

Lymphatic pump treatment enhances the lymphatic and immune systems

Lisa M Hodge^{1,2} and H Fred Downey^{1,3}

¹Osteopathic Research Center; ²Department of Molecular Biology; ³Department of Integrative Physiology, University of North Texas Health Science Center, 3500 Camp Bowie Boulevard, Fort Worth, TX 76107, USA

Corresponding author: Lisa M Hodge. Email: lisa.hodge@unthsc.edu

Abstract

The osteopathic medical profession has long advocated the use of osteopathic lymphatic pump treatments (LPT) to improve lymphatic circulation, reduce edema and combat infectious disease. However, until recently, there was no scientific evidence that LPT enhances function of the lymphatic and immune systems. This review discusses the physiological functions of the lymphatic system, the ability of LPT to increase lymph flow under normal and experimental conditions, the clinical benefits of LPT, current research models for the study of LPT and the potential mechanisms by which LPT enhances lymphatic and immune function.

Keywords: gastrointestinal lymphoid tissue, infection, lymphatic pump techniques, lymphatic pump treatments, lymphatic system, osteopathic manipulative medicine, thoracic duct, lymph, immunity

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Introduction

The lymphatic system provides a means to return excessive interstitial fluid to the blood circulation. In this process, interstitial cells and substances are also transported from tissue to blood. As leukocytes circulate between tissue, lymph and blood, they continuously sample the internal environment for foreign antigens, a process termed 'immune surveillance'.¹ Disease processes that impair lymph flow, such as infection and lymphedema, hinder lymphocyte recirculation and exacerbate the disease. Thus, interventions that improve lymph flow may relieve edema and treat infection by enhancing circulation of immune cells, immune products and pharmaceuticals.

The osteopathic medical profession has developed manipulative medicine treatments, specifically termed as lymphatic pump treatments (LPT), to increase lymph flow.² Although there are anecdotal reports of clinical benefits of LPT,^{3–7} there is a paucity of research to support this treatment modality. Recent investigations using animal models have demonstrated that LPT does increase lymph flow⁸ and leukocyte trafficking,^{9–11} and thus these investigations have provided insight into the mechanisms by which LPT enhances the lymphatic and immune function. This review discusses the physiological functions of the lymphatic system, the ability of LPT to increase lymph flow under normal and experimental conditions, the clinical benefits of LPT, current research models for the study of LPT and

the potential mechanisms by which LPT enhances lymphatic and immune function.

The lymphatic system

The lymphatic system helps to maintain extravascular homeostasis by transporting excess fluid and various substances from the interstitial space to the blood circulation. This transported tissue fluid is referred to as lymph, and it can contain immune cells, apoptotic cells, proteins, infectious organisms and antigens that exist in the interstitial space.¹ The movement of lymph through lymphatic vessels is maintained by pressure gradients from the interstitial space to the central venous circulation aided by phasic contractions of smooth muscle in lymph vessel walls.^{12,13} To prevent the backflow of lymph, a series of valves along the vessels ensures the unidirectional flow of lymph toward blood circulation.¹³

Several factors influence lymph flow. When engorged, segments of the lymphatic vessels between valves, called lymphangions, cyclically contract and thus act as lymph pumps.¹⁴ High lymph flow releases nitric oxide from lymphatic endothelium, causing relaxation of lymphatic smooth muscle and reduced hydraulic resistance to lymph flow.¹⁵ Additionally, skeletal muscle contraction, intestinal motility and respiratory motions increase lymphatic transmural pressure, compress lymph vessels and increase

lymph flow.¹⁴ Likewise, compression of tissue by external force will also compress lymph vessels and increase lymph flow.¹⁶ Interventions such as exercise,^{8,17,18} passive limb movement,¹⁹ expansion of the extracellular fluid space²⁰ and body-based manipulative medicine treatments⁸⁻¹¹ have been shown to increase lymph flow.

In addition to transporting lymph, the lymphatic system also transports cells of the immune system. These include migrating dendritic cells, macrophages and lymphocytes. During infection, lymph vessels carry antigens and immune cells from infected tissues into peripheral lymph nodes, where antigen-specific immune responses are initiated.¹ Once these antigen-specific lymphocytes become activated, they are transported by lymphatic vessels to the systemic venous circulation.^{1,21} These primed lymphocytes then pass through the pulmonary circulation and are subsequently distributed by the cardiac output back to the infected tissue. This recirculation of lymphocytes from tissue to lymph to blood to tissue is estimated to occur more than 40 times a day.^{21,22} Clearly, lymphatic transport facilitates interactions of lymphocytes with foreign antigens in blood and tissue, which is vital for the induction of antigen-specific immune responses.

Osteopathic manipulative treatment and the lymphatic system

The osteopathic medical profession stresses the importance of the lymphatic system in maintaining health.^{2,3} Osteopathic philosophy states that improved lymph flow cleanses the interstitial space of blood cells, particulate matter, exudates, toxins and bacteria that may adversely affect cellular activity and predispose tissue to dysfunction and disease.² Both intrinsic and extrinsic forces influence lymph flow,¹⁶ and many osteopathic manipulative treatments (OMT) are designed to promote lymph circulation by enhancing the rhythmic contractility of lymph vessels in addition to the direct application of external pressure.³

LPT is clinically used to treat patients with congestive heart failure, upper and lower gastrointestinal dysfunction, respiratory tract infection and edema.² LPT can be applied to the thoracic cage (thoracic pump), abdomen (abdominal pump), feet and legs (pedal pump) and the areas of the spleen and liver. The thoracic lymph pump transiently reduces intra-thoracic pressure by increasing thoracic range of motion and augmenting respiratory expiratory recoil. The abdominal lymph pump transiently increases abdominal pressure and thus augments the abdominal-thoracic pressure gradient for lymph flow. Pedal lymphatic pumps are thought to enhance lymphatic and venous drainage;² however, there are no studies that have quantified the effects of pedal pumps on the lymphatic system or determined its clinical benefits. Lymphatic pumps typically consist of manual compressions of a specific body region at a rate of 20–30 compressions per minute for 2–5 min.²

For over 80 years, LPT has been taught at osteopathic medical schools as a treatment to increase lymphatic flow; however, the first investigation that documented the effect of LPT on lymphatic function did not appear until 2000.²³

In this study, a fluorescent probe was injected into the interstitial fluid space of anesthetized rats. Thoracic LPT significantly increased the rate of appearance of the fluorescent probe in blood compared with that observed in untreated control animals. Since the probe could not cross the vascular capillaries, these results indicated that LPT enhanced the uptake of the probe by the lymphatic system and its transport from tissue to blood. In 2005, the first report of the direct effect of LPT on thoracic duct lymph flow was published.⁸ In this study, dogs were surgically instrumented to measure thoracic duct lymph flow. After recovery from surgery, the dogs received thoracic lymph pump, abdominal lymph pump or treadmill exercise. All three interventions significantly increased thoracic duct flow compared with pretreatment baseline measurements. The greatest increases were seen during abdominal pump (Figure 1) and exercise. Collectively, these studies demonstrate that LPT enhances both the uptake of lymph into the terminal lymphatics and increases thoracic duct lymph flow rate.

Splenic lymphatic pump treatments and the immune system

The earliest studies assessing the effect of LPT on the immune system were in the 1920s and 1930s.²⁴⁻²⁶ The first report to use an animal model to evaluate splenic LPT was by Lane in 1920. He found that splenic manipulation in rabbits increased the antibody titer against sheep red blood cells.²⁴ He also found that the antibodies persisted at higher levels for a longer period of time in rabbits that received manipulation compared with animals that had not received manipulation. These data suggest that LPT has an effect on the humoral immune system.

Later, Castlio and Ferris-Swift^{25,26} collected blood samples from healthy subjects before treatment and at intervals from 5 to 60 min after splenic LPT. Splenic

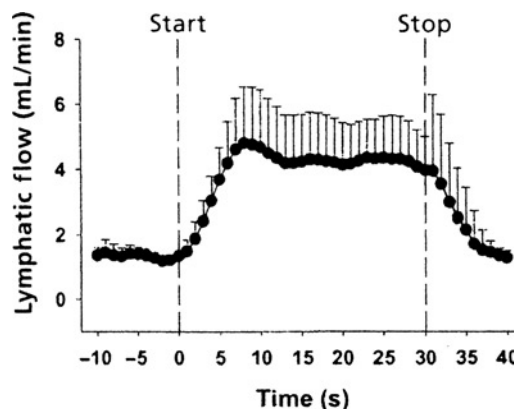


Figure 1 Thoracic lymph flow was measured in five conscious, surgically instrumented mongrel dogs before, during (between vertical dashed lines) and after abdominal LPT. Data are mean thoracic duct flow (mL/min) \pm SE. Lymph flow increased significantly from baseline values during 5–30 s of abdominal LPT ($P < 0.05$). LPT, lymphatic pump treatments. Republished with permission from Knott EM, Tune JD, Stoll ST, Downey HF. Increased lymphatic flow in the thoracic duct during manipulative intervention. *J Am Osteopath Assoc* 2005;105:447–56⁸

manipulation transiently increased the total blood leukocyte count and the serum opsonic index against *Mycobacterium tuberculosis*; however, there was no consistent increase in any specific leukocyte population during splenic LPT.²⁵ The authors later conducted a study in patients with acute infectious disease and found that splenic LPT produced similar results as seen in healthy individuals.²⁶ Collectively, their findings suggest that LPT enhances the immune system of both healthy individuals and patients with acute infectious disease; however, the long-term clinical significance of this effect is still unclear.

It is important to note that the studies from Castlio and Ferris-Swift had limitations in their experimental design and statistical analysis, which were common to that era. However, a recent analysis of their original data using modern statistics supported many of Castlio and Ferris-Swift's original conclusions.²⁷ Later, in 1998, Mesina *et al.*²⁸ examined the differential leukocyte count and found that splenic LPT induced transient basophilia in the venous blood of healthy subjects. Together, these studies support the theory that LPT enhances the innate immune system, which is vital for the control of acute infectious disease.

While reports suggest that the spleen has lymphatic vessel drainage,^{29,30} the majority of splenic leukocytes exit via the splenic veins³¹ and do not readily migrate into the thoracic duct.³² Therefore, it is unlikely that splenic LPT releases leukocytes directly into lymphatic circulation, but rather stimulates the release of splenic leukocytes directly into blood via the venous system.

Thoracic lymphatic pump treatments and the immune system

LPT has been shown to enhance the adaptive immune response to vaccine antigens.^{4,5} In 1982, normal male subjects were immunized against *Streptococcal pneumoniae* with Pneumovax vaccine.⁵ Control subjects received no LPT, while the treatment group received five minutes of LPT daily for one week. Blood samples taken at days 1, 3, 5, 7 and 14 following immunization were analyzed for passive and bacterial hemagglutination *in vitro*. LPT increased hemagglutination against bacterial cells and bacterial polysaccharide antigens. This finding supports the use of LPT to enhance vaccine-specific immunity. A later study measured the effectiveness of LPT at enhancing the antibody response to hepatitis B vaccine, which requires multiple immunizations to develop protective immunity.⁴ In this study, healthy subjects were divided into control (no treatment) and experimental (LPT treatment) groups and given the recombinant hepatitis B vaccine on weeks 0, 5 and 25. Individuals in the experimental group received LPT three times a week for two weeks following each vaccination. From the sixth week of the study onwards, subjects in the LPT group had higher protective antibody titers compared with the control group.

Collectively, these studies suggest that administration of LPT during the development of the vaccine-specific immune response will increase the production of protective antibodies. Currently, there are no published animal studies

exploring the mechanism by which LPT may enhance protective antibody titers during immunization. However, studies using rats and dogs have shown that LPT increases the lymphatic uptake of antigens,²³ thoracic and mesenteric lymph flow⁸ and the concentration of leukocytes in thoracic and mesenteric lymph.⁹⁻¹¹ Most vaccines are designed to induce B-cell activation, which leads to the secretion of high-affinity antibodies by plasma cells.⁴ By enhancing the lymphatic uptake of vaccine antigens, LPT may facilitate the activation of vaccine-specific lymphocytes within secondary lymphoid tissues. In addition, by increasing the number of T-cells and B-cells in lymphatic circulation,⁹⁻¹¹ LPT may increase antigen-specific T-cell and B-cell encounters within secondary lymphoid tissues. Both mechanisms could increase vaccine-specific serum antibody titers.

It is important to note that not all clinical studies had apparent positive outcomes. For example, serum interferon (IFN) levels of healthy subjects were unchanged throughout a 24-h period following thoracic LPT.³³ While IFN provides protection against viral and bacterial infections, it is important to note that IFN should not be elevated in healthy individuals. The results from this study suggest that without a stimulus (infection or tumors), LPT is not able to increase serum IFN levels.

Abdominal lymphatic pump treatments and the immune system

While there are no published reports measuring the effects of abdominal LPT on humans, we have demonstrated that the application of abdominal LPT to both rats and dogs increases the lymphatic concentration of leukocytes.⁸⁻¹¹ Specifically, we measured the effect of LPT on the release of leukocytes into central lymphatics.⁹ Lymph flow and concentration of total leukocytes, macrophages, neutrophils, total lymphocytes, T-cells and B cells, and their percentages in the thoracic ducts of dogs were measured during pretreatment and during eight minutes of abdominal LPT. LPT did not preferentially mobilize any specific immune cell populations, but significantly increased both thoracic duct lymph flow and total leukocyte concentrations, resulting in an approximately 10-fold increase in the lymphatic flux, i.e. number of total leukocytes per minute transported in the thoracic duct during LPT. This study provided the first direct evidence that LPT increases lymphatic transport of leukocytes, and thus, provides a scientific rationale for the use of LPT to enhance immune function.

In mammalian species, the majority of lymphocytes in thoracic duct lymph are derived from the gastrointestinal lymphoid tissues (GALT).^{31,32,34-36} Therefore, to determine if the GALT is a source of the lymph and leukocytes released during LPT, we cannulated the thoracic and mesenteric lymph ducts of anesthetized dogs, and examined lymph samples for cells produced by the GALT.¹⁰ Lymph samples were collected pretreatment, during four minutes of abdominal LPT, and for 10 min following cessation of LPT. Similar to our previous findings, LPT produced large increases in leukocyte flux in both thoracic (Figure 2) and mesenteric duct lymph. LPT significantly increased the

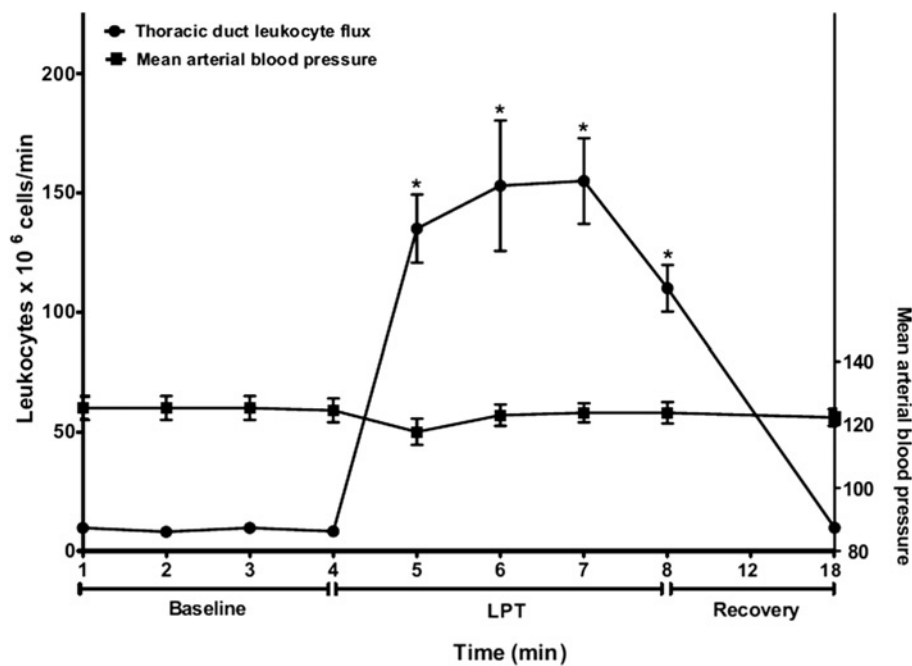


Figure 2 Thoracic duct lymph was collected from anesthetized dogs (1) during four-minute pre-LPT baseline, (2) during four-minute abdominal LPT; and (3) at 10-min post-LPT recovery. Data are mean \pm SE ($n = 6$). Scale does not permit illustration of SE for pre-LPT baseline and post-LPT recovery leukocyte data. Units of mean arterial blood pressure are mmHg. *Greater than pre-LPT baseline and post-LPT recovery ($P < 0.001$). LPT, lymphatic pump treatments. Republished with permission from Hodge LM, Bearden MK, Schander A, Huff JB, Williams A Jr, King HH, Downey HF. Abdominal lymphatic pump treatment mobilizes leukocytes from the gastrointestinal associated lymphoid tissue into lymph. *Lymphat Res Biol* 2010;8:103–10¹⁰

numbers of macrophages, neutrophils, CD4⁺ T-cells, CD8⁺ T-cells, IgA⁺ B-cells and IgG⁺ B-cells in both thoracic and mesenteric duct lymph. Of particular importance was the increase of IgA⁺ and IgG⁺ B-cells, suggesting that LPT is able to stimulate the release of mature, isotype-switched B-cells from the GALT into the lymphatic circulation. These cells may be especially effective in providing immune protection against infectious disease. Ten minutes following LPT, lymph flow and leukocyte concentrations in thoracic and mesenteric lymph were similar to pre-LPT values, demonstrating that the effect of LPT is transient.

To determine if LPT could stimulate the release of leukocytes from the mesenteric lymph nodes (MLN), we fluorescently labeled MLN *in situ*, and quantified the number of fluorescent leukocytes entering thoracic duct lymph.¹⁰ LPT mobilized 2.7×10^7 leukocytes from the MLN. Thus, our findings support the hypothesis that LPT mobilizes leukocytes from the GALT into the lymphatic circulation, and LPT stimulates the nodal release of leukocytes. Of clinical importance, these cells may traffic into infected or inflamed tissues and provide immune protection.

While canine research supports the use of LPT to enhance lymphatic and immune function, this research is complex and expensive. Therefore, we developed a rodent model to investigate effects of LPT on lymphatic function.¹¹ LPT was applied to anesthetized rats in a manner similar to a previous report,²³ and lymph was collected from the cisterna chyli. Similar to measurements in the dog, we found that four minutes of LPT markedly increased lymph flow and leukocyte concentrations (Figure 3). Furthermore, LPT increased the number of GALT-derived

leukocytes in rat lymph. The effects of LPT on lymph flow and leukocyte concentrations subsided after LPT, and no specific leukocyte population was preferentially mobilized. These results were consistent with our findings in dogs, and furthermore, they demonstrate that LPT enhances lymph flow and the lymphatic release of immune cells in

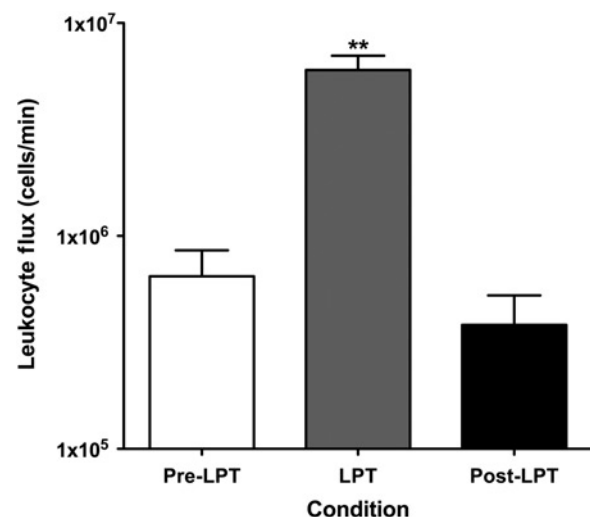


Figure 3 Flux of total leukocytes in lymph collected from the cisterna chyli of anesthetized rats. Lymph was collected during (1) pre-LPT, (2) four-minute LPT and (3) 10-min post-LPT. Data are mean \pm SE ($n = 6$). **Greater than pre-LPT and post-LPT ($P < 0.05$). LPT, lymphatic pump treatments. Republished with permission from Huff JB, Schander A, Downey HF, Hodge LM. Lymphatic pump treatment enhances the lymphatic release of lymphocytes. *Lymphat Res Biol* 2010;8:183–7¹¹

a smaller animal. As these findings have all been made in the authors' laboratories, it is important that they be confirmed by other investigators.

Lymphatic pump treatments and protection against infectious disease

The wide use of antiviral and antibiotic treatments has substantially reduced the rate of death from infectious disease. Unfortunately, the prevalence of organisms resistant to antimicrobial therapy has increased substantially in the last 10 years, and this raises the possibility that antibiotic treatments will become less effective for treatment of infectious disease in the future.³⁷ Therefore, there is a growing need to re-examine the benefits of alternative medicine procedures, such as LPT, for treatment and prevention of infectious disease.

Although clinical reports support the use of LPT as an adjunctive therapy for the treatment of pulmonary infection, the mechanisms by which LPT may protect the lung are still unclear. It is likely that by enhancing the numbers of leukocytes in circulation, LPT increases the numbers of leukocytes that traffic into tissue. In support of this notion, pilot studies from our laboratory have shown that LPT protects rat lungs during bacterial infection.³⁸ Specifically, during mycoplasma infection, LPT reduced the numbers of lung bacteria, pulmonary lesions and increased blood leukocyte numbers compared with sham treatment. In addition, we have shown that LPT protects rats from the development of pulmonary tumors. Specifically, LPT reduced the numbers of solid tumors by approximately 30% and increased the numbers of B-cells, CD4⁺ T-cells, CD8⁺ T-cells, natural killer cells and macrophages in the lungs.³⁹ Collectively, these data further support the hypothesis that LPT increases the number of circulating leukocytes that can traffic into the lung and protect the lung during pulmonary disease.

Furthermore, our data from animal models suggest that LPT protects against infectious disease by stimulating the release of immune cells from the GALT. Due to their constant exposure to commensal bacteria, lymphocytes in the GALT are more sensitive to antigen stimulation.^{40–42} Lymphocytes primed in the gastrointestinal tract are transported by lymph to the systemic venous blood, which carries them into the lungs where they fight pulmonary infection.^{43–46} Importantly, we have shown that LPT stimulates the mobilization of GALT-derived leukocytes into the lymphatic circulation of both dogs¹⁰ and rats¹¹, and that LPT increases the lymphatic flux of these cells. Thus, LPT may increase the redistribution, i.e. trafficking, of primed leukocytes from the GALT into an infected tissue, such as the lung.

It is also possible that by increasing lymph flow, LPT enhances the redistribution of antibiotics, cytokines, antibodies, antigens and other immune factors that would facilitate the clearance of infection. In dogs, we have shown that LPT increased thoracic duct lymph cytokine/chemokine fluxes approximately 10-fold, and intestinal lymph cytokines/chemokine concentrations approximately five-fold compared with baseline pre-LPT.⁴⁷ Furthermore, by

10 min following cessation of LPT, thoracic and intestinal lymph cytokine/chemokine concentrations were similar to baseline, suggesting that their release is transient. The greatest increases were seen in interleukin (IL)-2, IL-6, IL-8, IL-10, KC and monocyte chemoattractant protein-1. These results demonstrate that LPT is able to mobilize inflammatory mediators into lymphatic circulation.

The earliest success recorded for the use of osteopathic medicine to treat infectious disease was during the H1N1 influenza pandemic of 1917–1918. Osteopathic physicians reported that of 110,122 uncomplicated influenza cases treated with OMT, only 257 cases ended in death,³⁷ a mortality rate of only 0.23%. This rate compared very favorably with a national mortality rate of 3–5%. The mortality rate for influenza cases complicated by pneumonia was 10% when treated with OMT, as compared with the national average of 25%.³⁷ These results provided early evidence that OMT is effective in clearing pulmonary infection.

A later study examining the effect of LPT in patients with lower respiratory tract disease found that treatment with LPT in addition to standard therapy improved pulmonary function compared with standard therapy alone.⁴⁸ Specifically, LPT was associated with a more rapid cleansing of the tracheobronchial tree, increased sputum production and shorter duration of cough. A pilot study conducted in hospitalized elderly patients with acute pneumonia demonstrated that OMT, including LPT, combined with conventional medical treatment, reduced the need for intravenous antibiotics and reduced length of hospital stay.⁶ Thus, when used as an adjunctive medicine therapy, LPT enhances treatment against pulmonary disease.

In 2010, the Multicenter Osteopathic Study in the Elderly reported on the efficacy of osteopathic manipulation as an adjunctive treatment for hospitalized patients with pneumonia.⁷ This study utilized 406 elderly subjects who were hospitalized with pneumonia. Patients received conventional care, conventional care plus light-touch treatment (sham OMT) or conventional care and OMT, which included LPT. Consistent with the pilot study,⁶ OMT reduced length of hospital stay, duration of antibiotic use and respiratory failure or death. While these findings support the use of OMT as an adjunctive therapy for the treatment of pneumonia in the elderly, the use of multiple manipulative treatments makes it difficult to ascertain whether these benefits were directly related to the application of LPT.

While there are no published studies that suggest that LPT exacerbates or disseminates disease when administered to patients with infection, a recent clinical study reported that in patients with chronic obstructive pulmonary disease, OMT (which included LPT) mildly worsened pulmonary function measures immediately post-treatment when compared with pretreatment.⁴⁹ The authors proposed that OMT might worsen pulmonary function by triggering bronchospasm or loosening airway secretions, which could exacerbate air trapping. Despite this finding, the patients subjectively reported that they benefited from OMT. In a separate study, splenic LPT was applied to nursing home residents following immunization with influenza vaccine.⁵⁰ While splenic LPT did not increase influenza vaccine-specific

antibody titers, the authors reported a reduction in general antibiotic use during the influenza season.

Clinical studies show promise for the use of LPT to enhance the immune system and protect against respiratory disease; however, many of these were pilot studies with limited numbers of subjects. Also, the type of LPT, time points of sample collection, age of subjects, serological tests and other endpoints varied widely among the studies. Many studies utilized a variety of osteopathic manipulative treatments as well as LPT. Additionally, technology and understanding of the lymphatic and immune systems have advanced compared with the era when many early studies were published. Future clinical studies are required to confirm the efficacy of LPT for treatment of specific diseases. Finally, further development and use of animal models will be crucial to identify the mechanisms by which LPT protects against infectious disease.

Summary

Procedures to increase lymph flow and improve immune function are often performed by osteopathic physicians. However, only recently have experiments demonstrated that these LPT procedures when applied to rats and dogs do increase lymph flow. Furthermore, animal experiments show that LPT also increases the concentration of leukocytes in lymph. LPT stimulates the mobilization of GALT-derived leukocytes into the lymphatic circulation and the release of leukocytes from mesenteric lymph nodes. These experimental observations support case reports and limited clinical findings that LPT is a valuable complimentary therapy for infectious diseases, including influenza and pneumonia. Further research is required to confirm the efficacy of LPT for treatment of specific diseases and for identifying mechanisms by which LPT protects against infectious diseases.

Author contributions: HFD provided the scientific oversight for the data shown in Figure 1. LMH provided scientific oversight for the data shown in Figures 2 and 3. LMH and HFD prepared the manuscript.

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