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The prescription retroscope – tools for advocating critical and individualised therapy

Cook Stephane[a], Messerli Franz H.[b]

[a] Cardiology, University and Hospital Fribourg, Switzerland
[b] Cardiology, University Hospital Bern, Switzerland

Tick tock, tick tock, ticktock...

A high resting heart rate shortens life expectancy and conversely, a low heart rate may prolong life [1, 2]. Levine estimated that a reduction in mean heart rate from 70 to 60 beats/min throughout life could increase lifespan from 80.0 to 93.3 years of age. Palatini et al. compiled 43 papers encompassing the results of 39 studies on the risk of elevated heart rate for cardiovascular and/or all-cause mortality [3]. All but two of these studies reported a significant association between all-cause mortality and resting heart rate [4]. Acute and chronic stress with sustained catecholamine release is responsible for endothelial dysfunction/erosion (*primum movens* for atherosclerosis) and plaque rupture. Subsequently, amines promote ischaemia, infarction extension and arrhythmias. In short, prolonged sympathetic stimulation will kill us. Therefore, on the one hand, cocaine or phaeochromocytomas kill us and on the other, regular conditioning and relaxation techniques may protect us.

Adrenal-*ine* was isolated from the adrenals by Napoleon Cybulski (1859–1919) in 1895, but understanding of the impact of the adrenergic sympathetic system in cardiovascular pathophysiology was only made possible with the development of beta-blockers in the early 1960s. The motive for the development of propranolol by James Black's team was primarily to provide a reduction in myocardial oxygen demand in the patients of his colleague, the surgeon George Smith, but its introduction into clinical practice was one of the most important milestones in cardiology: Beta-blockers lower blood pressure and exert negative chronotropic, dromotropic, bathmotropic and inotropic effects on the heart. As modern cardiologists, we appreciate mainly the ability of beta-blockers to reduce the risk of rupture of vulnerable plaque, limit the size of the infarction, restrict arterial remodelling, reduce the risk of atrial and ventricular arrhythmia and improve haemodynamics. In short, selective (beta-1) beta-blockers have an undisputed and indisputable place in the therapeutic armamentarium of the management of ischaemic heart disease.

However, pharmacological heart rate lowering can paradoxically increase cardiovascular events, possibly because it elicits a ventricular-vascular mismatch, leading to increased aortic systolic blood pressure. Thus, either beta-blockers or ivabradine engender an increase in central (aortic) blood pressure and, consequently, reduce the expected decrease in myocardial oxygen consumption. Whether in heart failure, hypertension, or coronary heart disease, heart rate lowering consistently increases central systolic pressure. (fig. 1) [5].

The term pseudo-antihypertensive effect has been used to describe beta-blockers' effect on blood pressure. Not surprisingly, an increase in central systolic blood pressure is prone to antagonise the potential benefits of heart rate lowering interventions, possibly accounting for the failure to reduce outcomes in patients with hypertension [6] and stable coronary artery disease [7]. Whereas a low resting heart rate, however achieved, may prolong life, pharmacological heart rate lowering is by no means an easy way to achieve the same and does not confer longevity.

Moreover, like any active drug (unlike other magical substances!), beta-blockers have adverse effects, some of which are directly related to their cardiovascular effect (hypotension, cardiogenic shock, heart block, erectile dysfunction, peripheral arterial insufficiency) or to more systemic effects (fatigue, depression, bronchoconstriction, etc.). These adverse effects do not, however, prevent a sizable part of the population from using it for stage fright on an *ad hoc* basis: politicians, journalists, sportsmen and -women involved in precision sports, musicians, theatre actors or anxious people, who do not care too much about these effects.

People who survive an acute myocardial infarction have an increased risk of a second cardiovascular event, whether it is another myocardial infarction, sudden cardiac death, heart failure, or stroke. Depending on gender and clinical outcome, the risk of morbidity and mortality in myocardial infarction survivors is between 1.5 and 15 times higher than in the general population [8]. As such, beta-blockers are a cornerstone of the initial treatment, as are dual antiplatelet therapy, statins, and renin- angiotensin-aldosterone- system inhibitors.

So, should we give beta-blockers to all patients after myocardial infarction? And if so, at which dose and for how long?

For a physician, answering this question means looking in turn at the scientific evidence, the recommendations of cardiology societies, his or her own experiences, and the pa-

Correspondence:
Stéphane Cook, MD, Department of Cardiology, University and Hospital Fribourg, CH-1708 Fribourg,
stephane.cook[at]unifr.ch

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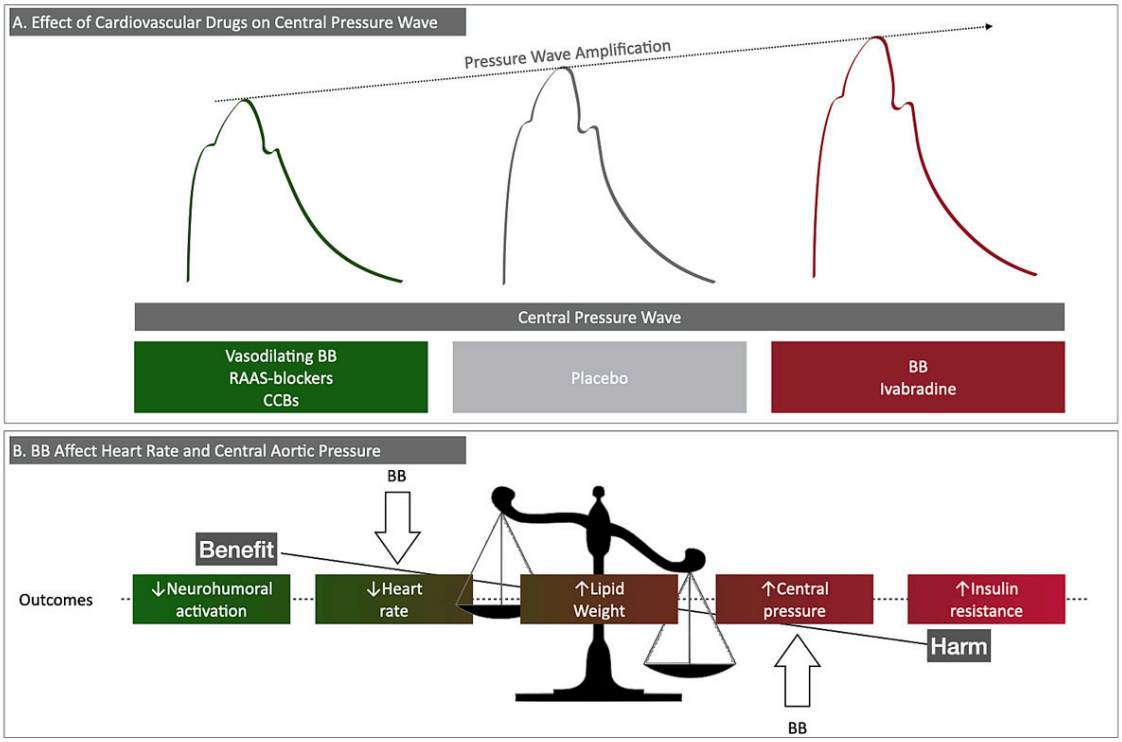
Figure 1: Panel A. Effect of cardiovascular drugs on central pressure wave. Lowering of resting heart rate increases central pressure (compared with placebo). **Panel B.** Duality of beta-blocker therapy in STEMI patients. Beta-blockers may affect clinical outcome on one hand by lowering heart rate, but on the other hand they increase the central aortic pressure.BB = beta-blocker; CCB = calcium-channel blocker; RAAS = renin-angiotensin-aldosterone system; STEMI = ST-segment elevation myocardial infarction



tient he or she is dealing with. In an age of over-information, fake news and social networking, these precepts can take unexpected turns. The article by Christel Bruggmann and colleagues [9], published in *Swiss Medical Weekly*, does the opposite: it looks at the prescriptions made by medical practitioners and how well they match with the manufacturers' guidelines. It is an elegant way of understanding the place (and the dose) of a treatment.

Looking at the result at the end of a football match does not allow us to change the score, but makes us wonder about strategies for the future. Here, Bruggmann et al. looked at the adequacy of prescriptions both in terms of number and dosage at hospital discharge and at 1-year follow-up in 266 patients who underwent primary angioplasty for ST-segment elevation myocardial infarction (STEMI) and of whom 18% had left ventricular dysfunction defined by an left ventricular ejection fraction (LVEF) <40%. The findings were that (a) 91% of patients with no obvious contraindications received a beta-blocker at discharge versus 83% at 1 year; (b) of patients receiving a beta-blockers at 1 year, 9% had a high dose (>50% of the manufacturer's recommended dose); and (c) during the year, only 20% had a change in dose, the majority (36 of 46) of which was a reduction or discontinuation of treatment.

Based on these findings, let us now attempt to answer the three original questions.

Should all patients be prescribed a beta-blocker?

The answer is no: beta-blockers are deleterious in those with symptomatic bradycardia, atrioventricular block, cardiogenic shock and some kinds of asthma. Consistently, beta-blockers are associated with excess mortality in elderly patients (>70 years), and in those with acute heart failure (heart rate >110 bpm and systolic blood pressure <120 mm Hg) [10, 11]. Besides, beta-blockers are of little necessity in those with low resting heart rate and those with preserved left ventricular function. Furthermore, beta-blockers should be used with caution in inferior STEMI (atrioventricular block!).

As widely demonstrated, beta-blockers decrease mortality after myocardial infarction. This was particularly well documented more than a quarter of a century ago, before the current revascularisation era, and has become uncertain at the present. Aggressive reperfusion therapy has drastically reduced the possible benefits of beta-blocker therapy [12]. This paradigm change is not surprising, since a reperfused, viable myocardium has little in common with a necrotic or scarred myocardium, which generates arrhythmias because of re-entry mechanisms, enhancing the capability of beta-blockers to prevent sudden death. From the mid-1980s onwards, beta-blockade was an iron-clad therapy for coronary artery disease and not uncommonly it remained a life sentence after the patient had suffered an acute coronary syndrome [13]. Fortunately, the guidelines have now evolved from a IA indication for all post-myocardial infarction patients until 2008 [14, 15] to IA only for those with residual systolic left ventricular dysfunction (LVEF <40%) [16, 17].

For patients with systolic left ventricular dysfunction, the evidence of the benefit of beta-blockers has been strengthened. Two different mechanisms support the systematic ad-

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ministration of beta-blockers in patients with systolic left ventricular dysfunction. On the one hand, they have a preventive effect on sudden death through the bathmotropic effects, which largely impact survival in patients with an ischaemic and/or dilated left ventricle. On the other hand, they beneficially effect ventricular remodelling: beta-blockers fight against the "negative staircase" (the higher the heart rate, the worse the LVEF). As such, beta-blockers improve haemodynamics in patients with LVEF dysfunction after myocardial infarction [18]. For these patients, heart failure guidelines prevail and should be followed.

But should beta-blockers be prescribed in patients with preserved LVEF? Some of you may remember that sympathetic (hyper-)activity is related to plaque rupture, ischaemia and may impact the infarct size (this is particularly true in some preclinical models with a preponderant collateral flow, such as dogs) [4, 19]. Nevertheless, these beneficial effects did not translate into clinical evidence: the absence of demonstrated preventive effect and similar myocardial infarct size on magnetic resonance imaging in EARLY-BAMI [20] no longer favour beta-blockers for all. Moreover, the risk of malignant arrhythmia remains low after acute myocardial infarction if LVEF is preserved. Consistently, for patients with preserved left ventricular function, current evidence does not show any significant protective effect after 1 month [21, 22]. This led the European Society of Cardiology (ESC) to modify the recommendations in these patients (IIa, level of evidence B if LVEF >40%).

In brief, beta-blockers are particularly beneficial early after acute myocardial infarction n patients with systolic left ventricular dysfunction and those at high risk of arrhythmia and sudden cardiac death. High resting heart rate, residual angina and uncontrolled arterial hypertension remain softer beta-blocker indications (fig. 1) [23].

In the Lausanne population, >91% of the 266 patients treated for STEMI between 2014 and 2016 were treated with beta-blockers at hospital discharge. This is in line with similar registries (78–93%) [24–27].

At which dose?

As proposed by Kjekshus and Gullestad, the protective effect of a beta-blocker post-myocardial infarction is directly related to its heart rate-lowering effect [28]. Bruggmann and colleagues considered the doses used in clinical trials to be the therapeutic target [9]. Nevertheless, tolerability of beta-blockers is variable and a significant proportion of patients will be unable to reach the so-called *target* doses. This is even true for clinical trials where the mean dose is usually 75% of the target (e.g., COPERNICUS – carvedilol 37 mg vs 50 mg [29], or MERIT-HF – metoprolol 159 mg vs 200 mg [30]), and should be less in everyday practice where patients are older and sicker.

Is there any benefit in increasing the dose of beta-blockers once a certain degree of heart rate reduction has been achieved? In the MERIT-HF study, patients taking a small dose at 3 weeks (<100 mg) had the same heart rate (67 bpm) and mortality reduction (38%) as those with a higher dose (>100 mg). These results suggest that heart rate– -and not the *target* dose – should be used to titrate beta-blockers. In the era of connected smartphones and watches with extended sensors, heart rate analysis has become simple and inexpensive.

For how long?

The decision to end, maintain or increase the dose will be taken on a case-by-case basis based on objective (heart rate, systolic left ventricular function, and the risk of arrhythmia) and more subjective factors. These latter "softer" parameters often include fatigue or erectile dysfunction and impact steadily treatment compliance in our society where performance and sexual health are pushed forward. Patients with persistent severe left ventricular dysfunction (HFrEF) require indefinite treatment. In these patients, the motto "start low, go slow, aim high" of the heart failure guidelines prevails. In contrast, patients with a normalised left ventricular function after a few weeks can discontinue beta-blocker therapy without major concerns. In practice, we recommend to start and titrate beta-blockers every 2–3 weeks to achieve a target heart rate of 60–70 bpm at rest. All patients should be followed up with a 48-hour ECG recording and transthoracic echocardiogram 3 to 6 weeks after a myocardial infarction. The finding of Bruggmann et al. is that beta-blockers are rarely up-titrated during follow-up (4.7% in <40% LVEF, 4.9% in >40% LVEF). This is a message of paramount importance since patients with left ventricular dysfunction would definitively profit from up-titration. Until then, the only ironclad indication for cardioprotection with beta-blockers remains heart failure with reduced ejection fraction, the very indication that half a century ago was the only contraindication for beta-blocker therapy [31].

In conclusion – and to paraphrase Socrates – *the highest form of* (medical) *excellence is to question oneself* ... and talk with our patients.

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