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Review

Stimulated skin wrinkling as an indicator of limb sympathetic function

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HIGHLIGHTS

- Stimulated skin wrinkling is a measure of limb sympathetic function.
- The underlying vasoconstriction causing stimulated skin wrinkling has been used to standardize and improve testing.
- Studies show evidence of diagnostic usefulness for small fiber neuropathy and cystic fibrosis.

ABSTRACT

Skin wrinkling upon water immersion has been used as an indicator of limb nerve function for more than 80 years. Until recently, routine use of the test has been hampered by a poor understanding of the physiology and lack of standardization. The process underlying stimulated skin wrinkling has been recently identified as dependent on digital vasoconstriction mediated via sympathetic nerve fibers. Vasoconstriction is postulated to drive wrinkling through loss of digit volume, which induces a negative pressure in the digit pulp and exerts a downward pull on the overlying skin and ultimately results in wrinkles. Improved test standardization has been achieved through substituting water with EMLA for inducing skin wrinkling. This has made testing much easier and has helped implement stimulated skin wrinkling as a practical routine clinical bedside test. A literature search identified 10 studies of sufficient quality for evaluating stimulated skin wrinkling as a diagnostic test of sympathetic under or over function. Seven studies provide level 1 or 2 evidence as a diagnostic test of small fiber neuropathy and three provide level 1 or 2 evidence for cystic fibrosis. There is reasonable evidence allowing the test to be employed as a simple and effective marker for small fiber neuropathy and cystic fibrosis.

Contents

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1. Introduction

Stimulated skin wrinkling is a curious phenomenon of reversible undulations of the skin of the palms and soles that occur 5–30 min after water immersion or exposure to vasoconstrictor substances such as EMLA (Wilder-Smith, 2004). Clinico-pathological correlations over the past 80 years have shown this phenomenon to be a useful bedside test of limb sympathetic nerve function (Lewis, 1936; Buncke, 1972; Braham et al., 1979; Clark et al., 1984; Vasudevan et al., 2000; Wilder-Smith and Chow, 2003a; Teoh et al., 2008). Reduced stimulated skin wrinkling (SSW) has been used as a diagnostic test of limb sympathetic nerve function in leprosy (Sheskin et al., 1983; Mende, 1985), diabetic neuropathy (Clark et al., 1984; Vasudevan et al., 2000; Ping Ng et al., 2013) autonomic dysfunction occurring with head-up tilt table testing (van Barneveld et al., 2010) and idiopathic small fiber neuropathy (Teoh et al., 2008; Wilder-Smith et al., 2009). Exaggerated stimulated skin wrinkling (in this context often referred to as aquagenic wrinkling) has been used as a diagnostic test for cystic fibrosis with test abnormality expressed in terms of time taken till wrinkles are formed (Berk et al., 2009; Gild et al., 2010; Arkin et al., 2012; Gild, 2012; Chinazzo et al., 2014).

In the following we will first consider what is known about the physiology of stimulated skin wrinkling and then review the literature on the usefulness as a diagnostic test for limb sympathetic function and cystic fibrosis.

2. Physiology of stimulated skin wrinkling

Stimulated skin wrinkling, has been proposed to represent a five step process, driven by digital vasoconstriction (Wilder-Smith and Chow, 2003b). The restriction of wrinkling to the most permeable sites of skin in the body (Scheuplein and Blank, 1971), the glabrous skin of palms and soles, highlights the first step involved, passive diffusion of stimulant substances to the digital pulp vasculature via the sweat glands. Two stimulant substances are in use: water and EMLA. Water requires 30 min of complete hand immersion; EMLA cream applied to cover the distal fingertip also requires 30 min. In the case of water, steps two and three represent dyselectrolytemia within digit pulp tissues leading to increased firing rates of the dense networks of sympathetic nerve fibers. For EMLA, it is more likely that there is direct stimulation of digital pulp sympathetic nerve fibers (Bjerring et al., 1989). In a fourth step, vasoconstriction of the digital pulp results in loss of pulp volume which, results in the final fifth step of the skin overlying the digital pulp being pulled down by the negative pressure force inside the digit pulp (Wilder-Smith, 2004; Hsieh et al., 2006, 2007). The physiological process of stimulated skin wrinkling is depicted in Fig. 1.

The dependency of SSW on limb sympathetic function was first established when patients with either central (Djaldetti et al., 2001) or peripheral lesions of the sympathetic pathways were shown to lose the ability to wrinkle on exposure to water (Braham et al., 1979). Although all individuals with an intact sympathetic nervous system display stimulated skin wrinkling, it is important to realize that several factors affect the degree and latency of wrinkling onset (Wilder-Smith, 2004). Since SSW is driven by vasoconstriction of the vessels within the palms and soles, any process interfering with vasoconstriction and the resultant loss of digital pulp volume will have an effect on SSW. The change in volume is small and we have identified a change in volume of one digit tip accompanying SSW to be about 30 μL (Fig. 2). Increasing age, affects the degree of wrinkling through reduced skin elasticity, extensibility (Batisse et al., 2002) and loss of subcutaneous tissue (Wysong et al., 2013). Since the degree of skin aging is known to vary among different ethnic groups, it is important for laboratories to establish their own normal results for SSW (Tsukahara et al., 2004). In our Asian population, the wrinkling response to EMLA and water in healthy subjects ($n = 25$, mean age 35 years; range 24–52) was consistently normal (grade 3 and 4) (Wilder-Smith and Chow, 2003a) and based on our own laboratory experience, the normal wrinkling response (to grade 3) is maintained up to age 80. Care has to be taken in particular to avoid interference of antihypertensive medication with SSW, since some may interfere with the vasoconstrictive process (Wilder-Smith, 2004). One study has suggested that peripheral vascular disease does not interfere with stimulated wrinkling, indicating that the distal segment where vasoconstriction occurs is not adversely involved in the peripheral artery disease process (Clark et al., 1984). This further supports the proposition that volume changes of the digit pulp and not hemodynamics are the primary prerequisite for wrinkling. Barrier creams reduce or even eliminate the wrinkling response by inhibiting the access of the stimulant to its site of action in the dermis (Pueschel, 1985). Furthermore, since the sympathetic nervous system is the major determinant of hand and foot temperature regulation, it is important that the temperature of the hands are monitored and kept constant. In our laboratory we maintain palm temperature above 32 °C when applying EMLA as a stimulant. Decreased water temperature reduces the speed and degree of wrinkling onset, probably due to diminished water diffusion. If water immersion is used to stimulate, the onset of skin wrinkling is fastest at a water temperature of 40 °C (Cales and Weber, 1997). The tonicity of the water used for immersion has been found to affect the speed of wrinkling onset and its degree necessitating standardization (Tsai and Kirkham, 2005).

The phenomena of increased skin wrinkling frequently alluded to as "aquagenic wrinkling" in subjects with cystic fibrosis is best interpreted as exaggerated SSW and is probably a result of the abnormal skin sweat electrolyte constitution resulting in a greater electrolyte change in the tissue surrounding the sweat glands which induces more pronounced and rapid skin sympathetic neuronal activity and thus more wrinkling (Wilder-Smith, 2013).

3. Stimulated skin wrinkling as a test parameter

Wrinkling is tested on the hand since foot testing has proven technically difficult in reading wrinkling. Since EMLA application and water immersion show similar wrinkling scores as well as reduction in hand digit blood, we have opted to perform SSW using EMLA for a number of reasons (Wilder-Smith and Chow, 2003a). EMLA induced wrinkling allows for easier visual detection of wrinkling; it gives the patient mobility (there is no need to keep the hand continuously submerged in water for 30 min) and there is no need for cumbersome meddling with water temperature and water immersion electrolyte concentrations. The standardized procedures for performing SSW are given in the Addendum 1.

Since environmental stimuli affect sympathetic nerve testing, it is important to maintain a standardized, quiet, temperature controlled environment for testing (Wilder-Smith et al., 2005).

Test quantification for *reduced* wrinkling, which is used for detection of small fiber neuropathy on the basis of reduced limb sympathetic function, consists of visual assessment of the degree of skin wrinkling after 30 min of stimulation. It needs careful training. With training, inter- and intra-observer reliability is good (Wilder-Smith et al., 2009; Datema et al., 2012). The five level grading scale we employ (Teoh et al., 2008), is based on the original Clark scale (Clark et al., 1984). Greatest wrinkling (grade 4) is defined as completely distorting the pulp of the fingertip, grade 3 as 3 or more lines of wrinkling. Abnormal wrinkling is indicated by all grades of wrinkling below 3. Grade 2 wrinkling is 2 or less