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Review

Eppur Si Muove: The dynamic nature of physiological control of renal blood flow by the renal sympathetic nerves

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ABSTRACT

Tubuloglomerular feedback and the myogenic response are widely appreciated as important regulators of renal blood flow, but the role of the sympathetic nervous system in physiological renal blood flow control remains controversial. Where classic studies using static measures of renal blood flow failed, dynamic approaches have succeeded in demonstrating sympathetic control of renal blood flow under normal physiological conditions. This review focuses on transfer function analysis of renal pressure-flow, which leverages the physical relationship between blood pressure and flow to assess the underlying vascular control mechanisms. Studies using this approach indicate that the renal nerves are important in the rapid regulation of the renal vasculature. Animals with intact renal innervation show a sympathetic signature in the frequency range associated with sympathetic vasomotion that is eliminated by renal denervation. In conscious rabbits, this sympathetic signature exerts vasoconstrictive, baroreflex control of renal vascular conductance, matching well with the rhythmic, baroreflex-influenced control of renal sympathetic nerve activity and complementing findings from other studies employing dynamic approaches to study renal sympathetic vascular control. In this light, classic studies reporting that nerve stimulation and renal denervation do not affect static measures of renal blood flow provide evidence for the strength of renal autoregulation rather than evidence against physiological renal sympathetic control of renal blood flow. Thus, alongside tubuloglomerular feedback and the myogenic response, renal sympathetic outflow should be considered an important physiological regulator of renal blood flow. Clinically, renal sympathetic vasomotion may be important for solving the problems facing the field of therapeutic renal denervation.

Contents

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1. Introduction

The maintenance of renal blood flow (RBF) is crucial for renal function. The kidney is accordingly endowed with two powerful autoregulatory mechanisms, tubuloglomerular feedback (TGF) and the myogenic response (MR), which are widely appreciated as important controllers of RBF (Carlström et al., 2015). Tubuloglomerular feedback is a mechanism that is unique to the kidney whereby changes in RBF-dependent NaCl flux in the distal thick ascending limb are sensed by macula densa cells and transduced to modulate the diameter of the anatomically juxtaposed afferent arteriole. The MR is observed in other vascular beds but is particularly strong in the kidney where it senses changes in transmural pressure and responds by adjusting afferent arteriolar diameter to preserve a near constant RBF. Together these mechanisms maintain RBF and glomerular filtration over a wide range of perfusion pressures by modulating renal vascular conductance (RVC).

Conversely, the classic dogma maintains that the renal nerves are quiescent in the control of RBF in a normal, healthy state, causing vasoconstriction and a reduction in RBF only in response to experimental stimuli or in the setting of disease, where renal sympathetic nerve activity (RSNA) exceeds physiological levels(DiBona and Kopp, 1997). This dogma, based mainly on steady-state measurements of mean RBF over minutes, has eroded as more dynamic approaches have revealed the involvement of the renal nerves in the beat-to-beat dynamic regulation of RBF. This review focuses on studies which have used pressure-flow transfer function analysis, leveraging the physical relationship between blood pressure and blood flow to yield insights into the physiological role of the sympathetic nervous system in RBF control.

1.1. Dynamic approaches for a dynamic phenomenon

Following the proliferation of techniques allowing for chronic, conscious recordings of renal sympathetic nerve activity, the dynamic nature of RSNA became obvious. Fig. 1 shows a 14-s sample of a recording from a conscious rabbit instrumented with RSNA electrodes that demonstrates rhythmicity, beat-to-beat variability, and baroreflex control of RSNA, with lower diastolic pressures followed by large RSNA bursts. The inarguably dynamic nature of RSNA necessitates the use of dynamic approaches to study the neural control of renal function.

One common dynamic method of analysis for studying rhythmic physiological time series data is frequency analysis. This decomposes a physiologic signal occurring in time into its multiple frequencies, allowing quantification of the power of each rhythm. Fig. 2A shows how a seemingly complex signal occurring in time can arise from a few simple rhythms and how frequency analysis facilitates the identification and quantification of these rhythms. Frequency analysis is a powerful tool for studying the control of physiological parameters as different physiological control mechanisms operate at different frequencies. By separating physiological mechanisms based on their operating frequencies, frequency analysis allows for their individual assessment as they operate in vivo. This is in contrast with classic, steady-state measures such as heart rate or RVC which have no ability to assess the contributions of individual physiological mechanisms working together to regulate the parameter of interest. For example, if heart rate increases, one does not know if this is due to vagal withdrawal or cardiac sympatho-excitation or both; if RVC decreases, one does not know if this is mediated by sympathetic vasoconstriction, MR, or TGF. Frequency analysis offers a window into the participation of individual physiological control mechanisms – although it is not without limitations.

One of these limitations is that the operating frequencies of different physiological mechanisms may overlap. Such is the case with heart rate: both parasympathetic and sympathetic input to the sinoatrial node

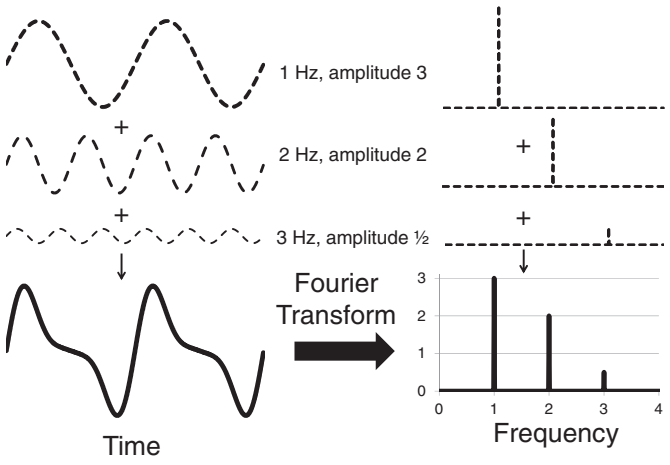

Fig. 2. Frequency analysis. A rhythmic signal which appears complex when viewed in time can be better understood after its transformation to the frequency domain. The composite waveform on the left is the simple addition of three other oscillations of different frequencies and amplitudes. When viewed in the frequency domain, the amplitude spectrum (right) reveals very clearly the frequencies of the underlying rhythms and their relative contributions (amplitudes). The phase spectrum (not shown) gives information about when each oscillation occurs (i.e. is at 0°).

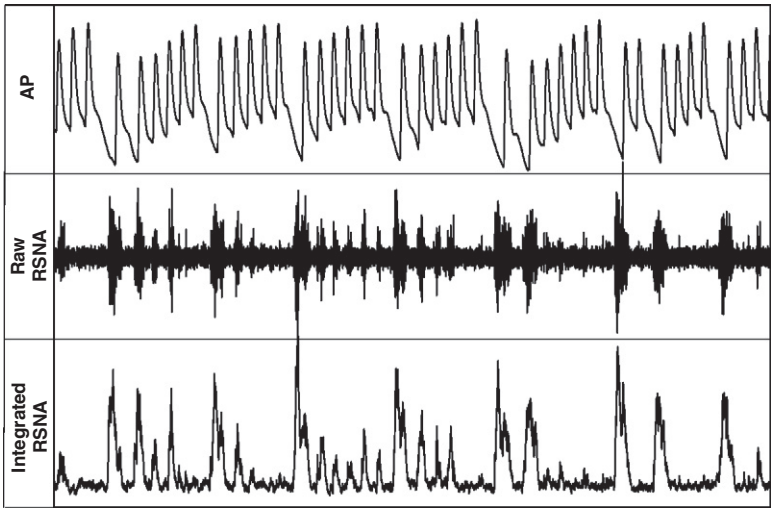

Fig. 1. RSNA is dynamically controlled. 14-s recording of AP, raw RSNA, and integrated RSNA in a healthy, calmly resting rabbit one-week after RSNA electrode implantation. Note the dynamic nature of RSNA and the strong baroreflex control of RSNA, with the amplitude and incidence of RSNA bursts strongly corresponding to DBP.