Closed Loop Stimulation Provides Baroreceptorsensitivity Clinical Relevance and Long Term Prognosis

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Introduction

One of the central topics in this issue of Progress in Biomedical Research is the concept of closed loop stimulation. This new era in treating bradycardiac rhythm disturbances is based on 8 years of research and clinical experience with DDD-CLS and VVI-CLS systems worldwide running in closed loop mode for years. A new milestone in closed loop pacing was achieved with the successful realization of the automatic initialization in the Inos^2 CLS pacemaker with the beginning of this year. The closed loop concept integrates the implantable device into the natural circulatory system. As a consequence, the heart rate is regulated by the circulatory centers. For the excellent work in their multicenter study concerning closed-loop stimulation, Andrade et al. received the *REBLAMPA* prize for scientific quality at the occasion of the XIVth Brazilian Congress of the DAEC in 1997. Several articles in this issue discuss clinical benefits of this system.
The following comments shall summarize the ideas of many physicians who gave us impact to the concept and development of closed loop stimulation.

Physiological background of blood pressure control

Guyton et al. describe the function of the heart as "..supplying a motive power for mixing most of the body's fluids, keeping a stream of fluid flowing continually through all parts of the body.." [1]. The aim of the cardiovascular control system is to maintain blood pressure in physiological range to guarantee the transportation of gas, metabolites, water, and electrolytes between the organs and the muscles. This circulation process is evident and loss of it is life-threatening within several minutes [2]. The autonomic nervous system controls the cardiac output and thus maintains the blood pressure [3][4]. The cardiac output is affected in three important ways: heart rate, strength of contraction of the heart, and the level of the mean circulatory pressure [5].

Autonomic effects on heart rate and contractile force

Even the normal heart is constantly affected by parasympathetic and sympathetic tone, which is several times lower than the vagal one [6]. The three-dimensional plot in figure 1 shows clearly that comparable variations of vagal and sympathetic activity lead to considerably different changes in heart rate (vagal > 100 bpm, sympathetic < 60 bpm). The other importance of the vagal influence is the short time constants: direct stimulation of the vagus nerve decrease the heart rate often in one beat down to zero [7]. For a long time it has been assumed that only sympathetic stimulation has a substantial influence on the strength of the ventricular beat, but further studies have shown, that also parasympathetic control affects contractility of ventricular muscle by 15 to 20 percent [8][9].

Effect of autonomic reflexes on blood pressure

Many discrete circulatory reflexes, activated during exercise and during other conditions, that are stressful to the circulation, are especially important in increasing the cardiac output. The primary circulatory reflex is the pressoreceptor reflex located in the walls of the internal carotid arteries slightly above the carotid bifurcation. The pressoreceptor impulses are transmitted by the Hering nerve, a branch of the glossopharyngeal nerve, to the medulla oblongata. In general, the pressoreceptor impulses inhibit sympathetic stimula-

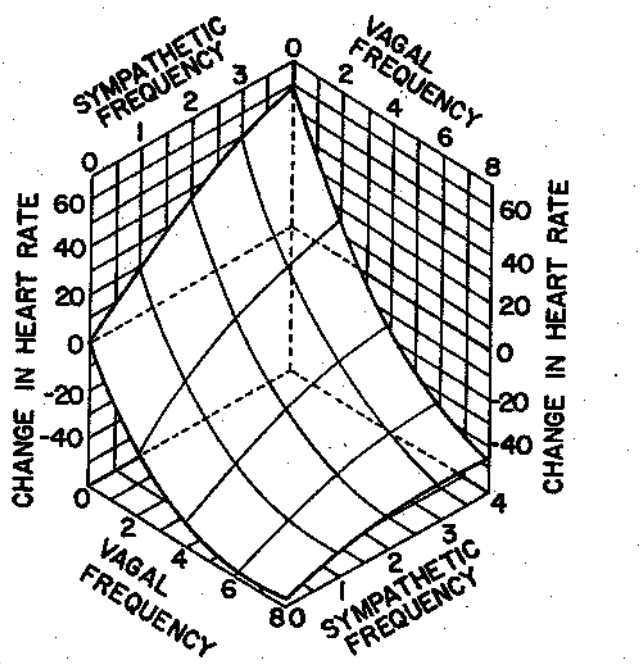

Figure 1: Influence of the vagal and sympathetic frequencies (indicated in independent arbitrary units) on the heart rate. Changes of the vagal frequency lead to a variation of the heart rate by 100 bpm, while a comparable sympathetic tone eases the heart rate by only 60 bpm, modified from [6].

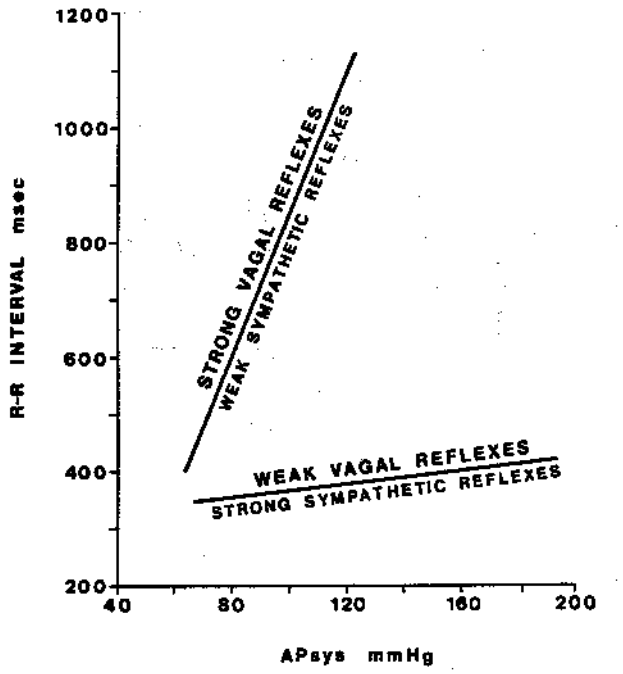

Figure 2: Two extreme patterns of heart rate response to systolic blood pressure. Baroreceptorreflex sensitivity is expressed by the slope of the regression line and quantified in msec lengthening of RR interval per 1 mmHg of blood pressure change. modified from [18].

tion of the entire circulatory system and enhance parasympathetic stimulation. It is universally recognized that the pressoreceptor reflex is primarily concerned with the regulation of arterial pressure [10].

Importance of blood pressure and blood pressure variability

Blood pressure (BP) is known to continuously fluctuate over time and both the amplitude and frequency of these changes have been reported to be clinically relevant [11]. Moreover, several studies have provided evidence that the end organ damage of hypertension is not only more closely related to 24h average BP values than to casual BP readings, it is also significantly and independently related to the degree of BP variability during day and night. Results from a recent follow-up study support the possibility that the degree of BP variability may also have prognostic relevance in hypertensive patients [11], reduce risk of coronary heart disease [12] and carotid atherosclerosis [13], and ventricular tachycardia [15,16,17]. The autonomic reflexes with the fast change of heart rate driven by the vagal tone avoid a high degree of BP variability and thus, provide a good prognosis by the patient. The degree of functionality of BP regulation is assessed by the baroreceptor sensitivity [16].

Baroreflex sensitivity (BRS) has rapidly gained considerable attention as a result of multiple experimental and clinical reports on its prognostic value after a myocardial infarction. The complex pathophysiology underlying BRS and the hypotheses proposed to explain its frequent reduction after a myocardial infarction are discussed. The section on experimental data also provides a rationale to understand the relation between increased vagal activity and reduced propensity for ventricular fibrillation. This focuses largely on BRS and the risk of cardiac mortality and includes several attempts to modify this marker of reflex vagal activation [15][16].

The autonomic nervous system and tachycardias

The autonomic nervous system has been demonstrated to play a decisive role in the genesis of sudden cardiac death. The loss of protective vagal reflexes, in particu-

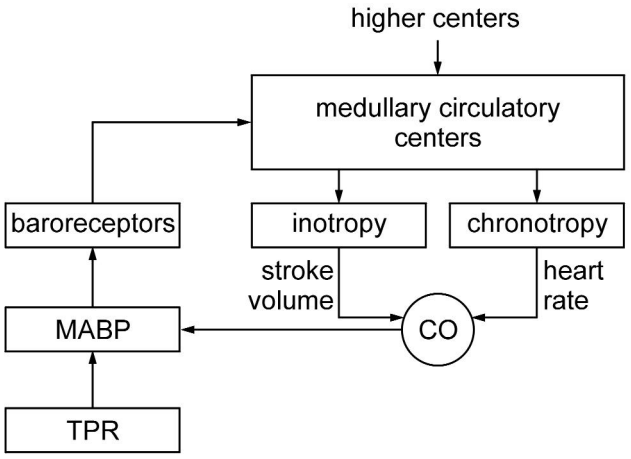

Figure 3: Re-establishing of the baroreceptor sensitivity in patients with chronotropic incompetence by extracting the

modified from [24].

lar, appears to be associated with an increased incidence of malignant ventricular tachyarrhythmias, determinated by heart rate variability and evaluation of baroreflex sensitivity [19]. The results indicate that postmyocardial infarction patients who develop life-threatening ventricular tachyarrhythmias, compared with carefully matched postinfarction patients without major arrhythmic episodes, differ strikingly in terms of baroreflex sensitivity but not in terms of heart rate variability. This finding may have implications for differential therapeutic strategy based on autonomic testing [20] and active influencing the autonomic tone. Recent studies have suggested that disordered autonomic function, particularly the loss of protective vagal reflexes are associated with an increased incidence of arrhythmic deaths following myocardial infarction (MI). Heart rate variability (HRV) and baroreflex sensitivity (BRS) are measures of myocardial autonomic function and predict arrhythmic deaths post-MI. Patients with ventricular tachycardia associated with a "normal heart" frequently have exercise-induced arrhythmia suggesting that the autonomic nervous system is important in the genesis of this form of ventricular tachycardia (VT) [21]. Specifically, sympathetic activation can trigger malignant arrhythmias, whereas vagal activity may exert a protective effect. Several experimental observations have provided new insights on the relation between sympatho-vagal interactions and the likelihood for the occurrence of ventricular fibrillation. The antifibrillatory effect of vagal activation is confirmed by the prevention of ventricular fibrillation during acute ischemia susceptible to sudden cardiac death by direct electrical stimulation of the right vagus [23].

Integration of active implantable device into cardiovascular control system

In the case of chronotropic incompetence the connection between blood pressure regulation and heart rate regulation is blocked and thus, this may influence the prognosis in hypertensive patients [11], increase risk of coronary heart disease [12], carotid atherosclerosis [13], and ventricular tachycardia [15,16,17]. The therapy of bradycardia must therefore take into account that still the circulatory centers control heart rate via the autonomic reflexes. The schematic figure 3 shows the basic concept of reestablishing the baroreceptorsensitivity by extracting information from the dynamics of the myocardial contractile force.

Conclusions

The integration of active implantable devices into the circulatory regulation system is not only evident in the therapy of bradycardiac arrhythmias but will also have impact on developing new antitachycardia systems with features for the preventive therapy. By extracting information not only from ventricular muscle but also from sinus or AV node imbalance of the autonomic system which precedes tachyarrhythmias [25-28] can be observed and a suitable preventive therapy can be provided. Thus, from my point of view, an implantable device with combined modules for antibradycardiac and antitachycardiac therapy will be the device of choice. Hence besides the reestablishment of baroreceptorsensitivity and the resulting better prognosis of the patient with the closed loop stimulation, the preventive closed loop therapy detects pending arrhythmias by evaluating either vagal or sympathetic hyperactivity and influences autonomic tone by overdrive stimulation and subthreshold stimulation [18].

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