Primo Vascular System: A Unique Biological System Shifting a Medical Paradigm

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The primo vascular system has a specific anatomical and immunohistochemical signature that sets it apart from the arteriovenous and lymphatic systems. With immune and endocrine functions, the primo vascular system has been found to play a large role in biological processes, including tissue regeneration, inflammation, and cancer metastases. Although scientifically confirmed in 2002, the original discovery was made in the early 1960s by Bong-Han Kim, a North Korean scientist. It would take nearly 40 years after that discovery for scientists to revisit Kim's research to confirm the early findings. The presence of primo vessels in and around blood and lymph vessels, nerves, viscera, and fascia, as well as in the brain and spinal cord, reveals a common link that could potentially open novel possibilities of integration with cranial, lymphatic, visceral, and fascial approaches in manual medicine.

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In an age where a profuse amount of scientific data is unveiled on a daily basis, it is rare to suggest the existence of a newly discovered body system. A novel circulatory system was first described by Bong-Han Kim in the early 1960s.[1] However, it was not scientifically authenticated until 2002. Advanced evaluation methods, such as histopathologic staining techniques, confirmed the existence of this system, renamed the *primo vascular system* (PVS), in multiple anatomical structures in humans and animals.[2]

The current article reviews the literature on the PVS through 2013. The presence of the PVS, if confirmed by ongoing research findings, suggests possible implications that may fundamentally reshape our vision of anatomy, physiology, and medicine, consequently affecting the practice of osteopathic manipulative medicine and manual therapy.

Discovery of the PVS

Two distinct eras of discovery of and research on the PVS have been documented, and they occured nearly 40 years apart.

1961-1965

Bong-Han Kim, a professor at the Pyongyang Medical School in Seoul, North Korea, embarked on scientific research to discover the substratum of the meridian system (*Kyungrak* in Korean). While head of the Department of Physiology, Kim announced his

discovery of this anatomical substratum, calling it the "Substance of Kyungrak," on August 18, 1961, which he then published in 1962.[1] He found evidence of the PVS in hydra, fish, amphibians, birds, and numerous mammals using a "blue dye." The Substance of Kyungrak, meaning the system of "acupuncture meridians and collaterals" in Korean, was subsequently referred to as the *Bong-Han system*.

In the 1962 publication, he wrote that the substrate of the meridian system "consists of bundles of tubular structures and it is clearly distinguishable from nervous, blood vessels and lymph systems in histological and experimental-biological characters"[1] and "the diameter of the tubular structures range between 20 and 50 μm."[1] Kim subsequently published 6 articles and a book on his research from 1962 to 1965.[1,3-8]

He applied biochemical and histochemical analyses of the Bong-Han system and found that the transparent fluid inside the ducts contains more nucleic acids, especially DNA, than any other known tissue. The Bong-Han ducts also contain *sanals*, meaning "live egg" in Korean, which seem to have a function equivalent to that of stem cells. Kim described these sanals, renamed *primo microcell* or *P-microcell*, as having hematopoietic functions as well as the ability to regenerate injured tissues and heal wounds.

Kim described 5 subsystems:

- *Intravascular Bong-Han system*: located inside the blood vessels, the heart, and the lymphatic vessels
- *Organ surface Bong-Han system*: freely floating on the surfaces of viscera
- *Extravascular Bong-Han system*: runs along the blood and lymphatic vessels, as well as the nerves, located just outside these structures
- *Nervous Bong-Han system*: located inside the central and peripheral nervous systems, floating in the cerebrospinal fluid
- *Intraorgan Bong-Han system*: located inside visceral parenchyma

Kim also measured electrical conductivity of a Bong-Han vessel and identified 3 periodic potentials of 15 to 30 seconds, 7 to 10 seconds, and 20 to 25 seconds.[1] The method used to measure these signals was not specifically described. Finally, according to the research of Bong-Han Kim, damage to Bong-Han vessels can "modify the frequency and amplitude of the heart and change the peristaltic motion of intestines." It can also reduce nerve excitability and decrease muscular contractions.

In his research he used histologic techniques (hematoxylin-eosin, Mason trichrome, Verhoeff stain, silver staining, Feulgen reaction, and acridine orange), radioactive tracers, and electrophysiologic methods. He identified the PVS using the unnamed blue dye. His reports lacked full scientific descriptions of his materials, methods, and protocols, however, which proved highly challenging for researchers who wanted to confirm his findings.

One of Kim's reports was translated into English and made available for research teams,[7] which led groups in China, Japan, and Russia to attempt to confirm his findings.[9] In Japan, Fujiwara and Yu,[10] were able to partially reproduce Kim's findings inside blood vessels and on the surfaces of the viscera, and Chinese teams may have also reproduced some of Kim's results in rabbits.[11] However, one of the main reasons that researchers could not properly reproduce Kim's results was that the blue dye that Kim used to make the system visible was never fully described. The scientific community of the time eventually abandoned the idea that this Bong-Han system of ducts and nodes existed.

At about 1965, the Pyongyang Medical School where Kim was working unexpectedly closed.[12] The Bong-Han theory was largely forgotten for almost 4 decades.

2002-2014

Kwang-Sup Soh, PhD, a professor in the Department of Physics at Seoul National University, formed a

biomedical physics laboratory around the year 2000 to investigate the existence of the meridian system. He chose Byung-Cheon Lee, PhD, to lead the research to reexamine the findings of Kim.

After a series of trials and errors, they observed the ducts described by Kim floating on the surfaces of rabbit viscera, such as the liver, stomach, intestines, and bladder.[13]

In 2002, Soh proposed that the name Bong-Han system be changed to *primo vascular system*. This change was later endorsed by the 2010 International Symposium on the Primo Vascular System.[14]

In 2008, Lee and his team discovered a dye that could be used to identify the PVS: trypan blue.[15] From that point, research at Seoul National University confirmed visualization of the PVS in the bovine heart,[16] in the brain ventricles in rats,[17] and in the central canal of spinal cords,[17] as well as, for the first time, in the abdominal adipose tissues.[15]

In 2011, Lee and Soh's team formed the Nano Primo Research Center of Seoul National University's Advanced Institutes of Convergence Technology, where Soh would head the research.

In 2014, Lee et al[2] found the PVS inside live blood vessels in the umbilical cord of a human placenta. The PVS was also observed both on the fascia and inside the blood vessels. The human primo vessels were no thicker than those of small animals. Since 2002, the PVS has been located in mice, rats, rabbits, dogs, pigs, cows, and humans.

During 2002-2010, Soh made some additional changes to the terminology: Bong-Han duct was changed to *primo vessel* or *primo vascular vessel* (or PV); Bong-Han corpuscle was changed to *primo node* (or P-node); Bong-Han liquid was changed to *primo fluid* (or P-fluid); and Bong-Han Sanal was changed to *primo microcell* (or P-cell).

Methods for Identifying the PVS

Advanced technology has been used to visualize the PVS,[18] including confocal laser scanning microscopy,[19] scanning electron microscopy (SEM), cryo-SEM, focused ion beam SEM, high-voltage transmission electron microscopy,[20] electron microscopy (for the surfaces of mammalian organs),[20,21] atomic force microscopy,[22] fluorescent nanoparticle,[17] immunohistochemistry,[23,24] proteomic analysis,[25] and the enzyme-linked immunosorbent assay for the primo fluid content.[26,27]

Staining

Before the discovery of trypan blue,[28] Janus green[29] and alcian blue dye[30] were used with moderate success to identify the PVS. Trypan blue is not a specific marker of PVS. The dye has been widely used to stain dead or dying cells in cell cultures and, as early as the 1930s, to stain damaged or inflamed tissue.[31] Trypan blue has also been used to stain lymphatic vessels.[32,33] To identify the PVS, the tissue under investigation must be in a nonpathologic state, and the procedures developed in the Nano Primo Research Center must be followed (Kwang-Sup Soh, PhD, e-mail communication, 2015). *Figure 1* shows the PVS in a rat, and *Figure 2* shows trypan blue staining of the PVS.

Electrophysiologic Measurement

Excitable nerve-like structures that express spontaneous electrical activity have been found in the PVS.[35,36] Electrical recordings of the internal organs identified 2 types of pulses produced by the PVS, with irregular electrical bursts of spontaneous activity that can be either transversal or longitudinal and that can be easily differentiated by neighboring smooth muscle contractions.[37,38] The contractility of the PVS is slowed down by activation of muscarinic acetylcholine receptors and modified by nifedipine, suggesting the presence of voltage-dependent calcium channels in primo vessels.[38,39]

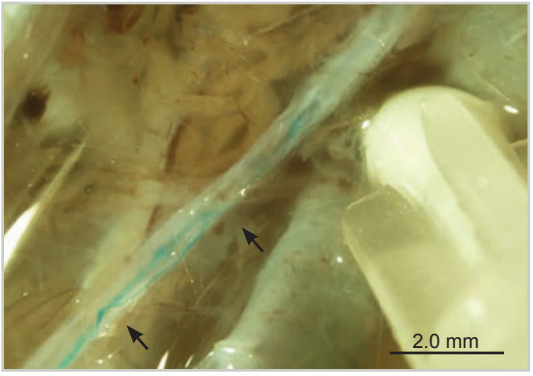

Figure 1.
Primo vascular system in the thoracic duct of a rat. Stereomicroscopic in situ image of a branched and rejoined primo vascular system (blue stain). Two regions of branching (arrows) and rejoining (arrows) are shown.[34] Reprinted with the permission of Kwang-Sup Soh, PhD.

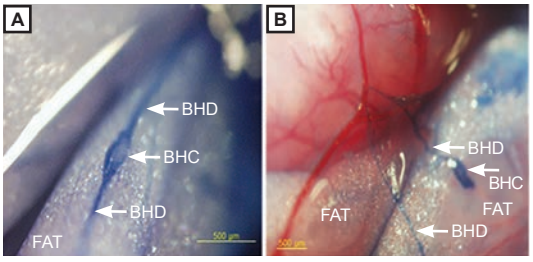

Figure 2.
Trypan blue staining of the primo vascular system shows (A) primo node (Bong Han corpuscle, BHC) and vessel (Bong Han duct, BHD) around the rat's small intestine and (B) primo vessel node and primo vessel near the small intestine of the same rat. Notice that the blood vessel and adipose tissue were not stained.[13] Reprinted with the permission of Kwang-Sup Soh, PhD.

Anatomical Overview of the PVS

According to experiments with chicken eggs, the apparition of the PVS precedes the formation of the extraembryonic vessels, arteries, veins, lymphatic vessels, nerves, and viscera.[40]

The primo vascular vessels have been identified in rabbits as thin, semitransparent structures with an average diameter of approximately 20 to 30 mm.[22,41,42] Each vessel contains up to 20 smaller ductules 3 to 10 mm in diameter that are lined by a single layer of endothelial cells and surrounded by extracellular matrix.[42] Each ductule is filled with primo fluid.[21,22,42] They can be connected to primo vascular nodes (PVN).[43]

Primo vessels are fairly easily differentiated from blood vessels and lymph vessels. Primo vessels do not express lymphatic vessel endothelial receptor 1, a CD44 homolog, nor CD31, a marker specific to blood vessels. The rod-shaped nuclei of the PVS endothelial cells are aligned parallel to the wall of the primo vessels, and can be specifically stained by acridine orange, fluorescent phalloidin (F-actin), or DAPI.[10,29,41,44-46] Rod-shaped nuclei are hallmarks of the PVS, regardless of which animals or organs the PVS was taken from. However, although the rod-shaped nuclei can easily be seen and identified in longitudinal views, they are difficult to identify in cross-sectional images (*Figure 3* and *Figure 4*).

Primo Fluid

The composition of the primo fluid in rats has been found to be rich in granulocytes and secretory granules, including mast cells (20%), histiocytes (53%), eosinophils (16%), neutrophils (5%), and round immature stem-like cells (3%), but relatively poor in lymphocytes (1%).[49] Researchers measured a high concentration of adult small embryonic-like stem cells expressing the stem cell biomarkers OCT4, NANOG, and CD133.[42,49,50]

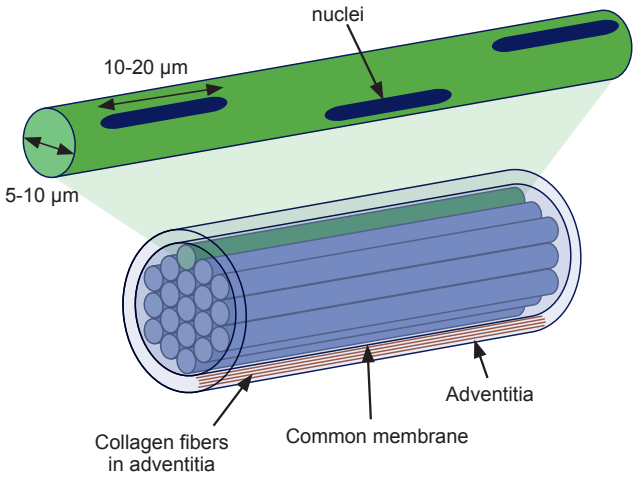

Figure 3.
Illustration of an isolated primo vascular subvessel (top) and a bundle of subvessels (bottom).[47] Reprinted with the permission of Kwang-Sup Soh, PhD.

PVS Locations

Primo vessels have been reported to be found in the following anatomical regions:

- *Heart*—Lee et al visualized a complex arrangement of endocardial vessels (20 mm in thickness) in the bovine heart[16] on top of the endocardium.[51]
- *Blood vessels*—Primo vessels have been identified in large blood vessels,[52-56] in particular, floating inside the abdominal artery and the caudal vena cava of rabbits,[57] rats,[58] and mice.[55] These vessels have also been discovered in the superior sagittal sinus of the rabbit brain[59] and in the venous sinuses of rat brains.[60]
- *Lymphatic vessels*[29]—Because lymph vessels are quite transparent,[44,48,62,63] the primo vessels inside the lymphatic vessels can often be seen with no contrast agent from outside the vessel. They have also been isolated floating inside lymph vessels using alcian blue[62] and fluorescent nanoparticles (*Figure 5*).[44]
- *Central nervous system*—In cerebrospinal fluid, primo vessels have been found within the central canal of the spinal cord by injecting fluorescent nanoparticles into the lateral ventricles[17] and underneath the superior sagittal sinus in the sagittal fissure of rabbits, where its characteristics were the same as those observed in other organs.[59]
- *Peripheral nervous system*—Primo vessels have been located around the perineurium of the spinal cord and in the epineurium, perineurium, and endoneurium of sciatic nerves in rats (*Figure 6*).[28]
- *Viscera*—Primo vessels have also been identified on the surface of numerous viscera, such as the stomach, intestines, liver, bladder, and heart.[16,21,24,26,63] They have also been identified floating in peritoneal fluid,[19] in the omentum, and in the peritoneum.[15]
- *Skin and adipose tissue*—In the hypodermis of rats[64,65] and in adipose tissues of other animals,[66] primo vessels were observed using trypan blue. In the rat hypodermis, primo vessels could also be found by using fluorescent nanoparticles.[65]

Functions of the PVS

Circulation and Transport

The primo fluid circulates in a network of vessels and nodes with multiple independent and interconnected paths. The entire PVS has yet to be fully mapped in humans. The mean (SD) speed of flow of the primo fluid was measured to be approximately 0.3 (0.1) mm per second in rabbits, using alcian blue 22, and at around 100 to 800 mm/s with direct measurement using fluorescent nanoparticles.[21,67,68]

The circulatory nature of the PVS can help transport chemical substances and factors of inflammation, as well as cancer cells (metastases), in the primo fluid. The PVS has been foreseen as a potentially novel drug delivery route, particularly for cancer treatment.[69]

Immunologic and Regenerative Functions

Primo fluid contains a high concentration of cells resembling stem cells called primo microcells, approximately 1 to 4 mm in diameter, whose exact function remains to be determined.[50,70] Kwon et al,[49] at the National Cancer Center of Korea, confirmed that primo fluid was abundant with other immune cells, such as macrophages, eosinophils, and mast cells.[20]

Endocrine Functions: Neurotransmitter Pathway

The PVS has also been described as an endocrine organ that transports hormones.[26,27,71] Catecholamines (eg, adrenalin, noradrenalin) have been identified in the primo fluid in vessels on the organ surface of rabbits and rats using enzyme-linked immunosorbent assay.[26,49]

Bioluminescence (Biophotons)

Popp,[71] Popp et al,[72] and Wang et al[73] described different types of biophoton emissions within living systems. The PVS contains a high concentration of nucleic acids and is surrounded by collagen. Consequently, Lee et al[61] and Soh[68] suggested that the PVS can be a good medium to transport or communicate tissue bioluminescence (biophoton).

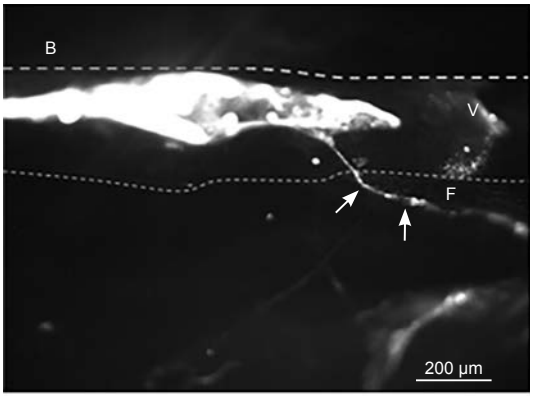

Figure 4.
Fluorescence image of a primo vessel (arrows) stained by DiI (a fluorescent lipophilic dye), which was injected into a lymph vessel (dotted lines) around the caudal vena cava of a rabbit. The image is a merge of bright-field and fluorescent images. The injected DiI flowed away with the lymph fluid but stained the primo node and its associated primo vessel. Notably, the primo duct came out through the lymph vessel wall and entered the surrounding fat tissue (F). *Abbreviation:* V, valve weakly stained by DiI.[48] Reprinted with the permission of Kwang-Sup Soh, PhD.

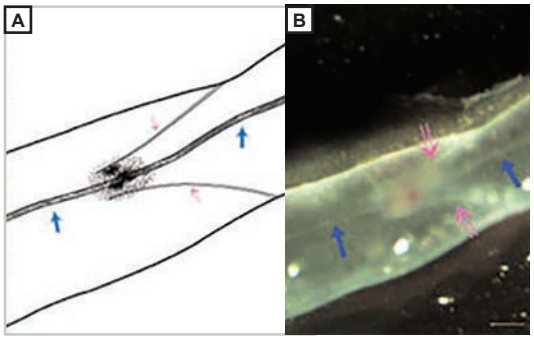

Figure 5.
Presence of a primo vessel within the lymphatic vessel of a rat.[62] Illustration (A) and micrographic image (B). Arrows points to primo vessel. Reprinted with the permission of Byung-Cheon Lee, PhD, and Kwang-Sup Soh, PhD.

Inflammatory Process

Wang et al[73] showed that the PVS of infected rats carried pathological products, such as polymorphonuclear neutrophils and fibroblasts, which may be involved in inflammatory processes.

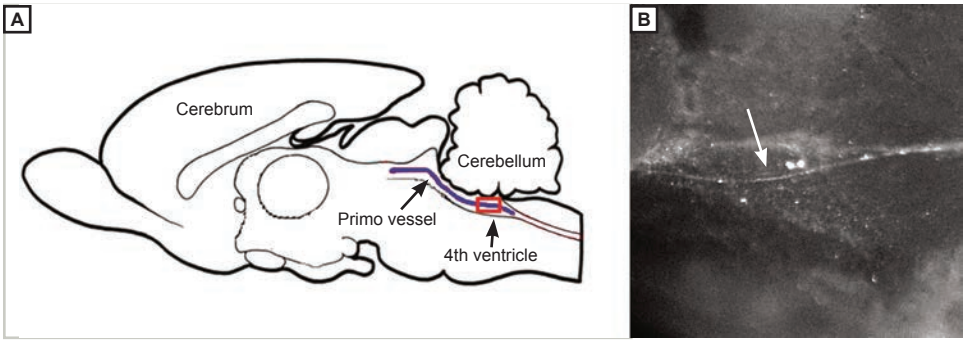

Figure 6.
Illustration (A) and image (B) of the primo vessel (arrows) floating inside the ventricular system of the brain.[17] Reprinted with the permission of Kwang-Sup Soh, PhD.

Cancer

In mammals, the PVS has been identified on the fascia surrounding tumor tissue, as well as found connected to tumors.[9,75,76] The PVS may be a newly recognized mechanism in cancer growth control but may also be a novel path for cancer metastasis, because primo vessels are more concentrated around tumor sites, and migration of tumor cells is more efficient inside the PVS than in the lymphatic system.[34,75]

Osteopathic Applications: Potential Integration of Cranial, Lymphatic, Visceral, and Fascia Approaches to the PVS

Primo vessels are ubiquitous channels for transporting fluid with immune and endocrine functions. The PVS could reasonably link tissue functions across systems. Because osteopathic manipulation can benefit vasculature, lymph, and capillary flow in tissues where primo vessels have been found, it is reasonable to suggest that the PVS can also be affected, which would positively influence and further expand the scope of osteopathic practice. We believe that primo vessels can be manually accessed initially through lymphatic vessels using osteopathic lymphatic techniques.

Discussion

The work of the Soh and Lee groups need to be confirmed by other researchers. Future research should help reveal the complete tracing of the PVS throughout the body.

The circulatory aspects of the PVS described by Kim[1] showed periodic potentials of 15 to 30 seconds, 7 to 10 seconds, and 20 to 25 seconds, but he did not describe the pulsatile-type measurement.[8] It remains a challenge to measure such rhythmic movements in the human body. Further research evaluating the physiologic importance and circulatory effects of the PVS is required. Future endeavors may reveal more convincing evidence and substantiate a rhythmic aspect of this novel circulatory system and the effects of palpation on the PVS, which is found on the surface of many organs and in the subcutaneous layer.

Medical applications of the PVS need further investigation. The potential administration of drugs through the PVS may circumvent the blood-brain barrier, for example. If the anatomy and pathophysiology of the PVS, in particular their roles in inflammation, endocrinology, and oncology, are confirmed, our understanding of human body systems and of medicine in general will shift.

Conclusion

It is difficult to fathom that the prolific PVS was not identified in medicine until the 21st century. Both Kim and Soh initially targeted their research toward the meridian system but found something more far reaching. The discovery of the PVS in intravascular and extravascular spaces, in the central and peripheral nervous systems, on the surface of and within viscera, in cutaneous layers, and in most body systems, may signify a novel and complete morpho-dynamic system, with the potential to reshape paradigms in medicine and manual therapy.

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