

IS THERE A ROLE FOR CONTRAST HYDROTHERAPY?

Paul W Baker

Contrast hydrotherapy involves the immersion or dousing of a limb in alternating hot and cold water. This 'tweaks' the peripheral autonomic nervous system, altering vascular tone and flow and improving nitric oxide production and vessel health. It has been shown (Elmstahl et al, 1995; Fiscus et al, 2005) to improve both short- and long-term distal blood flow and claudication in patients with significant peripheral arterial disease, as the vascular and lymphatic system share many similarities with regards their genesis, vascular biology and autonomic innervation. This paper shows why contrast hydrotherapy may be a preventative treatment for lymphoedema.

Key words

Contrast hydrotherapy
Lymphatic system
Innervation
Vascular biology
Oedema

Although thousands of years have passed since the first descriptions of lymph nodes in 500 BC, and lymph vessels in 300 BC (Ambrose, 2006), in relative terms the lymphatic system is still poorly understood. Indeed, as noted by Skandalakis et al (2007), 25 years ago the President of the International Society of Lymphology (ISL) stated, 'It is perhaps rather unusual for an international society to feel that it is essential to draw attention to the very existence of its subject matter... such is the general lack of knowledge about the lymphatic system'. It seems that our desire to understand the structure and function of its seemingly more pathologically significant cousin, the vascular system, has taken precedence. Perhaps rightly so in light of the fact that

vascular dysfunction is a more obvious cause of morbidity and mortality. Given emerging structural and functional interactions between the venous and lymphatic systems, and the pivotal role

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That said, in the last 20 years, our scientific understanding of the structure, function and physiology of the lymphatic system has grown considerably, as evidenced by a literature search using Medline (going back to 1948) for articles with either lymphatics or lymph(o) edema in the title. In this 62-year search period, a little over half of the work in this field has been published in the last 20 years, with around a third of all work

being published in the last 10 years. This explosion of knowledge is relevant to the concepts presented in this paper, as it has provided the scientific evidence giving biological plausibility.

The notion of why such a simple and cost-effective therapy as contrast hydrotherapy may be a *bona fide* treatment for lymphoedema was seeded by observations made in subjects at different ends of the spectrum of health and disease, namely athletes and patients with significant peripheral arterial disease. Specifically, contrast hydrotherapy, and even thermal sauna therapy, have been shown to improve peripheral blood flow with long-term improvements in vascular function (Elmstahl et al, 1995; Imamura, 2001; Kihara et al, 2002; Fiscus et al, 2005). This is most likely through gentle stimulation of the autonomic nervous system, with a subsequent change in sympathetic efferent activity to the peripheral vasculature. Evidence of similarities between the endothelium of the peripheral vasculature and that of lymphatic collecting vessels, with regards to cell biology and autonomic innervation, suggests that findings in the vascular system may apply to the lymphatics (Khaisman, 1982; Sjoberg and Stein, 1991; McHale, 1985, 1990, 1995; van Helden and Zhao, 2000; van Helden et al, 2006).

This paper examines these findings

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in the context of contrast hydrotherapy, and their relevance to the lymphatic system and patients with lymphoedema. It also touches on recent evidence showing that certain historical recommendations for the prevention and management of lymphoedema have now been shown to be incorrect (Liu and Olszewski, 1993; Rymal, 2002; McKenzie and Kalda, 2003; Hayes et al, 2009; Hayes, 2010; Kim et al, 2010; Rourke et al, 2010; Schmitz et al, 2010), paving the way for well-controlled studies into the effect of contrast hydrotherapy.

What is hydrotherapy and is it taken seriously by clinicians around the world?

To understand the concepts presented in this paper, it is first necessary to understand what contrast hydrotherapy is and how it is used. In Europe in particular, it is a respected treatment for patients with cardiovascular disease and heart failure, with Japanese studies validating its use (Imamura, 2001; Kihara, 2002). The ability of hydrotherapy to 'tweak' homeostatic mechanisms pertaining to thermoregulation, by affecting peripheral autonomic activity and vascular tone (Boron and Boulpeap, 2009), is thought to underpin its efficacy (Michalsen et al, 2003; Fiscus et al, 2005).

Hydrotherapy can be defined in lay terms as 'the use of water, either internally or externally, to maintain health and prevent disease' (Fine Life Wellness Spa, 2009). It is an age-old practice with reports dating back to at least the time of Hippocrates, around 500 BC (Greek Medicine, 2009). Hydrotherapy and communal baths were common practice in the Roman empire. At the fall of the empire, this widespread practice waned due to dominance of more conservative Christian views, especially regarding nudity (Moore, 2008). In central Europe in the eighteenth and nineteenth centuries however, hydrotherapy experienced a resurgence, commonly ascribed to the practices of Sebastian Kneipp (1821–97), a Catholic priest in Bavaria, who continued earlier work of Vincent Priessnitz (1799–1851), an Austrian peasant farmer (Greek Medicine, 2009). According to Michalsen et al (2003), 'hydrotherapy (according to

Kneipp) has a long tradition in central Europe and is established in some rehabilitative cardiological clinics for the adjunctive non-pharmacological treatment of patients with cardiovascular disease and heart failure'. Indeed, a growing body of scientific evidence exists in the conventional literature (as evidenced by Medline and Cochrane Summaries/Reviews) regarding the efficacy of hydrotherapy in the adjunct

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management of an array of conditions such as osteoarthritis, dermatitis, psoriasis, ankylosing spondylitis, fibromyalgia and congestive heart failure. It is important to recognise however, that among this evidence (e.g. Merial-Kieny et al, 2011), there are few well-designed randomised controlled studies, a factor that will hopefully be addressed in the future.

Specifically, contrast hydrotherapy involves the alternating immersion or dousing of the body, or parts of it, in warm (37–45°C) and then cold (10–15°C) water, with the ratios of time spent in each varying considerably from study to study, and presumably depending on the desired outcome (Cochrane, 2004; Fiscus et al, 2005; Morton, 2007; Vaile, 2008). A common trend is that the warm immersion is longer than the cold immersion, presumably maximising the effects of vasodilation, and that therapy finishes on a cold cycle (Fiscus et al, 2005; Morton, 2007).

The lymphatic system: fundamental concepts of its structure and function

The lymphatic system plays an integral role in immune surveillance and general

'housekeeping' of the interstitial space, forming lymph, a clear and colourless fluid, consisting of an ultrafiltrate of plasma, proteins, white blood cells, and other particulate matter (Swartz, 2001; Ohtani and Ohtani, 2008; Juric and Detmar, 2009). Postprandially, the lymphatic system is also involved in the absorption of dietary lipids and fat soluble vitamins (A, D, E and K) from the gastrointestinal tract (Cueni, 2008).

Lymphatic dysfunction causes a build-up of protein-rich fluid in the interstitial space. Clinically, this is referred to as lymphoedema, the hallmarks of which are limb swelling, inflammation, hypertrophy of adipose tissue and induration of the sub- and epifascial tissue. While it causes pain, disfigurement, embarrassment, depression and functional impairment (Lee et al, 2009), it can also cause morbidity, due to compromised immune function and increased susceptibility to infection (Mortimer, 1998; Rourke, 2010). Lymphoedema is defined on the basis of its aetiology as either primary or secondary (Piller, 2003). Primary lymphoedema is due to congenital dysplasia in the lymphatic system, usually a hypoplasia, resulting in reduced lymph transport. While there are many causes of secondary lymphoedema, in developed countries, it is most commonly the result of treatment for breast cancer (Rourke et al, 2010).

Of relevance to this discussion are factors responsible for the movement of fluid, electrolytes and protein into the interstitial space, and their subsequent removal by the lymphatics. Historically, based on a simplistic understanding and interpretation of Starling's hypothesis, the majority of fluid filtered from capillaries into the interstitium was assumed to be reabsorbed at the venule end of the capillary and subsequently removed by the vascular system (Michel, 2004; Swartz, 2001; Fu et al, 2009). At the heart of Starling's hypothesis is the concept that it is simply the balance between hydrostatic and oncotic pressures within the capillaries and the interstitial space that determine fluid movement across the capillary endothelium. While hydrostatic forces

are involved, meticulous studies have shown some of the earlier basic assumptions to be incorrect, and new theories regarding movement of protein and fluid into the interstitium have been proposed and substantiated (Michel and Curry, 1999; Michel, 2004; Levick, 2004; Curry, 2005). Interestingly however, they are yet to appear in most standard medical physiology teaching texts, perhaps due to the more complex nature of the model and the lag in updating textbooks.

Specifically, a thin glycoprotein matrix lining the vascular endothelium, referred to as the glycocalyx or sugar coat (Weinbaum et al, 2007), plays a significant role in determining vascular permeability. In short, the glycocalyx is a major barrier to protein movement into the interstitium, with such movement only occurring uni-directionally and predominantly via active transcellular vesicular transport. In contrast, fluid and electrolytes enter the interstitium, under the influence of hydrostatic pressure, through narrow tortuous inter-endothelial tight junctions. In this manner, filtration occurs along the entire length of the capillary, only dwindling to low levels at the venule end (Michel, 1999; Levick, 2004; Michel, 2004; Curry, 2005; Weinbaum et al, 2007). Importantly, in most tissues there is no sustained capillary resorption of fluid, electrolytes or proteins, with the lymphatic system being responsible for the resorption of the entire transcapillary filtrate. Only in the case of hypovolaemia shock is there said to be a transient net movement of fluid from the interstitial space back into the vascular system (Levick, 2004).

Lymph is formed by the movement of protein-rich fluid from the interstitial space into lymphatic capillaries that are distributed throughout the interstitium. These capillaries, at the most distal end of the lymphatic tree, are blind-ended tubular structures, composed of a single layer of overlapping endothelial cells that form simple, one-way valve-like flaps, enabling material to enter, but not leave. Lacking a basement membrane and smooth muscle, lymphatic capillaries have no intrinsic contractile properties. Their cytoskeletons however are

tethered to the interstitium by elastic fibres that move in concert with the surrounding tissue, opening and closing the valve-like flaps, creating a pumping activity that facilitates convection of the interstitial fluid and lymph uptake (Swartz, 2001; Cueni and Detmar, 2008; Ohtani and Ohtani, 2008). Once formed, lymph is returned to the systemic venous circulation, moving from the more distal lymphatic collecting vessels to larger lymphatic trunks and then ducts. For the majority of the body, the final stages of transport occur via the thoracic duct, a large lymphatic vessel emptying into the central venous system at the junction of the left subclavian and internal jugular veins; for the upper right side of the body, lymph returns via the right thoracic duct, emptying at the junction of the right subclavian and internal jugular veins (Swartz, 2001; Skandalakis et al, 2007; Ohtani and Ohtani, 2008; Fu et al, 2009; Jurisic and Detmar, 2009; Surgery Online, 2009).

The lymphatic system is a low pressure system relying on both intrinsic and extrinsic pumping activity to move lymph in a caudocranial direction, often against a significant hydrostatic pressure, especially when a person is standing (Zawieja, 2009). Of particular importance in this transport are the intermediate collecting vessels whose walls are sectioned into small segments, termed lymphangions, by one-way valves that prevent retrograde flow. Lymphangions are rich in smooth muscle and have intrinsic contractile activity, being able to modify their contractility and stroke volume, in response to changes in preload; analogous to that described by the Frank-Starling Law of the Heart (Boron and Boulpeap, 2009). As stated by Zawieja (2009), 'Elevated lymph pressure acting via an increase in the stretch of the lymphatic vessel is a classic activator of the lymph pump. Stretch of the lymphatics increases the lymphatic contraction frequency and initially increases the phasic contraction strength. However, further increases in pressure/stretch eventually produce a fall in the phasic contraction strength.' Intrinsic pumping by lymphangions is said to be the primary mechanism by which lymph moves, with extrinsic pumping

due to skeletal muscle contractions, respiratory movements and arterial pulsations playing an important but lesser role (von der Weid and Zawieja, 2004; Olszewski, 2008).

Neural and hormonal modulation of lymphatic function: similarities between the vascular and lymphatic systems

Many factors, hormonal, neural and myogenic, have been shown to modify the contractility of lymphatic collecting vessels and trunks, and hence the ability of the system to move lymph (McHale, 1985, 1995; van Helden and Zhao, 2000; Ohhashi et al, 2005; Surgery Online, 2009). Of particular importance to the possible effects of contrast hydrotherapy on lymphatics, are studies showing that the contractility of lymphatic vessels is enhanced by both direct neural stimulation and exogenous α -adrenergic agonists, an effect abolished by α -adrenergic antagonists. Notably, β -adrenergic agonists appear to cause relaxation of lymphatic vessels with evidence that this is mediated through nitric oxide production (Browse 1968; Khaisman, 1982; Mahe et al, 1989; McHale and Roddie, 1983a, b; McHale, 1985, 1990, 1995; McGeown et al, 1987; Ikomi et al, 1991; Sjoberg and Steen, 1991; Dobbins, 1992; von der Weid and van Helden, 1996). Such observations are consistent with histological and microscopic studies (Khaisman, 1982; Ohhashi et al, 1982; McHale, 1985, 1990) showing the lymphatics to be innervated by nerves displaying adrenergic morphological characteristics. These nerves originate in the nearby vasculature and extend to the lymphatic vessels where they enter the adventitia and penetrate as deeply as the smooth muscle layer. In comparison to the level of innervation of the surrounding vasculature however, the lymphatics appear to be less densely innervated (Alessandrini in McHale, 1985).

Studies in humans with complex regional pain syndrome type I (a.k.a. reflex sympathetic dystrophy) have confirmed that the peripheral lymphatics are under sympathetic control and that there is an intimate relationship between the neural vasomotor

control of the vasculature (also an α -adrenoreceptor mediated process) and that of the lymphatics (Howarth et al, 1999; Reinauer et al, 1994; Mamiya et al, 2001). Specifically, overactivity in the sympathetic nervous system in these patients was associated with peripheral vasoconstriction (mediated by α -adrenoreceptors), causing the limbs to be pale and cool. The limbs also displayed lymphoedema with reduced lymph flow, as shown by lymphoscintigraphy, presumably due to ineffective pumping by the lymphatics and perhaps subsequent flow arrest. Sympathectomy in these patients not only restored blood flow, colour and warmth to the affected limb, due to a reduction in α -adrenergic vasomotor tone and subsequent vasodilation, but also increased lymph flow, again demonstrated by lymphoscintigraphy (Howarth et al, 1999). That such increased levels of sympathetic stimulation can disrupt lymph flow seems contrary to experiments where vessel contraction and lymph flow have been shown to be stimulated by not only sympathetic neurotransmitters, targeted to α -adrenergic receptors, but also direct nerve stimulation (McHale et al, 1980; McHale and Roddie, 1983a, b; McHale, 1985, 1990; McGeown et al, 1987; Dobbins, 1992).

Much work has been done by McHale in elucidating the impact of the nervous system on the contractile activity of the lymphatics. The answers perhaps lie in observation made in early experiments summarised by McHale (1985). In particular, at low levels of sympathetic nerve stimulation, and hence synaptic noradrenaline release, contraction is coordinated and flow is induced, while at increased levels of stimulation contraction becomes uncoordinated and the vessel spasms, leading to ineffective pumping and flow arrest (McHale, 1990). Similarly, Mahe et al (1989) have shown that low levels of exogenous noradrenaline, and a concomitant β -adrenoreceptor antagonist to ensure activation of α -adrenoreceptors only, increased spontaneous lymphatic contractility, whereas high levels of noradrenaline decreased contractility. From these

observations, in the author's opinion, it seems likely that low levels of α -adrenergic sympathetic vasomotor tone to the lymphatics may enhance flow with higher levels leading to vessel dysfunction, with a reduction in flow and perhaps even flow arrest.

The identification of nitric oxide in the 1980s as a major vasoactive agent involved in the local control of vessel tone revolutionised our understanding of the biology of the vascular endothelium (Nobel Prize, 1998). Since then, nitric oxide has been shown to be an early marker of endothelial dysfunction in patients with vascular disease (Paniagua et al, 2001; Belardinelli, and Perna, 2002; Craiem et al, 2008). Vascular endothelial cells use nitric oxide synthase (NOS) to continually synthesise nitric oxide from (L)-arginine, with its synthesis increasing in response to flow and shear stress within the vessel. Although it has a short half-life, it acts on adjacent smooth muscle cells in the tunica media of the vessel wall causing their relaxation, which in turn increases vessel diameter, reducing shear stress and increasing flow. Of significance, recent studies have shown that lymphatic vessels also use nitric oxide to regulate tone, contractile activity and flow, with its production also being upregulated by increases in shear stress within the vessel (Mizuno et al, 1998; Hagendoorn et al, 2004; Ohhashi, et al 2005; Zawieja, 2005; Quick et al, 2009; Miteva et al, 2010).

As described above, elevations in lymph pressure are a classic activator of the lymphatic pump, but only up to a point where increased pressure and stretch in the system leads to a decline in pumping activity and flow arrest (Davis et al, 2009). Zawieja (2009) has shown that the flow arrest observed at high flow rates, and hence shear stresses, is dependent on the lymphatic endothelium and its constitutive NOS activity, as endothelial denudation and inhibition of NOS prevent the flow arrest. Also, Miteva et al (2010), through direct measurements, demonstrated increases in nitric oxide production in response to increased lymphatic vessel flow and shear stress, with Gasheva et

al (2006) showing that such increases in pressure and shear stress, lead to vessel relaxation and more efficient pumping. From these observations, it was hypothesised (Gasheva et al, 2006; Zawieja, 2009) that the lymphatic endothelium produces nitric oxide in response to loading and increased shear stress, relaxing the vessel wall, enabling efficient diastolic filling and more efficient pumping. It is an intrinsic mechanism, identical to that found in the vascular system. Moreover, at higher levels of filling, shear stress, and hence increased nitric oxide production, there is complete relaxation of the lymphatic smooth muscle with subsequent loss of intrinsic contractility and pumping activity. This hypothesis provides a hormonally mediated plausible explanation of flow arrest at high pressures.

The studies described above highlight how both sympathetic vasomotor tone and flow mediated nitric oxide production play a similar role in controlling vessel tone and the movement of fluid in the vascular and lymphatic systems. Given this, and the interdependence of lymph production and flow on hydrostatic pressure in the vascular system, in the author's opinion it seems reasonable to expect that some of the beneficial effects of contrast hydrotherapy on the vascular system, as described below, would also influence the lymphatic system in a positive manner.

Contrast hydrotherapy gives the peripheral vasculature and nervous systems a work-out: evidence from studies on athletes

In sports medicine, contrast hydrotherapy has been used for many years to speed recovery following training and competition, and to improve subsequent performance. While initially its use was based on anecdotal evidence, there is now a significant body of scientific data supporting the practice. For example, post-exercise, contrast hydrotherapy has been shown to reduce the time required to clear lactate from the blood (Kuligowski et al, 1998; Morton, 2007), for the heart to return to its resting rate (Hamlin, 2007; Buchheit et al, 2009), and for general physical

recovery following training (Coffey et al, 2004; Ingram et al, 2009). It has also been shown to reduce fatigue and muscle soreness post-training and to increase performance levels in subsequent exercise (Vaile et al, 2008). It is worth mentioning however, that while not all studies have shown significant effects, as noted in a review by Wilcock et al (2006), those that have appear to be scientifically robust.

A review by Cochrane (2004) of contrast hydrotherapy in athletes concluded that while 'the physiologic effects of hot-cold water contrast baths for injury treatment have been well documented... its physiological rationale for enhancing recovery is less known'. In this regard, there is a recurring, and somewhat attractive if not reductionist hypothesis in the literature regarding the mechanism by which contrast hydrotherapy promotes recovery in athletes. As noted in the review by Cochrane (2004), 'most experimental evidence suggests that hot-cold water immersion helps to reduce injury in the acute stages... through vasodilation and vasoconstriction thereby stimulating blood flow thus reducing swelling'. With more relevance to the lymphatics however, Prentice (1999) has suggested that 'contrast therapy causes a cycle of local vasoconstriction and vasodilation, creating a type of "pumping" action that would enhance venous and lymphatic removal of edema'.

A study into the effects of contrast hydrotherapy on blood flow in the legs of athletes demonstrated a 200–300% increase in arterial blood flow above control levels during a four-minute warm phase, followed by a rapid drop in blood flow, to around 30–40% below control levels, during a subsequent one-minute cold phase (Fiscus et al, 2005). Repetition of this cycle over 20 minutes saw transient increases and decreases in blood flow during respective warm and cold phases. This phenomena is due to a fundamental homeostatic mechanism essential in the regulation of core body temperature. It is mediated through changes in sympathetic efferent vasomotor tone affecting α -adrenoreceptors of vascular smooth

muscle in the cutaneous vessels of the skin (Boron and Boulpeap, 2009).

In the case of hydrotherapy, when thermoreceptors in the skin sense warm water they relay this to the central nervous system (CNS), which, in an attempt to maintain core body temperature, reduces efferent sympathetic vasomotor tone to α -adrenoreceptors in cutaneous vessels. This causes relaxation of smooth muscle in the vessel wall and vasodilation, lowering peripheral vascular resistance and facilitating heat loss. The opposite is seen upon cold water treatment, with such reciprocal changes in peripheral vascular resistance being well documented (Bonde-Petersen et al, 1992). Indeed, most body heat is lost through convection when it is carried by blood to cutaneous vessels in the skin, with only a small amount being dissipated by direct conduction through tissues to the skin (Boron and Boulpeap, 2009). Moreover, there is great capacity in this system, as cutaneous vasodilation through this mechanism can increase blood flow to the skin by up to 10-fold (Boron and Boulpeap, 2009).

From these observations it is important to reiterate two points. Firstly, contrast hydrotherapy causes marked cyclical changes in cutaneous blood flow. Secondly, such changes are due to corresponding changes in the tonicity of efferent impulses in the sympathetic vasomotor system, acting through α -adrenoreceptors in peripheral cutaneous vessels. In simple terms, contrast hydrotherapy is giving both the peripheral vasculature (as suggested by Woodmansey et al, 1938), and the vasomotor arm of the peripheral nervous system a work-out. This is of significance, as the lymphatics are also innervated by the sympathetic nervous system, as described above, with sympathetic activity also mediated through α -adrenoreceptors, stimulating the lymphatic pump (Browse, 1968; Khaisman, 1982; McGeown et al, 1987; McHale and Roddie, 1983a, b; McHale, 1990, 1995). Hence, it is possible that contrast hydrotherapy, by cyclically changing sympathetic tone to the peripheries, has a stimulating effect

on the smooth muscle of peripheral lymphangions, essentially giving them a light work-out and stimulating lymph flow (see below). Moreover, the significant cyclical changes in cutaneous blood flow, and hence pressures within the vascular capillary bed, should increase movement of fluid into the interstitium, as reported by Convetino (1987). This primes the lymphatic pump, which can be further synergistically activated by the increase in sympathetic tone.

Contrast hydrotherapy improves long-term blood flow and endothelial function: evidence from subjects with peripheral arterial disease

Contrast hydrotherapy, and even thermal sauna therapy, not only improve peripheral blood flow in the short term, as described above, but also appear to improve long-term blood flow and endothelial function by modifying the vascular endothelium. One study of patients with significant peripheral arterial disease with debilitating claudication demonstrated that a three-week course of contrast hydrotherapy, consisting of ten 25-minute sessions with alternating 45°C and 10°C water every three seconds, lead to a prolonged (one year) and significant reduction in claudication, paralleled by significant improvements in distal blood pressure and flow (Elmstahl et al, 1995).

Similarly, subjects with either risk factors for cardiovascular disease or chronic cardiac failure have shown significant improvements in endothelial-dependent flow-mediated vasodilation following thermal sauna therapy (Imamura et al, 2001; Kihara et al, 2002), with a similar study showing additional improvements in quality of life and resting heart rate (Michalsen et al, 2003). Imamura (2001) and Kihara (2001) suggest that such dramatic and long-term improvements in flow are triggered in the first instance by thermally mediated vasodilation, increasing flow and shear stress at the vascular endothelium, resulting in both acute increases in endothelial nitric oxide production and more long-term activation of endothelial NOS expression. As mentioned above, nitric oxide produced by the vascular endothelium causes relaxation of

smooth muscle cells in the tunica media of the vessel wall. This causes dilation of the vessels, reducing shear stress and endothelial damage, which subsequently improves blood flow, nutrient delivery and vessel health. This is a well-reported phenomena, with flow-mediated nitric oxide dependent vasodilation being used clinically as a sensitive marker of early vascular dysfunction (Paniagua et al, 2001; Belardinelli and Perna, 2002; Craiem et al, 2008).

If contrast hydrotherapy were able to stimulate lymph flow in the short term (Fiscus, et al 2005), and cutaneous thermal therapy can markedly increase lymph flow (Olszewski et al, 1977), there would be an associated increase in shear stress and hence nitric oxide production (Miteva et al, 2010). Such short-term changes in nitric oxide production should lead to improved pumping efficiency, as shown by Gasheva et al (2006). In turn, this may lead to more long-term upregulation of NOS activity in the lymphatic endothelium, with improvements in lymph flow, vessel growth and repair. Recent studies have shown that nitric oxide and endothelial NOS play a vital role in mediating vascular endothelial growth factor (VEGF) dependent lymphangiogenesis (Kajiyama et al, 2008; Lahdenranta et al, 2009). Again, this parallels the situation in the vascular system, where nitric oxide and endothelial NOS also play a central role in VEGF-mediated angiogenesis (Hagendoorn, 2005).

Current treatments for lymphoedema, the multifactorial aetiology of this disease and a possible treatment and preventative role for contrast hydrotherapy

The majority of conventional treatments for the management of lymphoedema are conservative, with their primary aim being a reduction in the volume of the affected limb, to restore function and quality of life (Horning, 2007). The more common and effective treatments, based on quality clinical evidence, include complex physical therapy, manual lymphatic drainage (MLD), limb elevation, and compression bandages

and garments (Moseley et al, 2007). While they provide short-term relief, in some cases up to 40% reduction in limb volume (Moseley et al, 2007), for patients with secondary lymphoedema they do not provide a long-term cure. To date, there is no effective cure for secondary lymphoedema, with studies suggesting that its progressive nature (Hayes, 2008; Sagen et al, 2009; Rourke et al, 2010) is due to a gradual decline in the contractile activity of the lymphatic vessels and subsequent valvular incompetence (Witte et al, 2000).

Advice aimed at reducing the risk of lymphoedema (Hayes, 2008; Schmitz, 2010) suggests the avoidance of activities that stimulate lymph flow, such as vigorous or repetitive exercise, and extremes of temperature. Such advice was historically given, as lymphoedema, especially following treatment for breast cancer; was thought to be due to a reduced capacity to transport lymph in the affected limb, secondary to a restriction in lymph outflow, caused by damage or removal of more proximal lymph nodes. It is now realised that development of lymphoedema in such patients is not simply due to proximal obstruction (Lane et al, 2005). If this were the case, it would be expected to present more immediately following treatment. Only a minority of cases present following treatment, with most cases presenting after a few months or years, being triggered by an event that damages the remaining lymphatics, such as a minor infection following a cut or graze (Pain et al, 2005).

There is a great deal of confusion surrounding the recommendations for exercise in patients with lymphoedema, or at risk of developing it. To date, some societies involved in the management of lymphoedema still advise patients to avoid using the affected limb for carrying objects (Schmitz, 2010). As discussed by Hayes (2008), such recommendations are not founded on good quality clinical evidence, but rather based on theory and limited data. In the minds of patients at risk of developing lymphoedema however; they lead to a mind-set (Lee et al, 2009), where the patient avoids using the limb, or uses it minimally. This

can lead to a deconditioning of skeletal muscles (Hayes, 2010). As hypothesised by Lane et al (2005), ultimately this may lead to a gradual decline in lymphatic function due to a lack of flow with vessel atrophy.

It is now apparent from a body of clinical evidence, that exercising a limb at risk, including aerobic exercise, targeted resistance training or weight training, does not exacerbate lymphoedema, and in some cases even leads to a reduction in limb volume (McKenzie and Kalda, 2003; Hayes et al, 2009; McNeely et al, 2009; Sagen et al, 2009; Godoy et al, 2010; Kim et al, 2010). In many of these studies, patients also reported improvements in general health, vitality, well-being and psychological health secondary to the exercise regimens. Of greater significance perhaps are the results of a recent prospective randomised controlled trial looking at the effects of exercise on the development of lymphoedema in patients who have survived breast cancer (Schmitz, 2010). Upon randomisation into the trial, none of the patients had clinical signs of lymphoedema. The intervention was a three-month supervised and slowly graded weight-lifting programme, followed by nine months of unsupervised weights, with the control not partaking in exercise. The end point was the incidence of lymphoedema at one year. This was significantly reduced in all women partaking in the exercise programme (11% vs 17%), an effect that was even more marked in those women who had five or more lymph nodes removed (7% vs 22%). Given these findings, it appears that clinical advice to avoid excessive and repetitive use of an at-risk limb, and to avoid carrying heavy objects with it, was ill-founded and perhaps detrimental. However, it is important to emphasise that when patients are instructed to exercise in the first instance following recovery from treatment, it be carefully monitored in the initial stages, with gradual increments to a point where the patient is gaining maximal benefit.

The example given above regarding exercise and lymphoedema highlights

the fact that not all historical guidelines for the prevention and management of lymphoedema, founded on theory and not based on clinical evidence, may be correct. This has relevance to contrast hydrotherapy, as similar recommendations exist suggesting that patients avoid exposing their at-risk limb to extremes of temperature. For example, Horning and Guhde (2007) advise patients to avoid:

- ▶ Exposure to extreme cold, which can be associated with rebound swelling, or chapping of skin
- ▶ Prolonged (>15 minutes) exposure to heat, particularly hot tubs and saunas
- ▶ Immersing the limb in water temperatures above 102°F (38.8°C).

Hayes (2008) also notes the advice to 'avoid heat, including sunburns or tanning, hot baths and saunas', but is again careful to make the distinction that, 'evidence supporting or refuting these guidelines (not all listed here) is scarce'. This was also highlighted by Rymal (2002) in a letter responding to the question, 'Can patients at risk for lymphedema use hot tubs?'. Here, it was reported that only anecdotal clinical evidence suggests that hot tubs can precipitate oedema, and that even the experts cannot form a consensus regarding this topic. To this end, there are no studies in the literature that investigate the effect of contrast hydrotherapy on secondary lymphoedema. There are, however, two studies showing that cutaneous thermal therapy (44°C hot water) can markedly improve lymph flow (Olszewski et al, 1977) and reduce the volume of lymphoedematous legs (Liu and Olszewski, 1993).

Conclusion

There has been much progress in the last two decades regarding our understanding of the lymphatic system. In terms of how best to prevent secondary lymphoedema in those subjects at highest risk there is still a long way to go, with recent studies giving hope that prevention may lie in simple graded exercise programmes (Schmitz, 2010b). This paper outlines a theoretical discussion as to why contrast

hydrotherapy may prove to be not only an effective treatment for lymphoedema, but perhaps also an effective prophylaxis. While this concept is theoretical, based on the many similarities between the vascular and lymphatic systems in terms of innervation and vessel biology, it is given some clinical credence by the marked improvement in claudication in patients with peripheral vascular disease following contrast hydrotherapy (Elmstahl et al, 1995). As appears to be the case with exercise however, a gradual introduction of contrast hydrotherapy with temperatures that are not too extreme may be the best approach in initial investigations of this hypothesis. It is an exciting new area that warrants clinical investigation with pilot trials. JL

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Key points

- ▶▶ Contrast hydrotherapy, which involves the immersion or dousing of a limb in alternating hot and cold water, has been shown to improve distal blood flow and vessel function in patients with peripheral arterial disease who suffer from claudication.
- ▶▶ It has been shown to cause acute changes in blood flow to limbs (\uparrow flow with warm water), presumably through autonomically mediated changes in the tone of the peripheral arterioles, secondary to the changes in the cutaneous temperature of the limb.
- ▶▶ Such changes in flow are known to increase shear stress within vessels and this is proposed as the mechanism through which increased flow improves vessel nitric oxide production and overall vessel health.
- ▶▶ Recent evidence suggests that the vascular and lymphatic systems have much in common with regards innervation by the autonomic nervous system and their cell biology, with respect to flow mediated nitric oxide production.
- ▶▶ This paper discusses the concept of contrast hydrotherapy as a possible therapy for the prevention and management of lymphoedema.

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