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COMMENT

Short-term blood pressure variability and reduced cytosolic calcium levels

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The health status of individuals is carried out based on measurements often assessed within an interval, which reflects the activity of homeostatic and allostatic processes. Therefore, physiological and biochemical measurements are interpreted within a comparable time of day and in context with other parameters. Miniaturisation and technological progress allow us to continuously measure many physiological variables at high frequency (thousands of measurements per second) for several months in freely moving animals and people. Therefore, there is a lot of research focused on beat-to-beat blood pressure and heart rate variability. Measuring these indicators involves analysing the short-term changes in heart and vessel activity. This research is relevant not only in experimental physiology but also in clinics, sports medicine and even for everyday health monitoring using wearables. The increased predominance of one autonomic nervous system branch causes a decrease in beat-to-beat variability (increase in low-to-high spectral power ratio), and the increased variability between individual heartbeats (decrease in low-to-high spectral power ratio) indicates a relatively balanced autonomic regulation [1]. Moreover, many hormones are released in a pulsatile manner, with minute-to-minute and hour-to-hour variability [2]. This variability is also reflected in blood pressure variability (Fig. 1). Load, stress, diseases and many others change the hormone release and, thus, the long-term blood pressure variability pattern. Autonomic and endocrine control is subsequently coordinated by the circadian (lat. circa = around; dies = day; ~24 h cycles) system, the biological clocks. The healthy, coordinated, hierarchically organised activity of the heart and blood vessels results in reduced homeostatic deviations and low day-to-day or visit-to-visit blood pressure and heart rate variability [3].

Due to many inputs, the minute-to-minute and hour-to-hour oscillatory patterns are complex compared to beat-to-beat variability, manifesting as seemingly chaotic patterns (Fig. 1). Many inputs interfere with each other; thus, several hormonal inputs determine one oscillation. At the same time, the activity of one hormone can result in several oscillations. Additionally, the characteristic blood pressure oscillations vary depending on age, gender, and other naturally occurring and changing factors. Last but not least, blood pressure fluctuates significantly due to the influence of random external factors, which often result in increased physical activity of the individual. Therefore, any paper that reveals the internal properties of blood pressure variability and thus helps understand the basic mechanisms is precious. In this regard, the present study by Danfeng Jiang et al. [4] is interesting. Their work complements the basic knowledge of beat-to-beat and fifteen-minute-to-fifteen-minute (15-to-15-min) blood pressure variability. The researchers used telemetry to measure the blood pressure of rats. Blood pressure variability was tested pharmacologically by applying noradrenaline, azelnidipine (L-type and T-type calcium channel blocker) and hydralazine (among others, it probably prevents the release of calcium ions from the sarcoplasmic reticulum by inhibiting the action of inositol trisphosphate). In the results, the authors showed that noradrenaline in normotensive rats not only elevated blood pressure but also induced an increase in systolic beat-to-beat and 15-to-15-min blood pressure variability and, at the same time, decreased the spontaneous baroreflex sensitivity. Azelnidipine and hydralazine, which reduce intracellular calcium levels by different mechanisms, caused, in addition to a decrease in blood pressure, a different normalisation of beat-to-beat and 15-to-15-minute variability and an increase in the spontaneous baroreflex sensitivity. Based on the research data,

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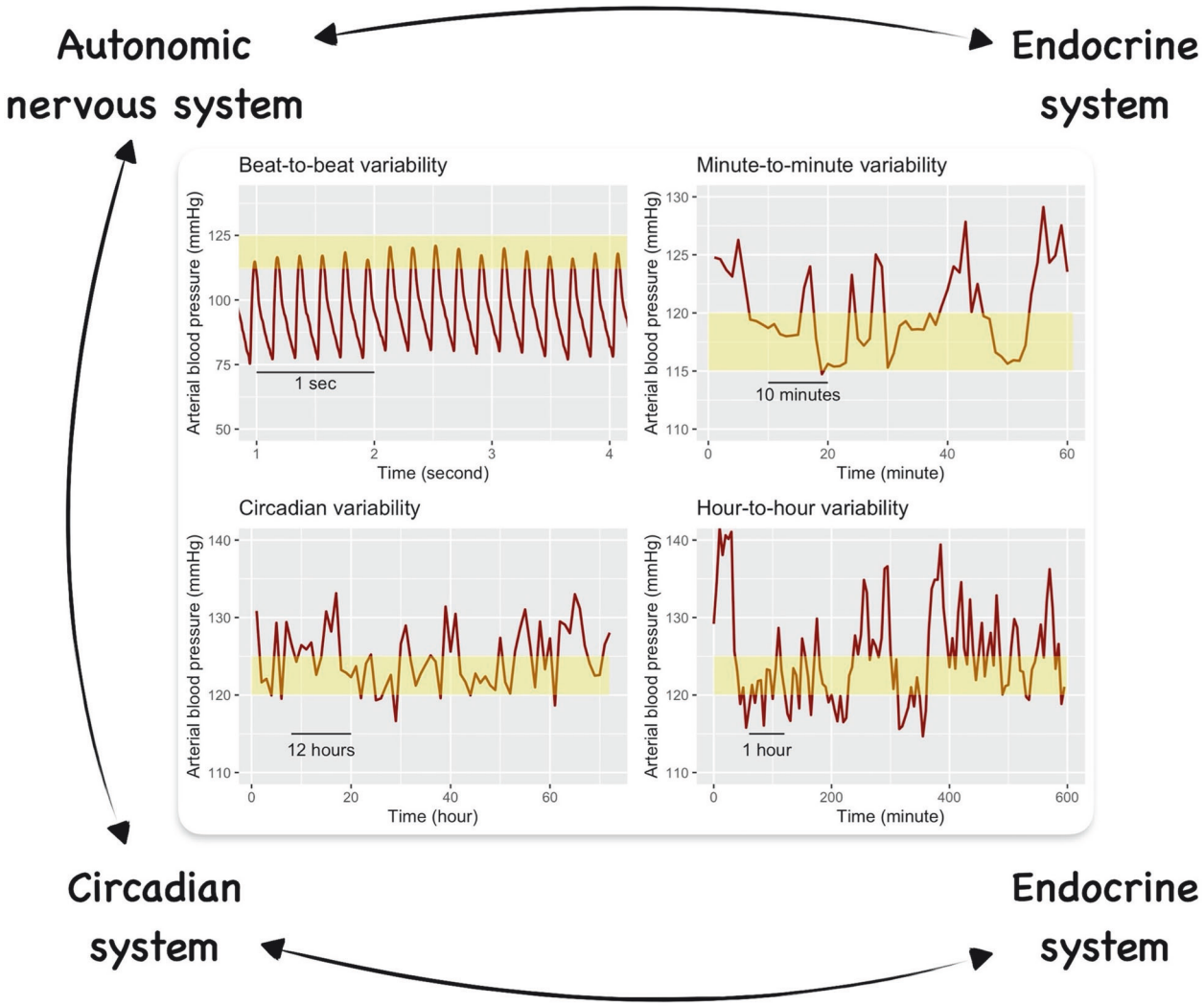

Fig. 1 Beat-to-beat, minute-to-minute, hour-to-hour, and circadian blood pressure variability reflect the activity of specific regulatory systems

we can assume that the source of calcium affects blood pressure and its variability differently (Fig. 2). Danfeng Jiang et al. also found that blood pressure regulation is related to blood pressure variability and baroreflex sensitivity adjustment. These effects are significantly affected by calcium levels. However, we should be cautious in interpreting the effects of hydralazine for two reasons. Firstly, its mechanism of action has yet to be fully understood, and it may interfere with other systems, for example, by affecting nitro-redox balance. Secondly, hydralazine has a very short half-life (90 min and more [5]); thus, its plasma level fluctuations due to administration in tap water can significantly impact short-term 15-to-15-min blood pressure variability.

However, the quality of the authors' work is reliable, as shown by their considerable expertise in the relevant field, and their other works are also noteworthy. For example, their previous research paper showed increased blood pressure variability after applying angiotensin II via an osmotic mini-pump [6]. A stress-free application of drugs is very suitable, either using osmotic mini-pumps or using modern programmable pumps. Programmable pumps enable the precise application of drugs at specific intervals and volumes, minimising the effects of random external and internal factors [1]. Thus, the advantage of the work of Danfeng Jiang et al. lies in pharmacological interventions that indicate a targeted decrease or increase in blood pressure variability. Moreover, the authors continuously study short-term blood pressure variability in telemetry-measured normotensive and hypertensive rats, which have higher blood pressure variability (higher homeostatic deviations) than normotensive rats. Therefore, the pharmacological approach, telemetric measurement, and various rat models help understand the influence of regulatory systems on blood pressure variability.

Telemetry data recording over a long period in high resolution generates a large amount of data. Analysing

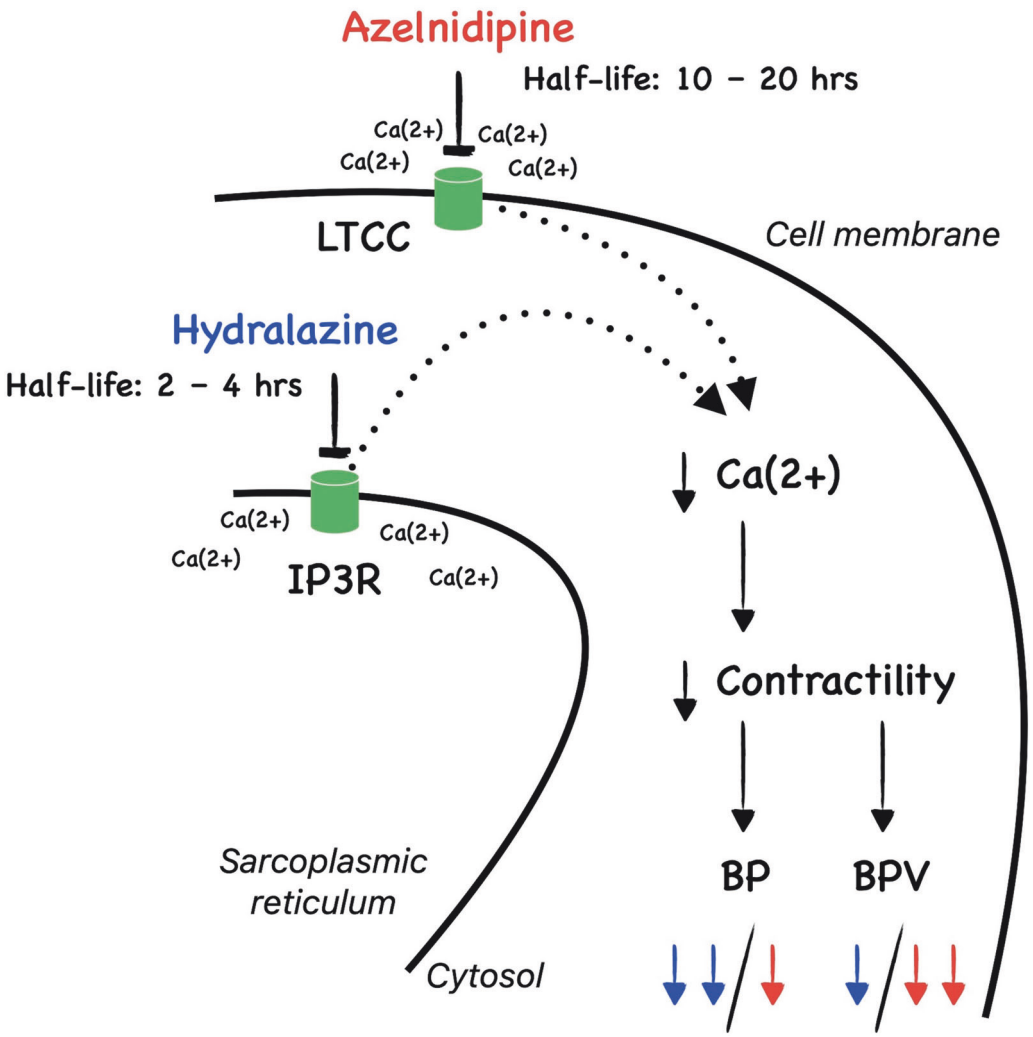

Fig. 2 A possible explanation for the different responses to azelnidipine and hydralazine on blood pressure (BP) and its variability (BPV). IP3R inositol trisphosphate receptor, LTCC L-type calcium channels

this data using spectral, attractor or nonlinear analysis methods can take time and effort. However, based on the analysis, it is known that blood pressure variability is not random; it follows its internal laws, regularity, and thus predictability, which we should fully understand [7]. Studying the variability of physiological variables can help predict the future state of physiological systems and even anticipate diseases before changes happen on the biochemical, anatomical and morphological levels. In other words, we can expect the development of certain diseases by observing and analysing changes in physiological variables. Early diagnosis of diseases could effectively reverse the developing pathophysiological processes; it would restore the original homeostasis with less invasive interventions and a less demanding pharmacological treatment.

Currently, increased blood pressure variability is affected in patients with pheochromocytoma, primary aldosteronism, renal diseases, heart failure and worsened cardiovascular prognosis [6, 8]. However, some papers did not find clear connections for clinical application [9]. Therefore, there needs to be more data in this area, such as the present study by Jiang et al. [4], which explores how different sources of calcium affect blood pressure variability in different time scales. Thus, a detailed blood pressure analysis could represent the basis for choosing an appropriate drug for a specific molecular mechanism to strengthen the contractility of the failing heart or decrease the contractility of blood vessels in hypertension. Finally, blood pressure variability not only reflects changes in the organism and could predict health problems, but, as new research has revealed, blood pressure pulsation impacts the activity of neurons in the central nervous system [10]. Thus, blood pressure variability is a fascinating phenomenon reflecting physiological changes and significantly affects physiological processes.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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