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Pin-evoked tachycardia: a new measure of neuropathic pain

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There is an ongoing and contentious debate regarding the extent to which current animal models mimic clinical pain. Advances in the development of neuropathic pain models are generated by improvements not only to the animal models themselves (to more closely reflect the human condition), but also to the development of endpoints that accurately reflect pain in humans [10]. In models of peripheral nerve injury, conventional endpoints typically involve withdrawal responses to a ramping mechanical or thermal stimulus. But because transient withdrawal responses are not necessarily mediated by pain transmission pathways, they have been criticized as being intrinsically flawed [8]. So it is not surprising that over the past decade, we have experienced an explosion of research directed towards the study of behaviors that better reflect the affective (unpleasantness) dimension of clinical pain, including more sustained, integrated somatomotor responses and operant measures. But even operant strategies carry complications, such as a motivational component that confounds determination of pain intensity [1].

In search of additional endpoints, the paper by Rigaud *et al* in this issue of *Pain* re-awakens the classic notion of Sherrington and others that a noxious cutaneous stimulus will produce not only a somatomotor reaction, but also an accompanying elevation in blood pressure, together termed the pseudoaffective response [11]. While numerous articles have supported this concept by showing a clear association between cardiovascular activation and pain-like behaviors in response to *sustained* noxious stimulation lasting minutes [7], Rigaud *et al* consider the hypothesis that *brief*, escapable cutaneous stimuli produce hemodynamic changes that coincide with aversive behavior. They use a powerful *in vivo* telemetric approach to measure blood pressure and heart rate in freely moving animals, thus allowing recordings over several days while avoiding confounds associated with anesthesia or restraint. They focus their studies on an established model of neuropathic pain, involving ligation of the 5th and 6th lumbar spinal nerves [5]. Importantly, at the hindpaw ipsilateral to nerve injury, they simultaneously evaluate somatomotor and cardiovascular endpoints to multiple stimuli : 1) graded stimuli that usually elicit a transient reflex paw withdrawal response (radiant heat or von Frey hairs); and 2) stimuli that often produce at least one second of lifting, shaking and/or grooming (noxious pin, stroking with a camel hair brush, or coolness associated with acetone evaporation), indicative of an integrated behavioral index of hyperalgesia.

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Unlike a sustained noxious stimulus, such as intraplantar formalin (5%, 50 μ l), which produces large pressor (~20 mm Hg) and tachycardia responses (~50 bpm) lasting dozens of minutes [7], Rigaud *et al* report that brush, von Frey, and heat stimuli produce small and variable changes in hemodynamics. This is consistent with our findings in the spared nerve injury model (published in abstract form several years ago [6]), and perhaps some would think the new results are not surprising, considering the low intensity of the stimuli. But Rigaud *et al* go further and suggest that these commonly-used endpoints are unreliable tests for neuropathic pain. In support of this bold and provocative stance, they recently reported that conventional use of von Frey hairs fails to produce conditioned place avoidance in rats with spinal nerve ligation [12]. However, behavioral responses to somatosensory stimuli vary considerably across laboratories. For example, while some laboratories (including that of Rigaud *et al*) report relatively small decreases in von Frey threshold after spinal nerve ligation [4], others report a robust tactile allodynia characterized by a logarithmic drop in threshold [13]. And the often-brief responses to acetone in the current study pale in comparison to the consistent, multi-second, integrated behavioral responses observed in the spared nerve injury model [2,3]. This could represent the somatomotor component of a pseudoaffective response. For example, while Rigaud *et al.* show that acetone produced only a small increase in mean arterial pressure (~5 mm Hg), we found that this stimulus produced reliable and robust increases (~25 mmHg) in animals with spared nerve injury [6]. These results challenge other laboratories to determine the necessary conditions by which brief cold stimuli will produce dramatic increases in blood pressure and/or heart rate.

Interpretation of the heart rate response to noxious pin stimulation is more straightforward. When associated with a brief reflex response, pin prick produced only a small increase in heart rate (~10 bpm). By contrast, pin prick produced a respectable increase of approximately 25 bpm when associated with an integrated hyperalgesia response. This amplified response supports the validity of using the pin prick test to assess neuropathic pain in the spinal nerve ligation model. Furthermore, as the authors suggest, heart rate monitoring in the rat can provide additional insight into the painful experience. On the other hand, because heart rate responses to cutaneous stimuli can arise from activation of numerous processes, including sensory reflexes such as orienting and defense [9], as well as pain, considerable work remains. It will be of interest, for example, to challenge pin prick-evoked tachycardia with drugs that are used for clinical neuropathic pain. Regardless of the results of such studies, Rigaud *et al* provide a compelling new strategy for the development of clinically-relevant endpoints in animal models of chronic pain.

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