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Baroreflex variability and "resetting": A new perspective

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ABSTRACT

A new framework is proposed for the interpretation of spontaneous cardiac baroreflex sensitivity data and the general concept of baroreflex resetting. The framework is used to explore baroreflex function along two separate lines of inquiry: one following a direct intervention in baroreflex function in individual subjects, another in a group of subjects where baroreflex function may have been compromised by coronary artery disease or aging. It is found that under baseline conditions the baroreflex is in a "free-floating" state in which the gain or "sensitivity" is highly variable, while under orthostatic stress or in the absence of or reduced vagal input the gain is more tightly controlled with an expected decline in sensitivity but a very large decline in the variability of that sensitivity. It is concluded that baroreflex "resetting" is better viewed not simply as a change in baroreflex sensitivity but rather as a change in the "focus" or "attention" of the baroreflex as expressed by an observed decline in the variability of the measured gain. The results do not support the interpretation of baroreflex "resetting" as a departure from or return to a universal "set point" as in homeostasis or open loop models.

1. Introduction

The baroreflex is a key mechanism in the control of arterial blood pressure. An important functional index of that mechanism is the so-called cardiac baroreflex "sensitivity", usually expressed in terms of observed change of heart rate or RR-interval, divided by the corresponding change in pressure. Because of the reciprocal relation between heart rate and RR-interval, either one can be used in this assessment and, for simplicity, we shall henceforth use only the latter. A considerable body of research and methodology has been devoted to the study of baroreflex sensitivity under different levels of physical activity, aging, disease and experimental conditions (Scher and Young, 1963; Kent et al., 1972; Bertinieri et al., 1988; La Rovere et al., 1998; Parati et al., 2000; Joseph et al., 2005; Raven et al., 2005; Baumert et al., 2006; La Rovere et al., 2008, Akimoto et al., 2011; La Rovere et al., 2011; Fitzgibbon et al., 2012, Okada et al., 2012; Wang et al., 2012).

A key concept which has been pursued vigorously in the past is that of baroreflex "resetting" whereby the baroreflex is found to become more sensitive, less sensitive or, in the limit, "switched off" (Verberne et al., 1987; Head and Adams, 1992; Rowell and O'Leary, 1990; Potts et al., 1993; Rowell, 1993; Parati et al., 1995; Parlow et al., 1995; Norton et al., 1999; Ogoh et al., 2003; Parati et al., 2004; Schelven et al., 2008). This concept has been central in studies of baroreflex function because one of the main aims of such studies has been to understand the clinical implications of a change in baroreflex sensitivity. However, while a change in baroreflex sensitivity can be measured by comparing the sensitivity under one condition with that at another, the concept of baroreflex resetting goes further to imply the existence of a universal or baseline value of the sensitivity which can be used as a reference, i.e. with which all other values can be compared.

The paradigm underlying this view has its origin in the results of experiments where "open-loop" conditions are induced to the effect that a change in arterial pressure is allowed to lead to a change in RR-interval through the baroreflex mechanism but the change in RR-interval is prevented from feeding back (through the vascular system) to cause a change in pressure (Chen and Bishop 1983; Barbieri et al., 2001). Under these highly controlled conditions baroreflex sensitivity reaches a maximum at a certain value of the pressure but declines continuously at higher or lower pressures. Thus, if for the purpose of this discussion pressure is denoted by x and RR-interval by y, then baroreflex sensitivity or gain (G) is simply the slope of a curve describing that behavior in the xy-plane, i.e.

$$G = \frac{dy}{dx} \tag{1}$$

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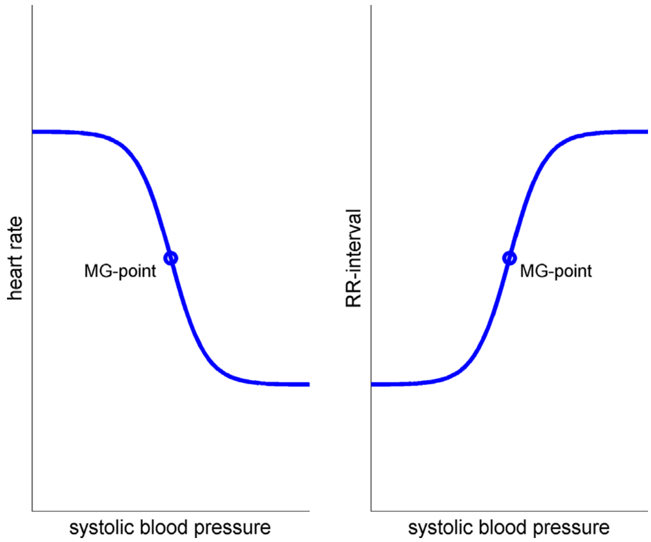

Fig. 1. Orientation of the logistic curve when the controlled variable is heart rate (left) or RR-interval (right). In both cases the underlying shape of the curve is such that baroreflex sensitivity is highest at the MG-point, the point where the slope of the curve is maximum. Baroreflex sensitivity diminishes at higher or lower pressures as the slope of the curve diminishes. Results in this paper are based on measurements of RR-interval and therefore the orientation shown in the right panel is used throughout the paper.

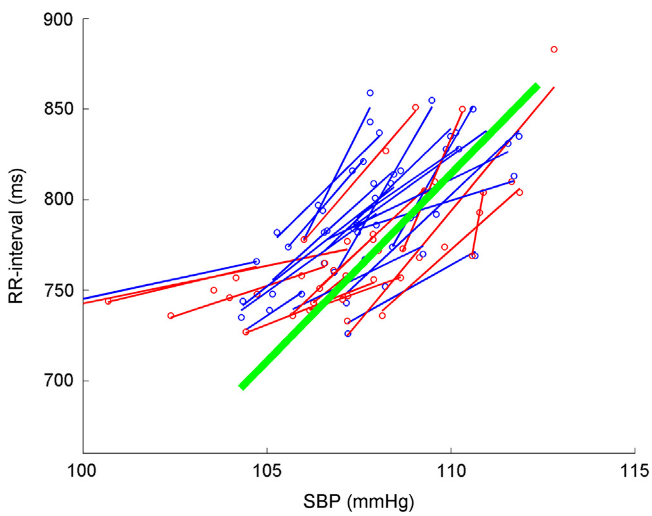

Fig. 2. An example of results obtained from spontaneous sequence analysis over a time period of 300 s. Each of the thin line segments is based on three or more data points in which the baroreflex was "engaged" during a rising (red) or falling (blue) SBP, the slope of the line being a measure of baroreflex "sensitivity" during that episode. Typically, there is wide variability in the slopes of the lines, therefore only an average slope (thick green line) is usually taken as a measure of baroreflex sensitivity during the time period.

A curve which has been used in the past to model the behavior described by the open loop experiments is the so called "sigmoid" or "logistic" curve (Fig. 1). The point of maximum gain has been referred to in the literature as the "set point" (Kent et al., 1972) or "centering point" (Raven et al., 2005). To avoid confusion we shall refer to it simply as the maximum gain point (MG-point, Fig. 1). The concept of baroreflex resetting has usually been discussed within the context of this open-loop logistic curve.

Measurements of baroreflex sensitivity in the intact physiological system (closed loop) have traditionally been based on simultaneous recordings of pressure and heart rate or RR-interval over a continuous period of time. By a technique generally known as "Spontaneous Sequence Analysis" (Blaber et al., 1995; Parati et al., 2000; Moffitt et al., 2005; Stauss et al., 2006; Laude et al., 2008; Hollow et al., 2011), these recordings are examined to detect brief intervals in which a rise or fall in pressure is accompanied, respectively, by a rise or fall in RR-interval. The coincidence of these two events is then seen as evidence of baroreflex "engagement" during these brief intervals, and the change in RR-interval divided by the corresponding change in pressure at each such interval is defined as the average baroreflex sensitivity during that interval.

A long-standing conundrum presented by the results of spontaneous sequence analysis data is that under physiological closed-loop conditions they generally show a considerable amount of scatter to the extent that there is no hint of the single logistic curve obtained under open-loop conditions (Figs. 2 and 3) and it is then not possible to determine what form of baroreflex resetting is taking place. In particular, it is not clear whether under closed-loop conditions this indicates that the baroreflex is operating at two different points along the same logistic curve, or that the two points are actually on two different logistic curves. The difference between these two scenarios has profound theoretical and clinical implications, particularly as they relate to the concept of baroreflex "resetting". Put in the wider context of baroreflex function, the question is how to reconcile the large scatter in baroreflex sensitivity

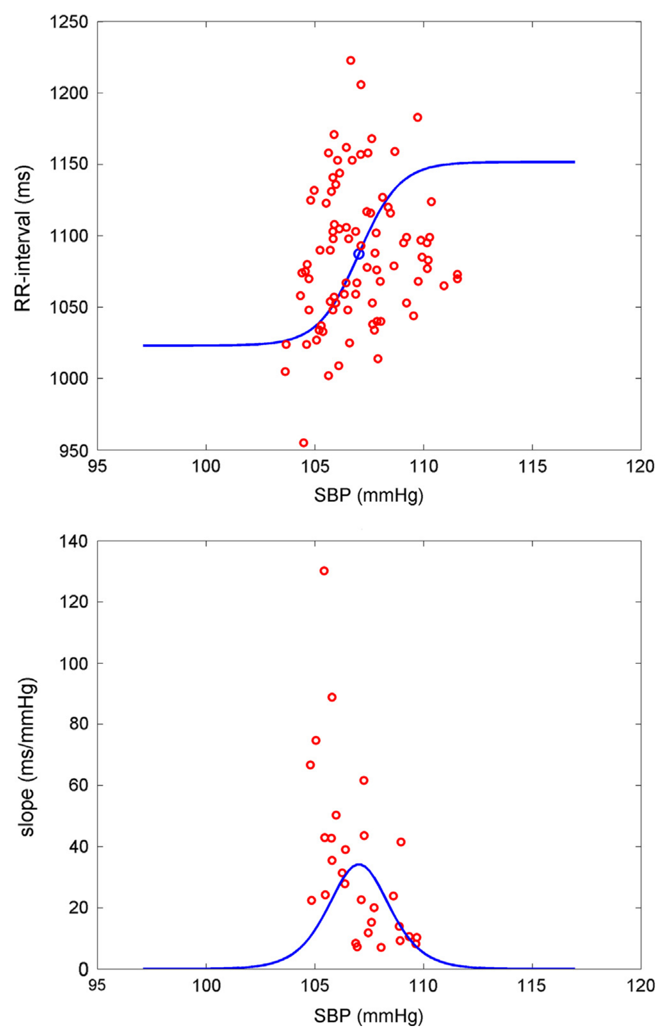

Fig. 3. (Top): A logistic curve based on mean properties of a sample spontaneous sequence data set. The large amount of scatter suggests that the data points emanate from more than one logistic curve. In other words, if the scatter of the data points is interpreted as baroreflex "resetting" then the figure suggests that resetting is not occurring along the same logistic curve. (Bottom): Slope along the logistic curve shown above, plus data points representing slopes recorded by the spontaneous sequence method and corresponding to the data shown in the top panel.