To Dip or Not to Dip
Of Arterial Pressure Physiology, System’s Analysis, and Information

Massimo Pagani

In real life, arterial pressure is never at complete rest but is continuously in a state of change. Both in humans and animals, arterial pressure rises during emotional arousal, stress, physical exercise, or the fight–flight reaction; conversely it decreases during periods of rest, relaxation, or sleep. There are several critical points in the study of arterial pressure (dys)regulation, particularly considering clinical applications. Importantly, the cardiovascular system is rarely addressed in its complex entirety, as a coordinated whole. Individual components are frequently singled out and addressed independently from one another. This approach is typically based on the Newtonian deterministic concept that the function of a system composed of multiple components, as is the case with circulation, can be deduced from the linear summation of the functions of the various parts. Disease can be resolved by simply correcting the faulty component.

Recently, several authors have pointed out that a better approach could be furnished by the view, traceable to Aristotle, that, in biology, time and context must be factored in, considering all of the involved components, in a nondeterministic, nonlinear, self-organizing whole. In this system approach, information about interrelations between various components, rather than simple physiology of individual elements, carries a critical importance. Treatment is individualized and directed at optimizing dynamical interrelations between components. Accordingly, simple markers of the system’s performance might be particularly helpful in clinical practice.

This approach could help to better integrate old and new data into hypertension medicine. A case in point is represented by the baroreflex, which is frequently taken as a master commander of short-term blood pressure regulation. This simplified view could be expanded by including the more efficient dynamic capacity offered by a control based on a double (negative and positive) feedback design and a system’s analysis approach (see the Figure). Ideally, the specific model and combination of variables should be explicitly indicated and factored in the study design.

In this issue of Hypertension, Sayk et al. tested the hypothesis that the spontaneous fall in arterial pressure, that is, dipping, that occurs in healthy humans during sleep is actively promoted through a neural mechanism and that its experimental abolition might have consequences lasting through the daytime. To this end, the authors considered a group of healthy volunteers, from whom they assessed (with noninvasive, repeated measures) the time profile of arterial pressure during sleep and in the following hours. At wake time, autonomic regulation was determined by way of multiple measures, such as sympathetic efferent activity, baroreflex performance, and variability of the RR interval. Then, the influence of the dipping phenomenon on circulatory regulation was gleaned from the comparison of data obtained during a control recording (dipping status) with data obtained, from the same subjects, during a period without dipping (nondipping status). It is important to notice that the inference of a function from its experimental abolition (frequently complemented by its stimulation) represents 1 of the typical strategies of the neurophysiological research.

Notably, to abolish dipping, the authors used a continuous titrated infusion of a α-agonist for several hours, pharmacologically counteracting the physiological night reduction in arterial pressure. This maneuver, while abolishing the sleep-induced pressure reduction, could have induced changes other than simply increasing blood pressure. In fact, >20 years ago, Peveler et al. observed that α-adrenergic stimulation in conscious dogs reduces carotid artery diameter and enhances baroreflex gain. In this context, it should be recalled that the physiological stimulus for arterial baroreceptors is not arterial pressure, per se, but rather the mechanical deformation of the arterial wall, where receptor endings are located (hence, the importance of arterial wall stress, a complex function of pressure, dimension, geometry, and material properties, strongly linked to vascular elasticity). To make things even more complex, the vascular wall response to vasoactive drugs is strongly dependent on the state of the subject: for example, the presence of anesthesia, as in the majority of animal investigations, drastically reduces vascular responsiveness.

Accordingly, the greater reduction in heart rate observed by Sayk et al. in response to the graded pressor stimulus in the morning after the nondipping night might, well reflect an increase in baroreflex gain, possibly induced as an aftereffect of the lack of blood pressure decrease induced by the nightly phylephrine infusion. Furthermore, muscle sympathetic nerve activity changes were not affected by the dipping (nondipping) status. The use of a nonlinear model of baroreflex regulation of muscle sympathetic nerve activity suggested that “the vascular baroreflex is shifted to lower blood pressure values.” The similarity of efferent sympathetic activity with lower pressor stimuli would thus, indicate greater sensitivity. However, the observation of a similar

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simplified schematic modeling for the arterial pressure–RR interval, baroreflex-mediated relationship. In A, a simple, open loop, linear model is represented, where systolic arterial pressure variability (ie, systogram, s) fully drives RR variability (ie, tachogram, t). The Hts function provides a complete description of baroreflex gain (working as a negative feedback). There is no allowance for additional influences. In B, a slightly more complex, closed loop model is depicted. In this model, the neural pathway (from s to t) notably allows for the presence of a dual feedback in the baroreflex block (see insets with + and − signs), and also noise (n) and the vascular sections are explicitly considered. Noise to t accounts for influences deriving, for example, from cardiopulmonary- or chemoreceptor-mediated reflexes that might change RR intervals independent from the baroreflex; noise to s accounts for mechanical effects directly modifying blood pressure (eg, respiratory variations). The central command block accounts for other neural effects, such as those deriving from different levels of arousal (eg, sleep–wake cycle) or stress or from muscular metaboreflexes. These factors are capable of changing baroreflex gain centrally. Redrawn from Reference 1; more details can also be found in Reference 4.

slope could also be interpreted as suggesting a “resetting” of the reflex. Again, this points to the importance of explicitly selecting the interpretative model,4 recalling, however, that only as a first approximation can mean arterial pressure be taken as the sole input to the baroreflex system. In the context of this study, cardiopulmonary afferents and metaboreceptors from skeletal muscles must, for example, be considered among powerful potential baroreflex modulators that might be more difficult to assess.

In the last 2 decades, the application of computer analysis to the assessment of RR interval or arterial pressure beat-by-beat variability has provided the investigative armamentarium with tools to estimate sympathetic–vagal interaction at the sinoatrial node (from low-frequency and high-frequency components of RR variability),5 simultaneously with vascular sympathetic modulation (from low frequency of arterial pressure variability) and baroreflex gain.1 The lack of changes in spectral indices of RR variability despite changes in baroreflex performance reported by Sayk et al2 further supports the developing concept of selectivity of autonomic changes, such as during sleep6 or in conditions of increased cardiometabolic risk.7 These findings further point to the complexity of the regulatory system and to the need for considering in integrated manner the information carried by different indices, such as those that can be derived from time and from frequency domain approaches.

In conclusion, the study of Sayk et al2 appears to be of importance as a clear example of a modern approach to the study of the dynamics of autonomic regulation in humans. The spontaneous lack of dipping in 24-hour profiles of arterial pressure is clinically associated with disease and poor prognosis. In this study, the induced lack of dipping opens a new window into the understanding of neural regulation of arterial pressure during night rest. Sleep is a period of complex rearrangement of autonomic activity, such as an overall increase in baroreflex gain and reduced sympathetic activity, interspersed by moments of sympathetic arousal,8 not only during rapid eye movement but even during non-rapid eye movement periods.6 Sayk et al2 definitely show us the feasibility of unraveling the still mysterious mechanisms responsible for the active central regulation of cardiovascular function during the sleep–wake cycle and suggest that autonomic assessment may furnish an, as yet unexplored, tool to the study of the mechanisms underlying relatively less studied circulatory properties, such as the nightly dipping.

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References

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