Significance of "beta blocker rebound phenomenon" and new suggestions how to avoid it

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Abstract: When beta adrenergic receptor blocker (BB) is stopped abruptly, tachycardia, blood pressure raise, increased number of anginal attacks, worsening of HF symptoms, etc. may ensue, which is known as "BB rebound phenomenon". Thus, the aim of the paper is four-fold: to review the topic (BB rebound phenomenon); to illustrate BB rebound presence in everyday practice; to provide Guidelines' view on BB rebound, and to suggest possible preventive measures (including the new ones) to avoid BB rebound. The majority of papers confirmed it, most of the studies showed even increased mortality in patients with coronary artery disease, and some patients from clinical practice clearly had BB rebound. Even if we suppose that BB rebound is rare, it is important because millions of patients worldwide take BB on daily basis. Moreover, an adverse cardiac event as a manifestation of BB rebound is unpredictable, making prevention more needed and more difficult. Thus, BB rebound concept remains useful, serving to remind us to warn patients not to withdraw BB on their own, particularly if BB dose is high. Comprehensive guidelines without a single exception suggest avoidance of abrupt withdrawal of BBs (BB rebound). Aiming to prevent BB rebound more efficiently, in the addition to already published suggestions, we recommend that selective and vasodilatatory BBs should be preferred. They have fewer side effects generally, which makes certain better drug adherence, decreasing the likelihood of BB rebound. Underestimation of problems with such potentially lethal diseases as acute coronary syndrome, heart failure, arrhythmias, etc. (where BB is indicated and, if abruptly ceased, can lead to rebound) may have very serious consequences.

Key words: Beta blocker, Rebound phenomenon, Arterial hypertension, Acute coronary syndrome, Heart failure.

1 Introduction

Beta adrenergic receptor blockers (BBs) are potent drugs. They are the mainstay, or at least an important component, of treatment of numerous diseases: stable angina pectoris (AP), acute coronary syndrome (ACS), heart failure (HF), ventricular and supraventricular arrhythmias, hypertrophic cardiomyopathy, etc [1]. **Definition**. BBs have strong useful actions on cardiovascular system, e.g. upon heart rate (HR), but BBs' sudden omitting often produces pronounced unwanted effects: tachycardia and arrhythmias, with palpitations; rise of BP, sometimes with hypertensive crisis; increased number of anginal attacks, worsening of HF symptoms, etc. [2]. This is called "**BB rebound phenomenon**". "Rebound phenomenon" in medicine generally means "after withdrawal of a useful drug, the condition becomes worse than before treatment".

2 Problem formulation

BB rebound was recognized as a problem long time ago -in **1973** [3]. It was first described in a series of case reports [4]. Between 1973 and 1976 about 33 cases with BB rebound were reported, all related to propranolol. These included patients who developed ACS or sudden death up to 3 weeks after propranolol withdrawal [5]. Indeed, 3 weeks seem too long a period for rebound to many clinicians.

Motivation for our paper comes from the ***relevance of the problem*** (BB rebound) in contemporary medicine:

1. **Indications** for BB are numerous, and **millions** of patients take BB. Moreover, BB is frequently part of therapy. Thus, many patients (including forgetful ones) take different doses of different drugs (usually unwillingly) which may easily result in the dose omission.
2. **Side effects** of BBs are higher than of many other drugs used in cardiology. The list of BBs' adverse effects is longer than any of other antihypertensive medications [2]. In many patients this may result in the idea to quit BB therapy, and it commonly occurs in a wrong way (without dose tapering). Thus, whatever the cause of mistake (patient is not responsible or is forgetful, or BB manifested side effect, or the doctor prescribed an inadequate dose, etc.), patient can quit BB therapy and experience BB rebound.
3. **Underestimation of problems** in cardiology, emergency medicine, general practice, etc. with such potentially lethal diseases as ACS, HF, arrhythmias, may have ***very serious consequences***.

Thus, the **aim of the paper** is four-fold:

1. to review the topic (BB rebound phenomenon);
2. to illustrate BB rebound presence in everyday practice;
3. to provide Guidelines' view on BB rebound, and
4. to suggest possible preventive measures (including the new ones) to avoid BB rebound.

3 Problem solution

3.1 BB rebound overview

BB rebound appearance include palpitations, arrhythmia, e.g. atrial fibrillation, headache and other symptoms due to BP raise, etc. BB rebound can lead to more dangerous manifestation: anginal attack, ACS, HF worsening.

3.1.1 Prognostic repercussions of BB rebound

Hypertensive patients who stopped taking their BB had a transient 4-fold increase in the risk of first events associated with coronary artery disease -CAD (**risk ratio -RR 4.5**, 95% CI 1.1 to 18.5) [6]. Moreover, selective BB discontinuation resulted in a higher risk of myocardial infarction (MI) in the first 30 days (**RR 2.70**, 95% CI 1.06 to 6.89) and between 30 and 180 days (**RR 2.44**, 95% CI 1.07 to 5.59) after BB cessation [7]. All 10 patients who received propranolol in a dose of 160 mg daily for 50 weeks had a marked increase in AP within 48h after drug discontinuation and a decreased exercise tolerance from their pre-treatment level [8]. A retrospective study of 140 patients who received BB preoperatively showed 50% mortality in the 8 patients who had BBs discontinued postoperatively. Such huge mortality was significantly greater than in the 132 patients in whom BBs were continued (**odds ratio 65.0**) [9]. In a study of 711 consecutive peripheral vascular surgery patients, withdrawal of BB was associated with an increased risk of 1-year mortality compared with nonusers (hazard ratio **2.7**, 95% CI 1.2 to 5.9) [10]. Many studies and case reports confirm the significance of BB rebound [11], [12], [13], [14], [15], [16], [17], [19], [20].

Thus, abrupt discontinuation of any BB may lead to a rebound effect and precipitation of severe AP, MI, or ventricular arrhythmias [21]. Moreover, BB rebound exists also in specific groups of patients, e.g. these with HF. BB withdrawal was first tested in patients with HF by the same Swedish group who first presented evidence that BBs were beneficial in HF [22]. We have witnessed even **aortic dissection following BB withdrawal** (partially triggered by BB rebound). There is also the case report on the same topic [23]. On the other hand, some studies did not find BB rebound. In large numbers of patients during acute MI, which is a hyperadrenergic state, abrupt withdrawal of BB did not result in either a greater incidence of creatine kinase -determined MI extension or in-hospital congestive HF, or arrhythmias, including nonfatal ventricular fibrillation [4]. In another study, in patients with stable even severe AP, the abrupt withdrawal of atenolol resulted in only minor clinical consequences [5].

3.1.2 Pathophysiologic mechanisms of BB rebound

Several mechanisms have been proposed to explain BB rebound phenomenon, including platelet hyperaggregability, increased plasma renin activity, an unfavorable leftward shift in the oxyhemoglobin dissociation curve, an increase in triiodothyronine levels, a reactive increase in plasma catecholamines, increased numbers of beta adrenergic receptors (β-AR) and/or an alteration in their affinity for adrenergic agonists, or rebound hypersensitivity to sympathetic stimulation [4].

The logical and **most accepted explanation** is the following. Exposure to a BB produces an increased number of postsynaptic β-AR [8]. The BB rebound phenomenon is likely to be **the result of increased β-AR responsiveness** (increased sensitivity to catecholamines or rebound adrenergic hypersensitivity), perhaps as a result of increased AR

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number [4], [8]. [19], [24]. BB rebound phenomenon is particularly dangerous in patients with CAD, in **whom β-adrenergic stimulation** can induce a sudden excessive increase in myocardial oxygen consumption [from elevated HR, BP, contractility, and free fatty acid use], and at times a concomitant reduction in myocardial oxygen delivery, possibly leading to acute ischemia, HF and arrhythmia [5], [22], [25]. On the side of oxygen delivery, with increased sheer stress, ischemia, and pro-aggregatory stimuli (norepinephrine, epinephrine) present, the likelihood of platelet aggregation or disruption of a plaque increases, creating a milieu for MI [22].

Thus, BB rebound ensues when sympathetic activity is high enough to override residual β-blockade [26]. BB rebound is **most pronounced during adrenergic stimulation**; accordingly, increase in heart rate was greatest in one study on standing with vasodilatation [19]. After BB withdrawal, HF patients had a significant vagal reduction to the level of the placebo group. This shift of the autonomic balance towards lower vagal and higher sympathetic tone, observed within 24h, could imply a potential risk when abruptly discontinuing BB [27].

3.1.3 Why is BB rebound worth of knowing and investigating?

BB rebound is important today, probably even more than earlier, because:

1. Individual ***chances to get symptom*** following the BB withdrawal (to "feel BB rebound") ***are high***.
2. Numerous and complex actions of BBs influence number of ***various unwanted effect*** in some cases of sudden withdrawal of BB.
3. ***Almost all manifestations of BB rebound*** (e.g. BP raise, tachycardia, myocardial ischemia, arrhythmia, HF worsening), and particularly their combination, ***can have deleterious (even fatal) consequences*** in a real-life clinical scenario.
4. Caution must be exercised when withdrawing any patient from any BB since **an adverse cardiac event is unpredictable** [24].
5. BB rebound is of potential clinical significance **even if it occurred in only one patient in the study** [24].
6. Moreover, tens and maybe even hundreds of ***millions of patients worldwide take BB everyday***, making any mistake very important.
7. ***The interest for BB rebound seems to be decreasing*** in medical publications; one can get a similar impression in clinical practice as well. Namely, PubMed search (on 12 April 2011) retrieved 157 papers about BB rebound before and including the year 2000, and only 19 publications thereafter. The worst thing doctors may do considering potentially lethal problem is to underestimate it.
8. *New information about BBs has accumulated* over the last years. BBs have profiled according to their pharmacokinetic and pharmacodynamic properties and their *widespread availability increases the need for a precise choice* [21].
   Therefore, one can reasonably hope for new modalities to improve solutions to an old problem – BB rebound.

3.2 Illustration of BB rebound in everyday practice

A) *Some patients may forget* to use the drug (or omit it on purpose).This happens because of time lack in modern life, forgetfulness of the patient, his/her intention to avoid side effect of a drug (which are remarkably frequent for BBs) such as fatigue, cold legs, impaired sexual function, nightmares, etc.

B) *A patient is suggested to omit the dose* for the purpose of conducting of e.g. exercise test. Namely, BBs are potent anti-ischemic agents and they may mask ischemic response to exercise /stress test. Namely, if a patient takes BB and the test on CAD is negative, it might be so either because it is true negative (patient has no significant CAD) or BB is effective in suppressing the manifestation of CAD (therapy is good). It is the rationale to suggest BB omission prior to an exercise test. Moreover, when dobutamine stress echo is used as a diagnostic tool to reveal myocardial ischemia, patients are usually advised to withdraw BB on the day before. Furthermore, to avoid a loss of sensitivity, it is suggested to interrupt carvedilol treatment at least 48 hours before the examination [25].

C) Many patients are told to withdraw BB preoperatively. The motivation for such advice comes from the wish to avoid hypotension and summation of negative inotropic action of BB and an anesthetic.

3.3 Guidelines' view on BB Rebound

Although data are limited, perioperative BB withdrawal should be avoided unless necessary [28]. BBs should not be stopped suddenly unless absolutely necessary (there is a risk of a ''rebound'' increase in myocardial ischaemia / IM and arrhythmias) [29]. Abrupt discontinuation of BBs after chronic treatment can lead to rebound symptoms (i.e., hypertension, arrhythmias,

exacerbated AP). This increased risk is related with upregulation of β-AR during chronic treatment [30]. Particular care should be taken to avoid withdrawal of BBs and clonidine because of potential HR or BP rebound, associated with a poorer outcome when noncardiac surgery is performed [31]. When a BB is withdrawn, the dose should be stepped down gradually [32]. BBs should be continued in those already established on treatment - to prevent rebound [33].

3.4 Suggestion of the possible practical preventive measures (including the new ones) to avoid BB rebound

1) **Knowledge** of the importance of BB rebound is essential. Thus, medical care providers should be repeatedly warned about it.
2) Compliance of patients should be continuously supported, including motivation for **adherence to the therapy**. Clear instructions should be given what should patients do if potential symptoms of BB rebound occur. Patients on **higher BB doses** should be especially instructed, because probability of clinical consequences of BB rebound is also higher in such patients [34].
3) BB tablet should be taken **soon after waking up** in the morning because of well known activation of the sympathetic nervous system upon awaking. The risk of stroke, MI, etc. in the first hour following the waking up are many times (up to 30-fold) higher as compared to some other periods of the day (e.g. during the hours of sleep) [35].
   This discovery led to the memorable title of the Editorial: "Should we get up in the morning [35]?
4) **Long-acting BBs** should be preferred both because of superior adherence and because chances for rebound diminish with prolonged effect. This is confirmed in medical literature [5], [36], [37], as well as in clinical practice.
5) **Selective** BBs may be preferable, because they have fewer side effects generally, by avoiding bronchial obstruction, by lesser impairment of lipid and glucose metabolism [21].
6) **Vasodilatatory** BBs have the aforementioned advantages, plus avoiding some additional side-effects of non-vasodilating BBs (cold legs, impotence, decreased physical capacity, etc). Staying away from side effects ensure better drug adherence which decreases the chances for BB rebound.
7) Taken altogether, the desirable characteristics of BB might be: vasodilatatory, β-1 selective, once-daily, approved and suggested from guidelines also for HF, cost-effective. Such one is available for clinical use.

4 Conclusion

1. It is wise to re-evaluate the approach to a persistent problem when the clinical scenario is changed (regarding diagnostic and therapeutic possibilities). BB rebound is not an unequivocally proved concept; nevertheless, the majority of papers confirmed it and some patients from clinical practice clearly had BB rebound. Also importantly, comprehensive guidelines without a single exception suggest avoidance of abrupt withdrawal of BBs (BB rebound).
2. It is often difficult to judge whether the clinical worsening following abrupt BB withdrawal is simply the result of absence of valid therapy or a real BB rebound happened (meaning that the situation got worse than it would be without the use of BB at all). Clearly, BB rebound occurrence depends on many factors (characteristics of the patient, the disease and the environment (e.g. cold weather), type of BB, how long BB is omitted, other treatment, patient's physical and psychical stresses, etc).
3. Thus, BB rebound concept remains useful, serving to remind us to warn patients not to withdraw BB on their own, because this may lead to unpleasant symptoms (which can decrease further drug adherence) and even serious complications. We should be aware that BB rebound can occur between day 1 and even 2 weeks, which is much longer period than intuitively expected.
4. It is very likely that BB choice can influence an eventual BB rebound occurrence, and we presented some known and some new, hopefully useful, suggestions.

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