF); (ii) spirometry becomes unreliable during a COPD exacerbation crisis, essentially due to fluid overload which implies a transient reduction in FVC and FEV1; and (iii) a concomitant airway obstruction may be present in patients with pulmonary arterial hypertension, which is poorly differentiated from that typical of COPD.

Underuse of β-blockers in COPD patients

β-blockers are certainly under-used in COPD patients, even in the absence of clinical or instrumental evidence of bronchial asthma. It is possible that the old 'bogeyman of failing' university exams, or even of the criminal trial, in case of prescription of β-blockers in these circumstances has remained deeply engraved in our minds. On the other hand, the concept of bronchoconstriction caused by the blockade of the β2 receptors, together with the relative 'non-selectivity' of the selective β1-blockers with the increase in dose may be further reasons for uncertainty and mistrust.

In one study, patients with concomitant HF and COPD had a 50% lower β-blocker prescription than patients with HF alone.[17] In a beautiful systematic review, Canepa *et al.* examined various HF registries, consistently recording β-blockers underutilization in patients with presumptive diagnosis of COPD.[3] In a study performed in New Zealand of 2637 patients with COPD and indication for β-blockers for acute coronary syndrome, only 57% of patients received such treatment.[18]

In a recently published Danish study, of 24 999 COPD and HF patients, only 57% of these patients were being treated

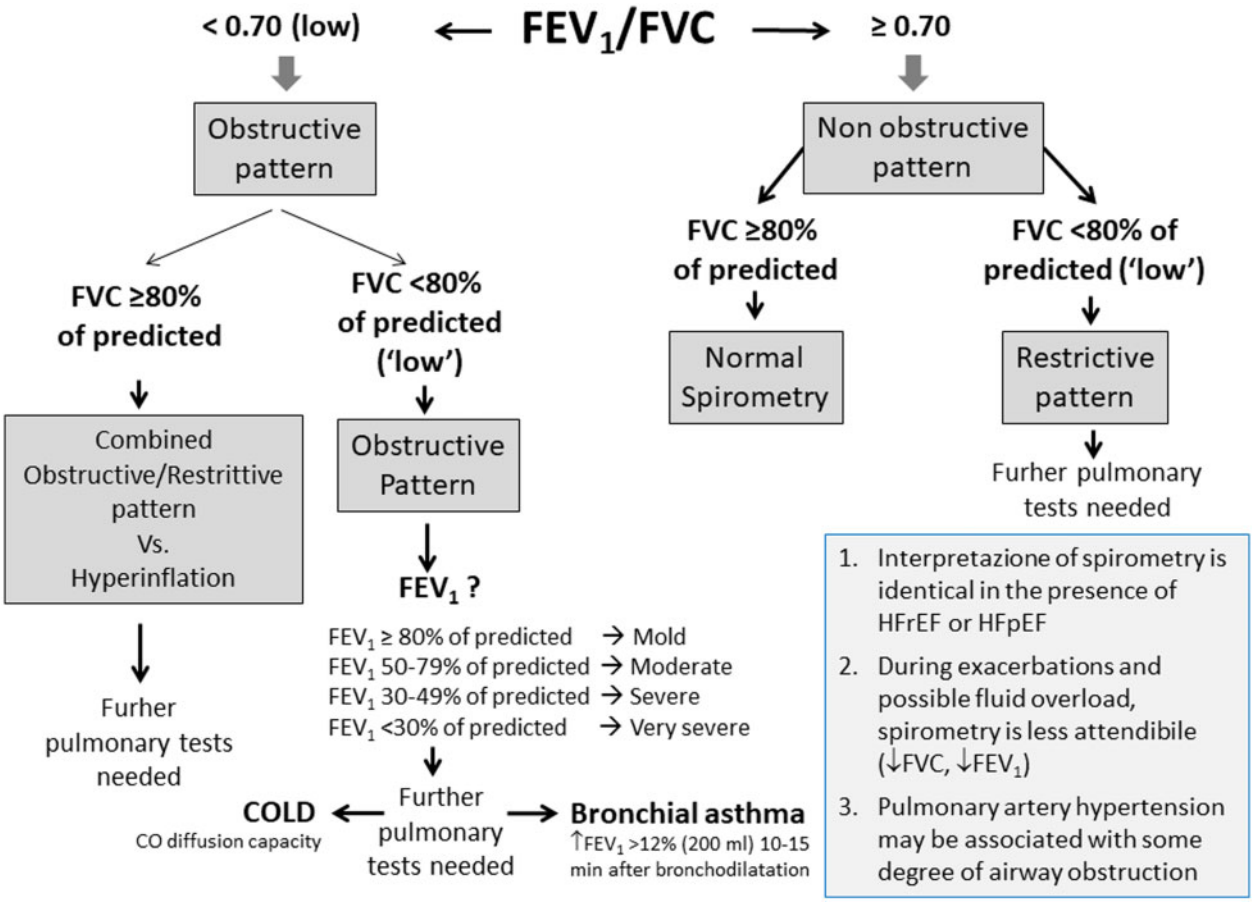

Figure 1 Interpretation of the spirometry in patients with heart failure and suspected COPD/bronchial asthma.

with β-blockers [among them: carvedilol in 27% and selective β-1 blockers (metoprolol, bisoprolol, nevibolol) in remaining 73%]. The carvedilol group presented an increased risk of hospitalization for HF (hazard ratio 1.61; 95% confidence interval 1.52–1.70), but no hospitalizations for COPD or all causes, and an increased risk of treatment discontinuation.[19]

Justification for β-blockers in COPD patients

Regardless of considerations related to tolerability, the use of β-blockers in COPD patients could be justified for two fundamental reasons:

(1) Preventing COPD exacerbations.
(2) Properly treat patients with COPD and indications for β-blockers (HF, chronic ischaemic heart disease).

Reason 1

Point 1 (prevention of COPD exacerbations) is related to the use of β-blockers in the absence of coexisting cardiac indications to the use of these drugs. This was a possibility raised by some individual studies and a meta-analysis of 15 retrospective studies which suggested that COPD patients on beta-blocker therapy had a reduced rate of exacerbations (−28%) and mortality (−28%). The finding was interesting, but subject to the various errors inherent in retrospective analyses including the so-called '*immortal time bias*' [i.e. compared to the group of patients NOT exposed to the risk factor, those exposed to this factor benefit from a period of time prior to their 'enrolment' in the study during which any deaths or 'end-points' go unnoticed and therefore not registered (as if the patients were 'immortal'), precisely because the patient had not yet been 'enrolled']. A randomized study was therefore designed in which 532 patients with moderate or severe COPD and no cardiac indication to the β-blocker were randomized to metoprolol or placebo. The study, discontinued for futility, showed no difference between metoprolol and placebo in terms of the first episode of COPD exacerbation, even in the presence of more frequent episodes of severe or very severe exacerbations in the metoprolol group.[20]

Reason 2

Point 2, which is what interests us most, has been widely presented in the latest ESC Guidelines on HF,[21] which we report in full:

(1) β-blockers are only relatively contraindicated in asthma, but not in COPD, although a more selective β1-adrenoceptor antagonist (i.e. bisoprolol, metoprolol succinate, or nebivolol) is preferred.
(2) The contraindication to β-blockers in asthma, as mentioned on pharmacy leaflets, is based on small

case series published in the 1980s and late 1990s with very high initial dosages in young patients with severe asthma.

(3) In clinical practice, starting with low doses of cardioselective β-blockers combined with close monitoring for signs of airway obstruction (wheezing, shortness of breath with lengthening of the expiration) may allow the use of profoundly effective β-blockers in HFrEF, especially in older people where true severe asthma is uncommon.

(4) Therefore, according to the 2015 GINA global strategy report, asthma is not an absolute contraindication, but these medications should only be used under close medical supervision by a specialist, with consideration of the risks for and against their use.

Therefore, the ESC Guidelines clearly reiterate the concept that β-blockers are not contraindicated in COPD without clear evidence of bronchial asthma, and are only relatively contraindicated in bronchial asthma, which therefore does not represent an absolute contraindication. In any case, β1 selective blockers are preferred. The list of β-blockers to be considered is shown in *Figure 2*.

It should be remembered that the contraindication to β-blockers in bronchial asthma is based on small series published in the 80s and 90s of the last century in which β1 selective blockers were used at rather high doses (with which β-1 selectivity is almost totally lost) in relatively young asthmatic subjects with a high intensity of bronchospasm. Therefore, in our clinical practice, we can very well resort to selective β1 blockers, starting at low doses and monitoring the patient for any adverse reactions related to bronchospasm. On the other hand, the generally elderly patients with whom we often deal only rarely have major bronchospastic reactions.

With regard to selective β1 blockers, some aspects should be underlined: (i) these drugs cause a lower reduction in FEV1 than non-selective; (ii) these drugs are accompanied by a greater bronchodilator response to bronchodilators (β2 stimulants) than non-selective β-blockers[22]; and (iii) nevibolol, β1 selective blocker with vasodilator effects mediated by stimulation of β3 receptors, with consequent release of nitric oxide, is the one with the highest block ratio β1/β2 (45:1), compared to metoprolol (2:1) and bisoprolol (14:1).[23,24]

The position of the ESC Guidelines is dictated by numerous individual studies and meta-analyses. In particular, a meta-analysis by Yang *et al*. which included 12 randomized studies and 37 observational studies performed in patients with COPD and cardiovascular diseases of various kinds documented a 33% reduction in-hospital mortality, and a 31% reduction in mortality from all causes, due to β-blockers.[25] In particular, the reduction in all-cause mortality rises to 38% when considering patients with HF and associated COPD. However, selective beta-blockers reduced all-cause mortality by 40% compared to non-selective beta-blockers.[25] Other meta-analyses provided comparable results. Coiro *et al*.[26] performed an analysis of 4 large randomized trials performed in a total of 28 771 patients with left ventricular dysfunction or HF, alone or in association, enrolled 12 h to 21 days after myocardial infarction, 8.3% of these patients had a concomitant COPD. In an analysis with propensity score matching after adjustment for 24 possible confounding factors, treatment with beta-blockers was associated with a 24% ($P = 0.032$) reduction in cardiovascular mortality, and a 29% reduction in cardiovascular and all causes mortality ($P = 0.003$).[26]

Drug	Receptors blocked	Initial dose	Target dose
Carvedilol	$\alpha_1, \beta_1, \beta_2$	3.125 mg b.i.d.	25-50 mg b.i.d.
Bisoprolol	β_1	1.25 mg o.d.	10 mg o.d.
Metoprolol	β_1	12.5-25 mg o.d.	200 mg o.d.
Nevibolol*	β_1	1,25 mg o.d.	10 mg o.d.

*Not approved in USA. Vasodilatatory effects due to β_3 receptor stimulation with NO release. Nevibolol has the highest β1/β2 ratio (45:1), versus metoprolol (2:1) and bisoprolol (14:1).

Figure 2 Drugs and doses to consider. Explanations in the text.

Conclusions

Based on these data, we conclude that in patients with COPD and clear indications for treatment with β-blockers (HF, chronic ischaemic heart disease), these drugs:

- Are not dangerous, especially if we use selective β1 ones, starting with low doses.
- They do not alter the bronchodilator effect of β2-stimulants.
- They are not contraindicated in COPD and are only 'relatively' contraindicated in bronchial asthma. Therefore, in patients with bronchial asthma and clear indication to the β-blocker (especially HFrEF), we also start with nevibolol or other low-dose selective β1 drug and we are still attentive to any episodes of bronchospasm, which is quite rare in elderly subjects with HFrEF. like the ones we usually see.

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