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EDITORIAL

Knowing the ropes of vasopressor dosing: a focus on norepinephrine

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Current shock guidelines recommend norepinephrine as the first-line vasopressor to increase mean arterial pressure (MAP) and eventually restore tissue perfusion [1]. Norepinephrine (or noradrenaline) is an endogenous catecholamine, produced both in postganglionic sympathetic nerves and adrenal glands. It became part of the therapeutic arsenal for the treatment of shock during the 1950s, gaining traction ever since. Despite its ubiquitous use throughout intensive care units (ICUs) and operating rooms worldwide [2], clinical practice related to its administration is still heterogeneous. We provide here a concise and practical article on the fundamentals of vasopressor administration in critically ill patients, using norepinephrine as a paradigmatic case example.

Pharmacological properties

Norepinephrine is metabolized by the enzymes monoaminoxidase and catechol-O-methyltransferase, or by reuptake into nerve terminals [3]. Norepinephrine pharmacokinetics can be modelled with a one-compartment linear model and first-order elimination [4]. It acts on both alpha- and beta-adrenergic receptors, triggering intracellular signaling processes mediated by G-proteins, producing a myriad of cardiovascular effects, as seen in Fig. 1 [3]. Of note, norepinephrine does not only increase MAP by increasing arterial vascular resistance, but concomitantly increases cardiac output by optimizing cardiac preload and direct inotropism.

Unlike pharmacokinetics, the pharmacodynamic response of norepinephrine is highly variable, depending mainly on the severity of illness [4]. In shock states, multiple factors may blunt its pressor effect, including acidosis, hypoxia, hypocalcemia, relative steroid deficiency, and receptors down-regulation, among others [5]. Although a maximum dose does not exist, further increments above higher-end dose ranges (e.g. > 1 mcg/kg/min [6]) might be less efficient on the pharmacodynamic dose–response curve, since receptors become progressively saturated [3]. This provides the theoretical rationale for multimodal strategies, since acting on parallel metabolic pathways controlling the vascular tone, such as vasopressin receptors, angiotensin receptors or nitric oxide modulation, could provide synergistic vasoconstrictive effects and decrease excessive (and potentially deleterious) exposure to catecholamines [7]. However, the value of these strategies should further be confirmed in clinical trials. Despite its predominant cardiovascular profile, there are non-cardiovascular properties such as decreased proinflammatory cytokine expression, a potential contributor to sepsis-induced immunoparalysis [8]. Among adverse effects, reports show an increased risk of arrhythmias, digital, abdominal, and cardiac ischemia in a dose-dependent fashion [7], and skin necrosis after inadvertent extravasation.

Current dosing strategies

Due to its short half-life (< 2.5 min), norepinephrine must be administered as a continuous infusion. Manufacturers recommend diluting norepinephrine in dextrose containing solutions, due to potential inactivation by oxidation on saline solutions. Usual adult preparations concentration ranges from 16 mcg/mL to 128 mcg/mL. Recent data have highlighted the relative safety of short term (< 48 h), low dose (< 15 mcg/min) administration of norepinephrine diluted at 64 mcg/mL through peripheral intravenous access [9], notwithstanding, administration through central venous access is still hegemonic and advisable in

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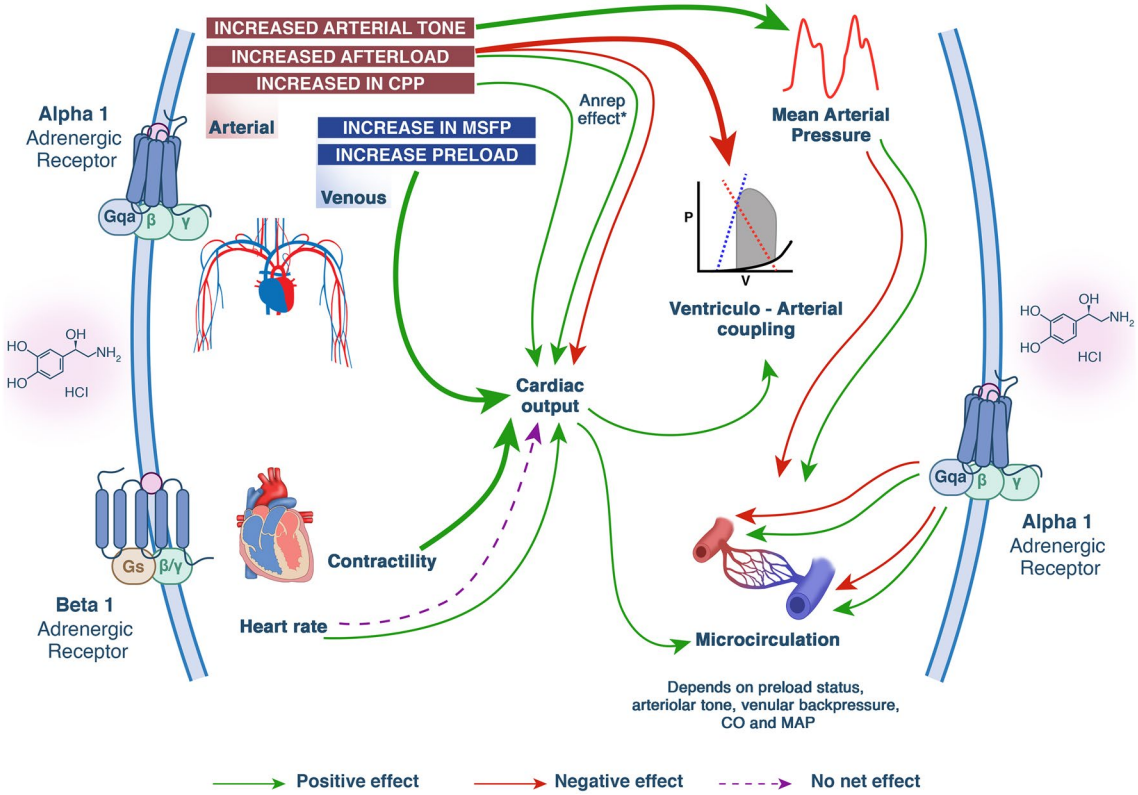

Fig. 1 Cardiovascular effects of norepinephrine. *Anrep effect: autoregulatory mechanism consisting of an increase in myocardial contractility and stroke volume due to sustained afterload-induced myocardial stretching. *CPP* coronary perfusion pressure, *MSFP* mean systemic filling pressure, *P* pressure, *V* volume, *CO* cardiac output, *MAP* mean arterial pressure

current ICU practice. There is significant worldwide variability on drug formulations, as norepinephrine can be found either as tartrate, bitartrate or hydrochloride salts, with different molecular weights and potency equivalence to norepinephrine base, being tartrate the weakest formulation [10]. Similarly, there is heterogeneity of practice on how to titrate the drug infusion, either using absolute (i.e., mcg/min) or weighted values (i.e., mcg/kg/min). Since its dose is tailored in the optics of a pharmacodynamic effect —blood pressure—it is titrated to meet clinical targets, regardless of formulation or dosing scheme. However, this heterogeneity could impact the interpretation and exchangeability of clinical data, design and execution of research, and compliance with expert's recommendations. Thus, homogenization and consensus should be sought [10, 11].

Current guidelines recommend titrating vasopressors to attain an initial MAP target of 65 mmHg [1]. In daily practice though, clinicians frequently aim for higher MAP values, especially in the context of previous hypertension [2], despite recent data drawn from randomized studies suggesting that targeting higher MAP levels did not impact on mortality [1]. Since the goal of hemodynamic resuscitation is to restore tissue perfusion, several physiological studies have assessed the impact of increasing MAP levels on microcirculatory variables, with a substantial heterogeneity on the response [12]. Thus, MAP targets individualization could be desirable, and testing different levels in a dynamic fashion (i.e., through a vasopressor test) while assessing tissue perfusion trends [5] could further aid to personalize therapy. On the other hand, in a recent randomized-controlled multicenter trial, titrating vasopressors and fluids based on sublingual microcirculation had no impact on microcirculatory flow nor mortality [13]. Further research is needed, especially considering the heterogeneous response to norepinephrine on regional circulation (i.e., renal or splanchnic) and organ-specific perfusion pressure targets.

Norepinephrine peak or accumulated dose (catecholamine burden) has been used as a bedside proxy for clinical severity. It is part of clinical scoring systems (i.e., Sequential Organ Failure Assessment score), and has been associated with organ dysfunction and mortality [6, 7]. In fact, norepinephrine dose thresholds have been suggested to trigger the initiation of other therapies such

as vasopressin or steroids [1, 5, 7]. Nonetheless, clinicians should consider integrating it with other variables (such as tissue perfusion and organ dysfunction) rather than relying in a sole parameter when confronted with complex decision-making scenarios, since multiple factors, such as sedative choice and dosing, mechanical ventilation, or homeostatic derangements could negatively impact on vasopressor requirements [5].

Take-home message

There are still many areas of uncertainties and room for improvement regarding norepinephrine use. First, consensus of clinical definitions is needed, such as refractory shock or high-dose vasopressors [14]. With the emergence of novel vasoactive drugs, endeavors proposing equivalences between medications (catecholaminergic and non-catecholaminergic) could facilitate comparison between agents and clinical settings [11]. Future studies should address the optimal timing of norepinephrine initiation, dosing strategies in special populations such as obese patients, and vasoactive drug weaning or de-escalation. Finally, the integration of closed loop-vasopressors infusion systems might enhance clinical practice in the near future [15].

In conclusion, norepinephrine is a pillar of ICU's pharmacological arsenal. Over the years, we have increased our understanding on the properties, clinical use, and adverse effect profile of this drug. Tackling the specific uncertainties in future research could translate into safer and better patient care.

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