The expanding role of the cold pressor test: a brief history

Guillaume Lamotte¹ · Christopher J. Boes¹ · Phillip A. Low¹ · Elizabeth A. Coon¹

Received: 2 March 2021 / Accepted: 3 March 2021 / Published online: 13 March 2021
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Keywords Cold pressor test · Autonomic · Baroreflex · Hypertension

The cold pressor test is a simple and validated test in which the subject immerses one hand or foot into ice water for 1–3 min while blood pressure (BP) and heart rate are monitored [15]. The cold stimulus activates afferent sensory pathways that, in turn, trigger a sympathetic response resulting in an increase in BP. The cold pressor test has been used in the clinical and research settings to evaluate non-baroreflex-mediated sympathetic neural control in humans [15]. If afferent or efferent neuronal circuits and pathways are damaged, the sympathetic vasomotor response is impaired and, therefore, the BP and heart rate responses to cold pressor test can vary significantly.

This brief comment provides an historical perspective on the discovery of the cold pressor test and its application to the study of cardiovascular and autonomic disorders. The Mayo Foundation for Medical Education and Research, and the W. Bruce Fye Center for the History of Medicine at Mayo Clinic helped in locating the primary source materials used in this project.

The cold pressor test was developed as a tool to study BP variability by Edgar A. Hines, Jr. (1906–1978), a physician in the division of medicine at the Mayo Clinic Rochester (Fig. 1a) [6]. As a fellow, Hines tried to find a test which could obtain the highest BP of an individual, comparable to the highest BP found either during an office examination or during a 24-h period [4]. Inspired by a protocol used by the Mayo Clinic physician Bayard T. Horton (1895–1980) in his 1927 description of cold allergy [8], Hines set out to determine whether the application of cold water to the skin of one hand had any effect on BP variability [4]. He started with one hand submerged to just above the wrist into cold water at 15 °C and found no change in BP. He then

used colder water (4–5 °C) and observed an average increment in systolic BP of 8.6 mmHg in 69 healthy subjects, an increase of 36.7 mmHg in 49 subjects with hypertension (whose baseline systolic BP was at least 140 mmHg), and an increase of 29.3 mmHg in 18 subjects with normal baseline blood pressure and no history of hypertension [4]. Hines also studied 26 subjects with different vascular diseases (e.g., Raynaud syndrome and thromboangiitis obliterans) but without hypertension, and their systolic BP increase was similar to the response seen in healthy subjects. The effect of the cold water on heart rate was quite small in all groups (+3 to 5 beats per minute). This resulted in what Hines referred to as “the cold pressor test”, as described in his doctoral thesis [4].

The cold pressor test consisted of a 30-min baseline period during which BP measurements were obtained, followed by a 60-s immersion of either a hand or a foot in ice water at 4–5 °C during which BP was taken after 30 and 60 s with the cuff placed on the opposite arm. Once the limb was taken out of the cold water, the BP was monitored every 2 min until its return to baseline. The highest BP reading obtained was recorded as the measure of the response. A normal response to the cold pressor test was defined as an increment in systolic BP by less than 20 mmHg, whereas subjects whose systolic BP increased by at least 25 mmHg or whose diastolic BP increased by at least 20 mmHg were considered ‘hyperreactive’.

In their 1932 seminal paper [6], Hines and Brown performed the cold pressor test in 40 healthy subjects, 8 with normal BP and risk factors for hypertension (e.g., positive family history of hypertension), 7 with early essential hypertension defined as systolic blood pressure > 140 mmHg without organ damage, 11 with essential hypertension with evidence of end organ damage in the retina or the heart, and 13 with marked ‘atherosclerosis’ including 5 with hypertension [6]. In this study, the cold stimulus was applied for only 20–30 s. This was in contrast to the protocol employed in

✉ Guillaume Lamotte
guillaumelamotte14@gmail.com

¹ Department of Neurology, Mayo Clinic, 200 1st St SW, Rochester, MN 55902, USA

Fig. 1 **a** Brief history of the cold pressor test. A. Edgar A. Hines, Jr. from the division of medicine at the Mayo Clinic in Rochester, MN. Photo taken in July 1931. We acknowledge the W. Bruce Fye Center for the History of Medicine at Mayo Clinic and its staff for their help to find this picture. The Mayo Foundation for Medical Education and Research granted permission to use this photograph. **b** Systolic blood pressure response to the cold pressure test. Illustrative examples of

the moderate increment in systolic blood pressure in normal subjects (average +8.9 mmHg) and subjects with atherosclerosis but without hypertension (+13.1 mmHg). The average rise in systolic blood pressure during the cold pressor test was higher in subjects with a family history of hypertension ('prehypertension group', +30.1 mmHg), and subjects with hypertension with (+29.1 mmHg) or without atherosclerosis (+38.4 mmHg). From [6]

subsequent studies using immersion in cold water for 60 s with BP measurements at 30 and 60 s. The authors observed graded BP responses and distinguished three categories: (i) healthy subjects who demonstrated a minimal increase in BP (average rise in systolic BP of 8.9 mmHg); (ii) patients with hypertension, who demonstrated an exaggerated response with a slow return to baseline beyond 2 min; and (iii) subjects deemed at risk for developing hypertension, who demonstrated a 'hyperreactive' response close to the one seen in patients with hypertension. The authors suggested that the cold pressor test could identify subjects at risk to develop future hypertension. In 1933, Hines and Brown reported a decrease in the magnitude of the vasomotor reactions following selective sympathectomy, suggesting that, for the cold pressor response to occur, activation of sympathetic noradrenergic pathways was necessary [7]. These results supported the notion that interruption of the sympathetic flow to arteries could be used to ameliorate hypertension.

The cold pressor test was not devoid of controversy. The use of the cold pressor test to predict the development of future hypertension was debated. In 1936, Pickering and Kissin concluded that the rise in BP during the cold pressor test was fairly constant for each individual, and tended to be more pronounced in older subjects [11]. The protocol used by Pickering, however, was different than the one by Hines and Brown, regarding the duration of hand immersion (3 min) and the brief period of measurement of the BP at baseline for only 10 min. Furthermore, the patients studied were prison inmates who had been bedridden for

several days before the cold pressor test was performed, which likely underestimated their baseline BPs [11]. In 1942, another study in 350 subjects with normal BP found no relationship between the responses to the cold pressor test and a family history of hypertension [3]. The authors obtained the family history through interviews and argued that statistical comparisons of medical histories taken from medical records, as performed by Hines and Brown, have significant limitations related to documentation bias [3]. Similar negative results were reported by others [2, 14].

In 1934, Hines, using the cold pressor test, studied 300 students enrolled in St. John's School in Rochester, MN and about 100 other children [5]. Reevaluating 207 of these subjects 27 years later, Barnett reported that, of 40 healthy subjects with hyperreactive responses to the cold pressor test, 4 became hypertensive, whereas none of 167 normal reactors did [1]. In a 45-year follow-up study of 142 subjects who were originally studied by Hines, Wood and collaborators from the Mayo Clinic Rochester reported that early hyperreactivity was associated with an increased risk of future hypertension [16]. Menkes and colleagues confirmed the value of an abnormal response to the cold pressor test as a predictor of the development of hypertension, especially among subjects in whom hypertension developed before age 45 [10]. The results may vary in different populations. For instance, the cold pressor test did not predict hypertension in a study of 315 African American male physicians prospectively followed for up to 30 years [13].

Several studies have investigated the effects of the cold pressor test on peripheral circulation, coronary circulation, heart failure, ischemic heart disease, and peripheral vascular disease [12]. The effects of the cold pressor test on coronary vasculature are complex and depend on the degree of associated atherosclerosis. In healthy individuals, the cold pressor test induces coronary vasodilatation possibly from catecholamine action on β_2 -adrenergic receptors on coronary vascular smooth muscle cells, and the stimulation of nitric oxide synthesis via stimulation of α_2 -adrenergic receptors on the endothelial cells of the coronary arteries [12]. In patients with coronary artery disease or hypertension, the opposite phenomenon has been observed, i.e., the cold pressor test elicits sympathetic-mediated constriction of epicardial coronary arteries [12]. Presumably, coronary vasoconstriction could be associated with endothelial dysfunction that results from chronic cardiovascular pathology.

The cold pressor test has been used as a research method to test the integrity of the autonomic nervous system. Its response depends on intact sympathetic noradrenergic efferent neurons but also on intact afferent baroreflex nerves responsible for the short-term control of arterial pressure. For example, patients with acquired afferent baroreflex failure, in whom neck radiation and / or surgery damages baroreceptors or vagal and glossopharyngeal afferent baroreflex fibers of the baroreflex, the cold pressor test causes a marked increase in BP, caused by unrestrained activation of the efferent noradrenergic pathways. The standardized application of a cold stimulus could thus provide valuable information when studying other autonomic syndromes such as efferent baroreflex failure (i.e., autonomic failure), orthostatic intolerance, and spinal cord injury [9].

The cold pressor test has limitations. The physiological basis of the BP and heart rate responses to the cold pressor test are not yet fully understood and factors such as age-related changes in cardiac β -adrenergic sensitivity or α_1 - and α_2 -adrenergic receptor sensitivity may influence the hemodynamic responses. The stimulus itself is complex and dynamic, and may cause pain, numbness, and distress which, in turn, can contribute to sympathetic activation. If intense and prolonged, these could even trigger a vasovagal reaction, which may have contributed to the hypotensive response reported by Horton [8]. The response can be variable among subjects and normative values for age and sex are needed. Finally, some patients may have a remarkable ability to tolerate prolonged cold pressor testing with minimal BP responses, such as patients with erythromelalgia.

In summary, developed by Edgar A. Hines, Jr. in 1932 to study BP variability, the cold pressor test remains a useful research tool to investigate sympathetically mediated increases in BP in patients with cardiovascular and autonomic disorders. Further research is needed to determine

the role of the cold pressor test to predict the occurrence of future cardiovascular events, and to develop normative values for age and sex.

Funding Supported by NIH (P01NS44233, U54NS065736, R01 FD004789, and R01 NS092625) and Mayo Funds. We are thankful to The Mayo Foundation for Medical Education and Research, and the W. Bruce Fye Center for the History of Medicine at Mayo Clinic and their staff, who helped to locate the primary source materials used in this project.

Declarations

Conflicts of interest None.

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