CHAPTER 2

LITERATURE REVIEW

2.1 Therapeutic ultrasound

Therapeutic ultrasound is an electrophysical agent based on an application of the inaudible high frequency between 0.7 MHz and 3.3 MHz from electrical deformation of a piezoelectric crystal within the transducer or ultrasound head. The intensities between 0 and 3 W/cm^2 are utilized to generate mechanical vibrations to tissues and vasculature a few centimeters below the skin[30, 31]. Therapeutic ultrasound at a lower-frequency has greater depth of penetration than higher-frequency but it is less focused[32]. For example, the wave at frequency of 1 MHz is absorbed primarily by tissues at a depth of 3-5 cm and is therefore recommended for deeper injuries and in patients with more subcutaneous fat. A frequency of 3 MHz is recommended for more superficial lesions at depths of 1-2 cm[32-34].

During the ultrasound waves are being transmitted through the tissue, the energy is progressively lost due to the absorption and dispersion of the waves[35]. Human tissues absorb ultrasound waves at different amount depending on acoustic impedance and density of each tissue combine with the characteristics of the ultrasound such as frequency, intensity, amplitude, focus and beam uniformity. The dense collagenous tissues or high collagen tissues such as ligament, tendon, fascia, capsule and scar tissue can absorb the energy most efficiently. Other, muscle and

nerve can absorb the energy but it would be less effective than collagenous tissues[31, 32, 36].

Therapeutic ultrasound has two modes of delivering waves with different biophysical effects. First, continuous ultrasound mode that delivers sound wave throughout the treatment period, produces thermal effects with continuous molecular vibration. Second, pulsed ultrasound mode which delivers ultrasound only a portion of the treatment period resulted in non thermal effect or mechanical effect with stable cavitations and microstreaming[30, 37].

Ultrasound has been regularly used by most of orthopaedic physiotherapy. It is widely accepted that ultrasound can help to manage selected musculoskeletal conditions[38-41]. For example, increases of soft tissue extensibility, modulation of inflammation, alteration in nerve conduction velocity and stimulation of the cutaneous thermal receptors[30]. Alterations of these conditions mainly help to reduce pain.

Effect of ultrasound on pain perception has been conducted. Williams [19] studied the effect of continuous ultrasound and found that threshold to pain produced by electrical current was decreased. Mardiman et al [20] investigated the effect of ultrasound on pain threshold produced by a pressure dolorimeter and found that pressure pain threshold in healthy subjects increased when 1.1 MHz ultrasound was being applied continuous at 1.0 W/cm^2 for five minutes. The authors also reported that pain threshold increased only in the area treated by ultrasound, and not at an untreated site or at a site receiving sham ultrasound. Srbely [21] studied the effect of therapeutic ultrasound on the pain sensitivity of myofascial trigger points induced by

hand-held force gauge dynamometer and found a decrease in short-term trigger point sensitivity after ultrasound application. Results from these studies suggest that ultrasound can have a direct effect on pain.

Modulation of inflammation is a result of non-thermal effects more than thermal effects of ultrasound. Several studies found that the non-thermal effects of ultrasound or pulse ultrasound could increase blood flow[2, 3], increase macrophage responsiveness[4], increase the rate of protein synthesis by fibroblasts [6, 7], reduce inflammation and improve healing process[5, 8]. Hsieh [42] proposed that ultrasound not only reduced peripheral tissue inflammation but also modulated nociceptive input and transmission at the spinal cord level by reducing the number and distribution of spinal neuronal nitric oxide synthase (nNOS)-containing neurons. It may reflect the neuroplasticity of the spinal cord in response to peripheral input. The result from Hsieh's study [42] is consistent with Mortimer & Dyson [43] and Dinno and coworker [44] who reported modulation of intracellular calcium, skin and cell membrane permeability.

Increasing temperature of soft tissue by ultrasound has been claimed to improve extensibility of soft issue [1]. If collagenous soft tissue such as tendon, ligament, scar tissue, or joint capsule is heated prior to prolonged stretching, plastic deformations will occur to elongate and maintain length of tissue. In addition, the soft tissue receiving heating before stretching may require less force to gain greater muscle length and also decrease the risk of tissue tearing. However, some studies on

the efficacy of ultrasound failed to identify any significant changes in soft tissue extensibility[45, 46].

Moreover, increasing tissue temperature has been shown to increase nerve conduction velocity and decrease the conduction latency of both sensory and motor nerve[9-11], for both of themal effect [10, 16, 47, 48] and non-thermal effect of ultrasound[49]. It has been reported that for every 1ºC (1.8ºF) increase in temperature, nerve conduction velocity increase by approximately 2 meters/second. Although the clinical implications of this effect are not well understood, it may contribute to the reduced pain perception[30]. Increasing or decreasing of nerve conduction velocity depended on the intensity and duration of ultrasound application, that attributed to the thermal or mechanical effects of the ultrasound[10, 16, 50]. Nerve conduction velocity represents the function of large and fast nerve fiber type (Aβ fibers) while small nerve fiber type; Aδ and C fibers are undemonstrated.

2.2 The effect of therapeutic ultrasound on neural function

The effects of ultrasound on neural function have been studied for decades. Most studies measured the nerve conduction velocities (NCV) which represent function of large myelinated nerve fiber (Aβ fiber) [9, 11-15] and the results are inconclusive. However, majority of studies found that nerve conduction velocity of the large afferent increased with the application of the ultrasound and this increase is related to the raise of temperature and vice versa.

Alteration of NCV as a result of ultrasound application is directly related to intensity and duration, a fact attributed to the thermal or mechanical effects of the ultrasound[10, 11, 15, 16]. Possible explanation is that thermal heating effect of continuous ultrasound increase nerve conduction velocity while non thermal effect such as cooling effect of gel from placebo and micromassage action from pulse ultrasound decreases nerve conduction velocity[11, 13, 15]. Moreover, previous studies proposed that low doses of therapeutic ultrasound may facilitate recovery of compression neuropathy, but higher doses may induce an adverse effect[14, 50].

While numerous studies focus on large nerve fibers function, studies investigate effects of ultrasound on small nerve fibers are limited. Function of small nerve fibers can be evaluated using mechanical and thermal stimuli. Recently, Mardiman et al [20] found that continuous 1.1MHz ultrasound applied at 1.0 W/cm^2 for 5 minutes can increase mechanical or pressure pain thresholds on dorsum forearm in healthy adult. One possible explanation is that the pain transmission may be blocked with the absorption of therapeutic ultrasound by nociceptive nerve fiber which are Aδ and C fiber. At this stage, the effect of ultrasound on small nerve fiber in particular thermal perception has never been reported.

2.3 Thermal perception threshold

2.3.1 Cold and warm receptors

Sensation of cold and warm can be discriminated by cold receptors and warm receptors. Both of cold and warm receptors are specific and located separately in the

skin with different densities, each having a stimulatory point about 1 millimeter. In most parts of the body, cold receptors are 3 to 10 times more than warm receptors[51]. For hand surface, the density of cold receptors (1-5 cold receptors/cm^2) is higher than warm receptors (0.4 warm receptors/cm^2)[52]. Cold receptors are found at a depth of approximately 150 μm, near the interface between the dermis and epidermis which are more superficial than warm receptors[53]. Studies on cold- and warm-sensitive spots in the skin found the presence of innocuous thermosensitive neurons that evoked only sensation of cold and warmth respectively but do not respond to any other stimuli such as mechanical deformation [52, 54, 55].

The sensation of cold and warmth are known to derive from separate cold and warm cutaneous thermoreceptors in different afferent nerves. Over the skin temperature range of 13-45ºC, purely thermal receptors are activated by thermal stimuli. At the normal skin temperature range of 30-36ºC, both cold and warm thermal receptors reveal equal spontaneous firing. Outside this range, continuous firing is essentially limited to one class of thermal receptor[56]. For example, when temperature suddenly dropped within an alteration of temperature in range between 10ºC to 45ºC, cold receptors are activated with increasing the firing rate of cold-sensing nerves. In contrast, warm receptors lead to the shutdown of the firing rate of warm-sensing nerves[57, 58]. During first few seconds, cold fibers also adapt rapidly by decreasing their firing frequency and progressively fade to new equilibrium [57] within the next 30 minutes or more. Similar phenomenon occurs for warmth receptors when respond to increasing temperature within an alteration of temperature in range between 30 ºC to 50 ºC (Figure.2.1).

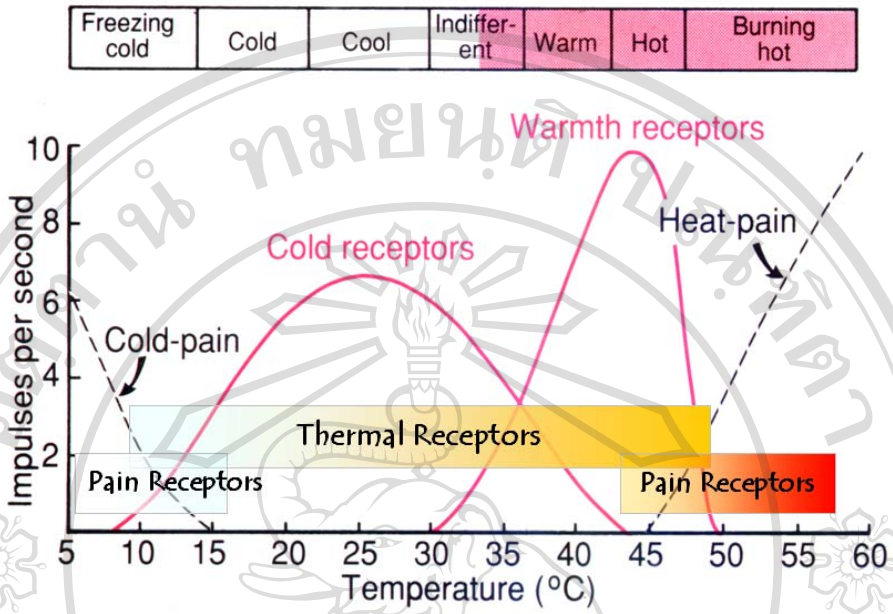

Figure 2-1 Frequencies of discharge of a cold pain fiber, a cold fiber, a warmth fiber, and a heat pain fiber (adapted from Guyton and Hall, 2006 [51])

2.3.2 Thermal receptors proteins

Accumulated evidence of thermosensation suggests that the principal temperature sensors in the sensory nerve endings of mammals' skin belong to a class of receptor proteins. It is called the temperature-sensitive transient receptor potential ion channels (thermoTRPs). At present, six thermo TRPs [55] have been described and together they cover almost the entire range of temperatures that mammals are able to sense. Four transient receptor potential (TRP) channels belong to the TRP vanilloid subfamily (TRPV) are activated by heating, with characteristic activation temperatures ranging from warm temperatures (>25ºC for TRPV4;>31ºC for TRPV3) [59-63]to heat (>43 ºC for TRPV1) [64] and noxious heat (>52 ºC forTRPV2)[65]. Two TRP channels: TRP-

Melastatin8 (TRPM8) and TRP-Ankyrin1 (TRPA1) are activated by cooling (<28 ºC for TRPM8; <18 ºC for TRPA1)[66].

Perception of change in temperature is not the result from direct physical effect of heat or cold on the nerve ending but from chemical stimulation such as Na^+, K^+, Ca^{2+} of the endings as modified by the temperature. It is up to the thermo TRPs receptor that permits Na^+, K^+ and Ca^{2+} to pass. The TRPM8 and TRPA1 are the ion channel of cold receptor that closes more frequently the colder the temperature, and opens less frequently. While, heat receptor (TRPV1-4) such as TRPV1, performs opposite function to TRPM8, its closing rate slows and opening rate increases rapidly as heat increases. In addition, TRPV3 is activated at the first time a role for the skin in the conductance of warm temperature sensation of ~33-37ºC. TRPV3 exhibits marked sensitization with repetitive heat challenges and increasing responses at higher noxious temperatures. TRPV3 is active at both of warm and noxious temperature that this phenomenon could advise an organism of a potentially damaging stimulus. At the same time, the opposite responses of TRPV4 originally identified as an osmosensory ion channel to heat show desensitization on repeated heat applications (~37-42ºC). Therefore, TRPV4 might be constitutively active at body temperature[55, 59, 61, 63, 67].

2.3.3 Transmission of thermal signals

Cold signals are mainly transmitted through type Aδ myelinated nerve ending, 1.5-3μm diameter, at velocities of about 20 m/sec and some cold signals are also transmitted via type C nerve fibers. Alternatively warmth signals are transmitted mainly over type C nerve fibers, 1-2μm diameter, at transmission velocities of only

0.4 to 2 m/sec which are a lot slower than cold signals[53]. The primary afferent neurons transduce the chemical stimulation into an electrical impulse to the central nervous system. On entering the spinal cord, the signals travel for a few segment upward or downward in the tract of Lissauer and then terminate mainly in laminae I, II, III of the dorsal horn. After small amount of processing by one or more cord neurons, the signals enter long, ascending thermal fibers that cross to opposite spinothalamic tract and terminate in the reticular areas of the brainstem and the ventrobasal complex of the thalamus. A few thermal signals are also relayed to the somatosensory cortex from the ventrobasal complex (Figure 2.2)

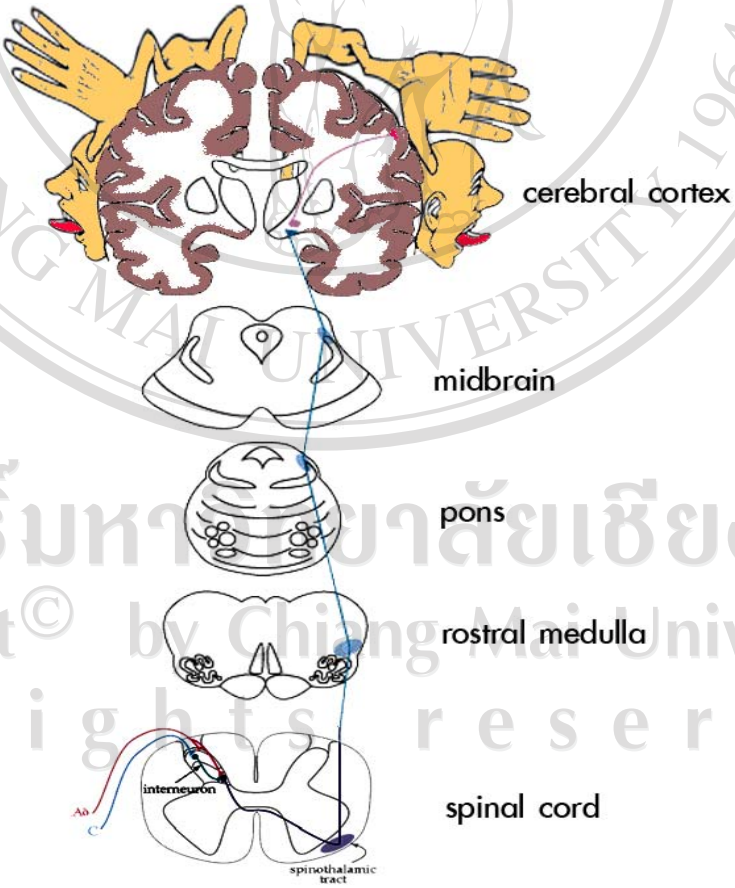

Figure 2-2 Transmission of thermal signals in the nervous system (adapted from Molavi et al., 1997[68])

2.4 Quantitative sensory testing

2.4.1 Introduction

Quantitative sensory testing (QST) has been developed for decades as an alternative approach to investigate sensory nerve abnormalities. QST is a set of methods used to assess and quantify sensory function in human based on well-developed psycho-physiological methods that define both of the stimulus (type, characteristic, quantity, presentation, testing format and environment) and the response (form and analysis). While the sensory stimulus is an objective physical event, the response represents the subjective report from a patient or control subject[18, 69, 70].

QST methods require cooperation from the patients or control subjects in term of competent cognition, attention and ability to follow instruction and respond to the test stimuli. It is a non-invasive and pain-free technique, which can assist in early detection, therapy selection and monitoring progression or recovery of patients with peripheral nerve disorders. For example, metabolic diseases such as diabetes mellitus[22, 23], non neuropathic pain [25] such as migraine, tension-type headache and local compression of a peripheral nerve such as carpal tunnel syndrome, sciatica and radicuropathic pain[26-29].

QST devices can be classified into two separate systems: devices that generate specific physical thermal stimuli (i.e. warm, cold or thermal to pain) or vibratory stimuli and those that deliver electrical impulses at specific frequencies to distinct

neuro-anatomic pathways with discrete fiber populations[70]. The thermal sensory threshold testing (TSTs) is the QST commonly used in the assessment of small A-δ and C-fibre function[71]. For TSTs, thermal stimuli were generated and delivered to the skin via surface temperature of contact thermode through testing. The intensity and direction of temperature delivered are based on the Peltier principle. Thermal stimuli are used to assess the thermal perception thresholds of two sensory sub-modalities: warm detection thresholds (WDTs) and cold detection thresholds (CDTs)[70].

Warm or cold detection threshold was determine as the temperature at which each subject experienced the sensation of an onset of a change in the resting temperature (32ºC) or started to feel warmth for increasing temperature (WDTs) or started to feel cold for decreasing temperature (CDTs) on the skin tested[72]. During testing, subjects must consciously perceive the stimulus, process the information, and generate an action to indicate a response. In normal subjects, WDTs is usually at 1-2ºC above resting temperature (32ºC). CDTs is usually at 1- 2ºC below resting temperature. Two methods of thermal sensation thresholds testing commonly used are the method of limits and the method of levels[73].

2.4.2 Method of limits

The method of limits as shown in Figure 2-3(A) is used to measure dynamic thermal sensitivity[22]. Starting from a baseline temperature of 32°C, thermal stimuli are delivered to the surface thermode with constant rate of change in thermal intensity to increase or decrease temperature. Three warm or cold stimuli with a ramp rate of

1°C /sec are presented to the subject. The subject is required to activate a hand held switch as soon as an increasingly thermal stimulus is perceived (warmth) or when a decreasing of thermal stimulus is perceived (coolness). After that, the temperature of the thermode returns to baseline (32°C). For preventing tissue damage, temperature is set between 0°C and 50°C to be a safety cut-out temperature[18, 70, 74].

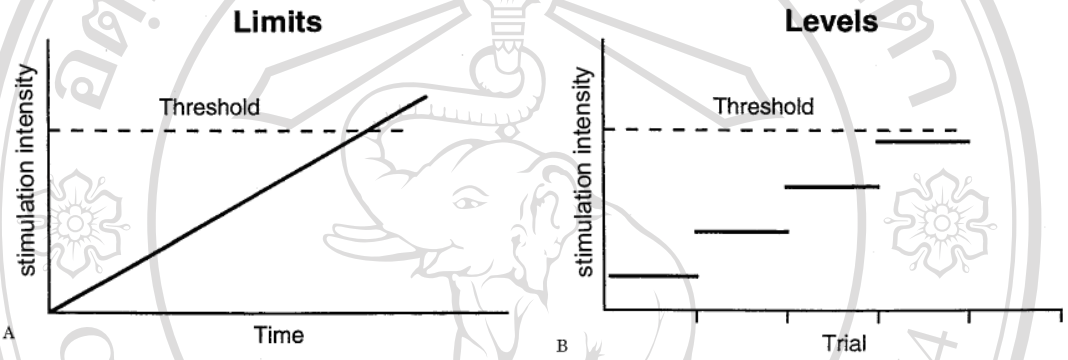

Figure 2-3 Method of limits (A) and Method of levels (B) [70]

2.4.3 Method of levels

The method of levels as shown in Figure 2-3(B) is used to measure static thermal sensitivity[22]. Thermal stimuli are predetermined levels of stimulus intensity and duration. When using this method, thermal stimuli of defined intensity levels are tested with the subject. At the end of each stimulation, the subject is forced to choose whether the specific stimulus level was perceived. The success or failure of the subject's response ('Yes' or 'No' answer of the subject) on single thermal stimuli determines the thermal intensity of next level (doubled intensity for a 'No' and halved intensity for a 'Yes' answer in range 0.1- 2ºC). Therefore, it is also referred to as a "forced choice" algorithm[18, 22, 70, 74].

Among two methods of TSTs, the thermal thresholds from the method of limits are artificially raised above actual TSTs when compared with the method of levels. It is caused by the timing that spent for recognizing, indicating the thermal perception and reaction time (RT) to respond stimuli from subject in the method of limits but not in the method of levels[75]. However, the method of limits is frequently chosen in clinical assessments because it is simple to perform and takes less time than the method of levels.

2.5 Factor affecting thermal perception threshold and thermal pain threshold

Factors which may influence thermal perception thresholds testing are gender of subjects, age, gender of experimenter, and body region [76].

2.5.1 Gender of subjects

Previous studies have investigated gender differences in thermal perception and thermal pain thresholds. The influence of gender differences in thermal perception threshold is inconclusive. Some studies found no gender difference [77, 78] while, recent study have shown that female were significantly more sensitive than male to both warm and cold sensation for small temperature changes at the thenar region[79].

For thermal pain threshold, both results of the psychophysical [78, 80-82] and psychometric studies [83] are consistent and impart support to the gender role theories.

It is suggested that male and female are socialized to respond differently and have different expectations relative to pain perception. In healthy subjects, male reported significantly higher pain threshold and pain tolerance when compared to female[78, 81], while female reported higher pain rating and pain unpleasant than male[82]. The differences in thermal pain perception may be associated with different pain mechanism such as differences in opioid activity and baroreceptor-regulated pain systems [82] or a potential role of epidermis thickness in the gender difference of thermal sensitivities[79].

2.5.2 Age

According to age-related changes in thermal pain perception, it has been reported that thermal sensitivity is age dependent[84]. A number of studies have shown that warm perception and cold perception thresholds increase with age while heat pain threshold shows no age-related changes in normal subjects[84-88]. Haanpää and colleague [86] suggested that the age- dependent changes both in the skin and in the nervous system are important determinants of somatosensory thresholds. Changes of the skin in older age group such as degeneration of elastin fibres, deterioration of the collagen bundles, loss of subcutaneous fat, and degenerative of neural systems tend to increase the detection threshold compare to younger age.

2.5.3 Gender of experimenter

Apart from gender of subjects, gender of the experimenter might also influence pain reports. Aslaksen and colleague [89] suggested that when race, age, and

status were controlled for both subjects and experimenter, the main effect on pain report was due to gender. Several studies have shown that males reported significantly less pain intensity or more pain thresholds when tested by a female experimenter but this phenomenon was not found in female[90, 91]. Some authors found interaction between experimenter gender and subject gender on pain tolerance [92] and pain intensity[93]. Subjects tolerated pain longer when they were tested by an experimenter of the opposite gender [92] and lower pain report in male subjects to female experimenters[89].

The effect of experimenter gender on pain report may be explained by traditional gender roles[91, 94]. In general, gender role refers to a society's widely assumed set of characteristics for each sex and may comprise beliefs regarding appropriate pain behaviors[91]. Another possible explanation for the effect of subject gender and experimenter gender on pain report may be the gender differences in emotional activation during painful stimulation[95]. In a clinical context, the pain report fulfils a function by communicating the problem to the physician thus facilitating diagnosis and therapy. In the absence of the necessity to deliver a vital message, as is the case in most experimental settings, the subject's pain report is likely influenced by additional parameters[94]. While most studies reported the influence of gender on pain, no studies found gender effect on thermal detection.

2.5.4 Body region

Several studies have shown that thermal perception thresholds vary between different body regions but not between left and right sites of same area[77, 81, 84, 96].

Both of cold and warm receptors are specific and located separately in the skin with different densities[79]. Stevens & Choo [84] found that the better a region is at detecting cold, the better it is at detecting warm. It has been suggested that the processing of sensation intensity of warmth and cold may share a common system. This conclusion was drawn from highly correlated perception ratings to innocuous warm and cold stimulations[79, 97].

Several studies suggest that any site at the hand or wrist is practically suitable for the evaluation of cool and warm detection thresholds[77, 96]. Inter individual variation of perception threshold at thenar eminence was found smallest compare to other parts of the body surface[77, 79, 96]. Also, thenar eminence was the most sensitive and suitable for testing thermal perception thresholds when compare to multi-site test on the volar part of the hand[79].