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Focus Article

Fluid transport from the dental pulp revisited

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In the dental pulp surrounded by rigid dentinal walls, an increase in fluid volume will be followed by a rapid increase in interstitial fluid pressure. To maintain pressure homeostasis, a fluid drainage system is required. The dental pulp and apical periodontal ligament lack lymphatic vessels, and the questions are how the transport can take place inside the pulp and where the lymphatic vessels draining fluid from the apical periodontal ligament are located. The drainage of fluid within the pulp must be governed by a tissue pressure gradient (driving pressure) and the fluid is likely transported in loose connective tissue (gaps) surrounding vessels and nerve fibers. We suggest that aging of the pulp tissue characterized by fibrosis will reduce the draining capacity and make it more vulnerable to circulatory failure. When the fluid leaves the pulp, it will follow the nerve bundles and vessels through the periapical ligament into bone channels, where lymphatic vessels are found. In the mandibular canal, lymphatic vessels are localized and the fluid washout rate from the canal is slow, but chewing may speed it up by increasing the fluid pressure. In acute apical periodontitis, inflammatory mediators and bacterial components can be spread to regional lymph nodes via lymphatic vessels inside the jaw bone.

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The dental pulp can be classified as loose connective tissue surrounded by stiff dentinal walls. This organ is relatively well supplied by blood vessels with the highest density in the most coronal part of the pulp. The arteries enter the pulp through the apex and leave the pulp as venules. A dense network of capillaries supplies the odontoblasts, as well as all other interstitial cells, with nutrients. The capillaries in the dental pulp have a continuous endothelium, except in the odontoblastic area where the endothelium may be fenestrated (1), which probably reflects the need for increased fluid exchange due to high metabolic activity in this part of the pulp. The fluid flux across the capillaries is bulk flow and represents the exchange of substances between the compartments. In situations with increased filtration, such as inflammation, the interstitial fluid volume is increased and fluid has to be removed before homeostasis can be re-established.

The existence of lymphatic vessels in the pulp has been debated for many years, and such lymphatic vessels were previously thought to contribute to fluid volume control in the tissue (2). New evidence shows that the dental pulp lacks lymphatic vessels (3–5), and in this review we discuss the regulation of fluid transport within and from the pulp in light of this new information.

Regulation of transcapillary fluid flux

The forces governing the transcapillary fluid flux in the body are described in the Starling equation:

$$J_v = \mathrm{CFC}\left((P_c - P_{if}) - s\left(\mathrm{COP_p} - \mathrm{COP_{if}}\right)\right) - L,$$

where J_v = net flow across capillary, CFC = capillary filtration coefficient, P_c = capillary hydrostatic pressure, P_{if} = interstitial fluid pressure, σ = osmotic reflection coefficient to plasma proteins. $\mathrm{COP_p}$ and $\mathrm{COP_{if}}$ = colloid osmotic pressure in plasma and interstitium, respectively, and L = lymph flow.

The fluid transport between the blood vessels and the interstitial space is regulated by differences in colloid osmotic and hydrostatic pressures in the plasma and the interstitium, and by properties of the capillary membrane. From the interstitium, excess fluid is transported back to the blood circulation through the lymphatic system. During normal conditions, a steady state is achieved, as the fluid filtered into the interstitial space equals the amount of fluid transported out of the same compartment.

The Starling forces acting on the capillary wall have been investigated in the pulp and measurements of interstitial fluid pressure with the micropuncture method have given values in the range from 6 to

10 mmHg (2). A corresponding capillary pressure has been calculated to be approximately 30 mmHg (6). Colloid osmotic pressure (COP) measurements in interstitial fluid isolated from rat incisors have shown a relatively high pulpal COP, reaching 83% of plasma COP (7). The high value may imply that the normal permeability of pulpal vessels to plasma proteins is relatively high and/or that the drainage of plasma proteins is ineffective. We have shown that the interstitial, i.e., extravascular, fluid volume in the pulp is 60% of the wet weight (7). Such a high hydration level is followed by a high hydraulic conductivity, allowing fast fluid movements (8).

The localization of the pulp inside the dentin chamber gives the tissue little possibility to expand when fluid volume increases, such as in acute inflammation, due to vasodilation and/or increased permeability. In these situations, the interstitial fluid pressure increases concomitantly due to the low compliance (9). Heyeraas & Kvinnsland (10) observed that an increase in interstitial fluid pressure induced by inflammation could remain localized for long periods of time (more than 8 h). The main feedback mechanisms counteracting a build-up and spread in tissue pressure are increased fluid drainage out of the pulp and possibly some net absorption in capillaries in the adjacent un-inflamed tissue due to bulk flow. Both factors will reduce the interstitial fluid volume in the pulp and consequently lower the pressure (2). It cannot be excluded that extravasated plasma proteins are reabsorbed along with the fluid by vesicular transport through the capillary wall (11) (see Fig. 1).

The excess protein in the interstitium, which accumulates when vessel permeability is increased, must be transported from the inflamed area to reestablish homeostasis. From clinical observations, we know that acute pulpitis can be reversed when, for example, a leaky restoration is replaced or exposed dentine is covered. This healing process requires a functional fluid transport system that allows the removal of excess protein-rich fluid.

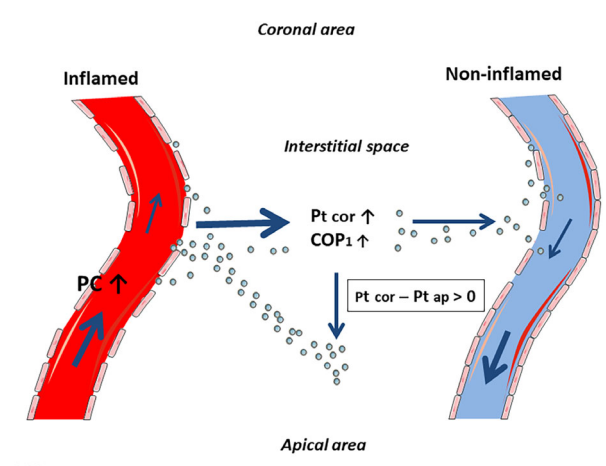

Fig. 1. Fluid and plasma protein (dots) removal from inflamed (left) and un-inflamed (right) coronal pulp tissue. Black arrows indicate relative magnitude and direction of fluid transport (COPi, colloidal osmotic pressure in interstitial fluid; Pc, capillary blood pressure; Pt, tissue pressure). ap, apical; cor, coronal. [Colour figure can be viewed at wileyonline library.com]

For many years, it has been debated whether protein-rich fluid can be transported by pulpal lymphatics. Due to a lack of specific markers, it was not possible to determine if the pulp had lymphatic vessels, but investigations during the last 10 yr have conclusively shown that the pulp is one of a few organs in the body without such vessels (3–5).

The next question to ask is how pulp tissue without lymphatics able to drain fluid with macromolecules. We suggest that this may occur through the transport of protein-rich fluid in the interstitial compartment toward the apical part of the pulp and furthermore out of the apex, either alone or combined with fluid reabsorption into pulpal blood vessels (Fig. 1). Transport of protein-rich fluid in clefts in the pulp tissue was suggested by Heyeraas (12). She injected a small volume of radioactive-labeled albumin mixed with fluorescent dextran into the coronal pulp in cats and, at the same time, measured the interstitial fluid pressure to control for pressure increases due to the injection. She found that tracer accumulated relatively fast in the apical part of the pulp close to nerve fibers, but not in vessel-like structures, and concluded that a transport system must exist in the pulp, possibly via tissue clefts. In favor of transport through the parenchyma is the fact that the hydraulic conductivity of the pulp is high (13) and has been shown to increase dramatically during increase in temperature in the tissue (14) occurring, for example, in inflammation. Taken together, transport of fluid from the coronal to the apical part can take place in clefts in the tissue as long as there is a pressure difference in the tissue. Due to the low compliance in the pulp, the pulp tissue is under fluid pressure changes due to pulsation in pulpal arteries (15) that may contribute to pulpal fluid movement. In the brain, another organ in the body lacking lymphatic vessels, interstitial fluid moves through the parenchyma via paravenous drainage pathways to the central nerve system (16) named the glymphatic system. A similar system has recently been described in the eye, which also lacks lymphatic vessels in the retina and optic nerve head (17). In the brain, cerebrospinal fluid is driven by arterial pulsations in the parenchyma (18). We propose that a similar glymphatic system exists in the pulp.

Drainage of fluid outside the pulp

Another remaining question is where the uptake of macromolecules from the pulp into the lymph takes place. We have recently shown that there are no lymphatic vessels in human granuloma tissue or in rat apical periodontal ligament (19, 20). We know that patients with acute apical periodontitis can develop lymphadenitis, meaning that the infectious material is spread via the lymph to the draining lymph nodes. In a study on mice, dendritic cells from the coronal pulp

were challenged and found in the local lymph nodes 16 h after dentin exposure (21). However, the afferent lymphatic vessels that were responsible for the transport were not localized. We have recently demonstrated lymphatic vessels in close proximity to blood vessels and nerves in *canalis mandibularis* in rats (20). Lymphatic vessels were also found in the bone just below the apical periodontal ligament of molars (Fig. 2) and above the molar roots in the rat upper jaw (20).

Furthermore, injection of a depot of radioactive tracer bound to the plasma protein human albumin into the rat pulp chamber, after the tissue removal and apical foramen widening, resulted in an immediate transport of tracer within the whole mandibular canal (20), which is most likely due to a high hydraulic conductivity within this loose connective tissue. No tracer was found in gingiva surrounding the rat molar. Four h after tracer application, radioactivity was observed in the lymph nodes and serum. The level of radioactive tracer within the lymph nodes remained low, whereas higher amounts were detected in the serum. This may imply that the tracer fluid was mainly absorbed into blood capillaries and transported out of the jaw by blood vessels, and that the lymphatic vessels play a minor role in this transport. The washout rate of tracer from the mandibular canal was slow and took place mainly during the first 4 h of observation time. The slow washout rate is probably due to small pressure changes in this bone-embedded connective tissue in the mandibular canal, and further suggests that lymphatic vessels are only in part responsible for the drainage that took place.

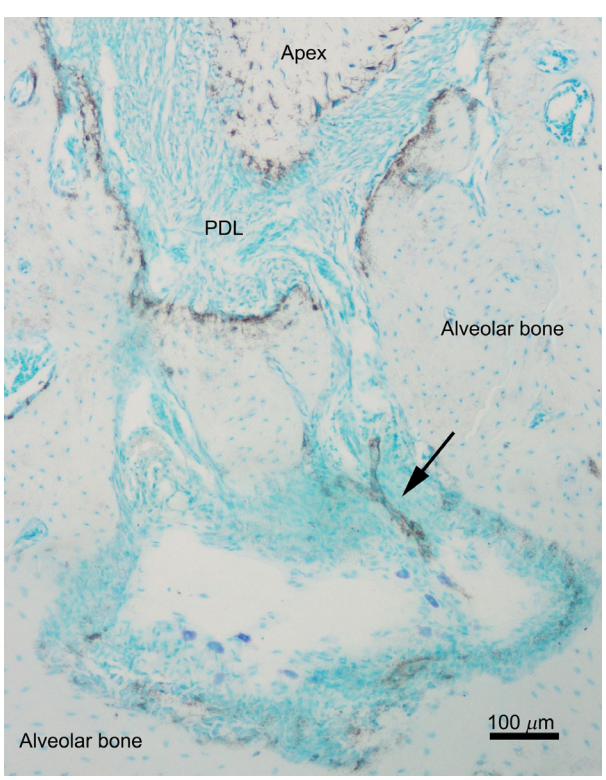

Fig. 2. Podoplanin + lymphatic vessel localized below the apical periodontal ligament (PDL) in the mandibular canal (arrow) in a rat jaw (partly modified from (20)). [Colour figure can be viewed at wileyonlinelibrary.com]

Tooth movement during chewing may cause cyclical periodontal ligament compression. Such pressure increase might promote the transport of fluid from the periodontal ligament toward the mandibular canal in the lower jaw and toward channels in the bone in the upper jaw. It is unlikely that the fluid will be drained upward/downward into the coronal periodontal ligament due to simultaneous compression and pressure increase in all parts of the periodontal ligament. Taken together, it seems unlikely that fluid from the apical periodontal ligament is drained via gingival lymphatics, which is also supported by the observation in the study described above.

Transport of protein-rich fluid via side channels from the pulp is a possibility. Whether this fluid will be drained in an apical or in a cervical direction in the periodontal ligament, depends on the pressure differences in the areas. The fluid will flow in the direction of the pressure gradient.

Clinical considerations

An inflamed pulp is at risk of developing circulatory failure unless tissue fluid volume, and thereby tissue pressure, is controlled. When lymphatic vessels are lacking, it may be favorable that the tissue is a loose connective tissue with relatively few cells and a high hydraulic conductivity that allows fluid to move into the root pulp and further out of the apex. The fenestrated vessels in the coronal part of the pulp are favorable for reabsorption of excess interstitial fluid due to inflammation, which will prevent a tissue pressure increase. However, depending of the magnitude of fluid filtration and the proportion of inflamed to healthy pulp tissue, the pulp is at risk of developing circulatory failure and necrosis. A healthy young pulp with a large pulp chamber will resist failure better than an old pulp with a reduced pulp chamber size and hydraulic conductivity due to fibrosis, as well as diminished blood vessel area and blood flow (22–24). Narrowing of the apical constriction that takes place during aging will further reduce the drainage capacity from the pulp.

An inflammatory process that is spread into the apical periodontal ligament may, in an acute situation, promote lymphadenitis. Lymphatic vessels are localized relatively close to the periodontal ligament in the bone (illustrated in Fig. 2) and fluid with bacterial components and inflammatory mediators can be absorbed by lymphatic capillaries, which open up when the interstitial fluid pressure increases. The inflammation is thereby spread to the regional lymph nodes, which increase in size and become tender to palpation.

Conclusions

The lack of lymphatic vessels in the pulp requires that the excess protein-rich fluid derived in the pulp be

transported in the interstitial tissue toward the apex due to a pressure gradient. From the apical periodontal ligament, the fluid will flow toward the mandibular canal (in the lower jaw) and probably follow nerves and blood vessels upward in the bone in the upper jaw. In the bone, fluid will be reabsorbed into blood vessels and/or removed by lymphatic vessels. Due to fibrosis, an old pulp will have a reduced fluid transport rate and be more vulnerable to becoming necrotic and, thereby, generate a need for endodontic treatment.

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