Lymphology 57 (2024) 107-115

AUTHOR'S RESPONSE TO LETTER

BIOBRIDGE™ COLLAGEN MATRIX FOR LYMPHEDEMA THERAPY

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We cordially thank Dr. Michael Paukshto and Gregory King (henceforth P/K) for reading our paper carefully, providing criticism and commentary. It was our very aim to stimulate discussion and historically contextualize lymphangioplasty techniques. We are therefore very pleased to receive their immediate reply. While having the utmost respect for P/Ks efforts and viewpoints, we acknowledge part of their criticism. We, however, do not endorse many of their arguments and think there are quite some misunderstandings among our viewpoints. Therefore, we reply to their criticism in an attempt to make our viewpoint clearer.

1. Misleading Title?

P/K state that the title of our paper was "misleading": "The BioBridge™ device was not related to … Handley's efforts using threads in treatment of lymphedema, but it was developed from a tissue engineering research effort to promote and direct the formation of lymphatic vessels … and based on a fundamental discovery of the mechanisms that regulate lymphangiogenesis …"

We understand that, from a commercial standpoint, it is now preferred to present the implantation of BioBridge™ as a completely new approach that does not have predecessors and cannot be compared to any, seemingly similar, older, or contemporary technique. We are nevertheless surprised to read such a statement from Mr. Paukshto.

For in a paper by him, published in 2014 (1), Mr. Paukshto explicitly makes reference to Handley's lymphangioplasty with silk threads (2) as well as to a 1976 study on lymphangioplasty with Teflon threads (3). In this context (1), BioBridge™ is presented as "a new twist to an old idea", as Paukshto terms it, i.e. an improvement of Handley's classical thread lymphangioplasty! In this paper by Paukshto, capillary flow is identified as a major factor, both in classical thread lymphangioplasty as in BioBridge™ implantations, and "fibrotic encapsulation" the major problem of classic thread lymphangioplasties (which were, of course, only performed with non-absorbable threads, as shown in our paper). Thus Paukshto writes: "Unbeknownst to Handley, providing a physical channel for lymphatic fluid flow has further benefits beyond immediate relief of swelling provided by the capillary forces. Recent studies have shown that interstitial flow is a major factor in the formation of new lymphatic capillaries [reference to (4)]. BioBridge™'s form factor takes advantage of this capillary flow along and through the thread, … A substantial improvement in comparison with the formerly described historical materials is that the device has been designed to naturally degrade and safely disappear in the body after a few months"

The "substantial improvement in comparison with the formerly described historical materials", as stated here, is absorption. But an absorption and thus prevention of capsule formation can be achieved by implanting any absorbable surgical thread, capillary flow also takes place along any implanted thread

or biomaterial.

As we stated in our paper there are two effects of lymphangioplasty, an immediate one by capillary drainage and a delayed one through (possible) formation of new lymph vessels. This seems to be acknowledged by Paukshto (1) the very way we put it in our paper.

2. Directed Lymphangiogenesis; the Studies by Boardman et al. (4-6)

Lymphangiogenesis was studied by Boardman et al. (4-6). In their animal model, a circular portion of skin of mouse tails was resected and the defect was bridged by collagen gel. After some days, fluid channels could be observed along the collagen bridge and later, lymphatics were restored along the collagen patch/bridge, following the fluid channels.

P/K comment as follows: "There are a few statements that are not exactly correct, and we would like to address them too. Concerning the references [4,6] that "prove that simple collagen (not aligned nanofibrillar one) promotes directed lymphangiogenesis as well". Actually, in the studies by Boardman and Swartz the injected type I collagen solution formed at least partially aligned fibrillar collagen gel during the gelation under the directional flow of interstitial fluid (1-dimentional model). These experiments have been repeated in VA Palo Alto and also used BioBridge™ scaffold."

"At least partially aligned fibrillar collagen gel", as P/K claim, conversely means that the collagen bridge in the animal model contained mainly non-aligned collagen. Potential small fractions of aligned fibrillar collagen cannot be made responsible for the whole effect. Up to our knowledge, aligned fibrillar collagen has never been tested in comparison with unaligned one, proving or disproving that there is any significant difference as for neo-lymphangiogenesis. Boardman et al. do not claim that collagen (especially not aligned nanofibrillar one) needs to be involved in the process of neo-lymphangiogenesis at all. They rather interpret their findings of their animal model very generally: "lymphatic vessel formation is initiated along preestablished routes of fluid flow" (4, p. 807). What else than "preestablished routes of fluid flow" are subcutaneously implanted threads or biomaterials in different lymphangioplasty methods, along which capillary drainage takes place?

Implantation of BioBridge™ is, at any rate, is not exactly the same as a continuous collagen patch that bridges a dermis defect and through which fluid channels cleave their way under higher pressure (4, 5), as in the studies by Boardman et al. Rather, in BioBridge™ implantation, as in Handley's classical thread lymphangioplasty, lymphatic fluid flows along the thread (in BioBridge™ additionally through the cavities of the thread), by capillary forces. This effect is immediately visible in ICG imaging (see below). Paukshto (1) correctly explained this effect: "Unbeknownst to Handley, providing a physical channel for lymphatic fluid flow has further benefits beyond immediate relief of swelling provided by the capillary forces. Recent studies have shown that interstitial flow is a major factor in the formation of new lymphatic capillaries"

P/K continue: "We are not aware of, nor have the authors presented any evidence of, the formation of new lymphatic collectors after implantation of plastic tubes or surgical threads."

This is indeed our interpretation of the findings by Boardman et al. Their conclusion "lymphatic vessel formation is initiated along preestablished routes of fluid flow" (4, p. 807) is so highly redolent of what happens in thread or tube lymphangioplasty where new interstitial routes of fluid flow are established. Paukshto (1) seems to interpret Boardman's studies in a similar way: "Recent studies have shown that interstitial flow is a major factor in the formation of new lymphatic capillaries … BioBridge™'s form factor takes advantage of this capillary flow along and through the thread, …". Here the capillary flow along a wick is in the focus, not the material of the thread. Of course, it needs to be backed up by experiments whether new lymphatic vessel formation (beyond the "Yamamoto effect"

[see below]) takes place in thread or tube lymphangioplasty as well. Our aim was to encourage such research in our paper.

3. Term "Neocollectors" – Subdermal Dissection

P/K claim that our use of "the term "neo-collectors" [was] clearly introduced [in our paper] in the context of "neo-lymphangiogenesis" presented in [a study by Yamamoto (7)] and reflects the possibility of new lymphatic collector creation through neo-lymphangiogenesis induced by subdermal dissection."

In our paper, we neither made reference to Yamamoto's article nor did we discuss the effects of subdermal dissection. By "neocollectors" we simply mean the artificial subcutaneous channels with a biomaterial inlay or "wick", be it a thread, silicone tube, or whatever, along which drainage though capillary forces takes places. This immediate capillary drainage effect is sometimes visible in ICG lymphography. When the subcutaneous tunnel with an inlay (surgical thread or Bio-Bridge™) is rather superficially and near a depot of intradermally injected ICG it can be seen in lymphangiography how ICG dyed lymph spontaneously drains along this new channel. The dyed lymph can also be massaged along the channel (*Fig. 1*). Since the implanted threads somehow behave like natural lymphatics, with a capillary flow traceable in ICG lymphangiography, we think that these artificial pathways for capillary drainage can quite rightfully be called "neocollectors" or "lymphatic neocollectors", as has previously been done in the literature (7).

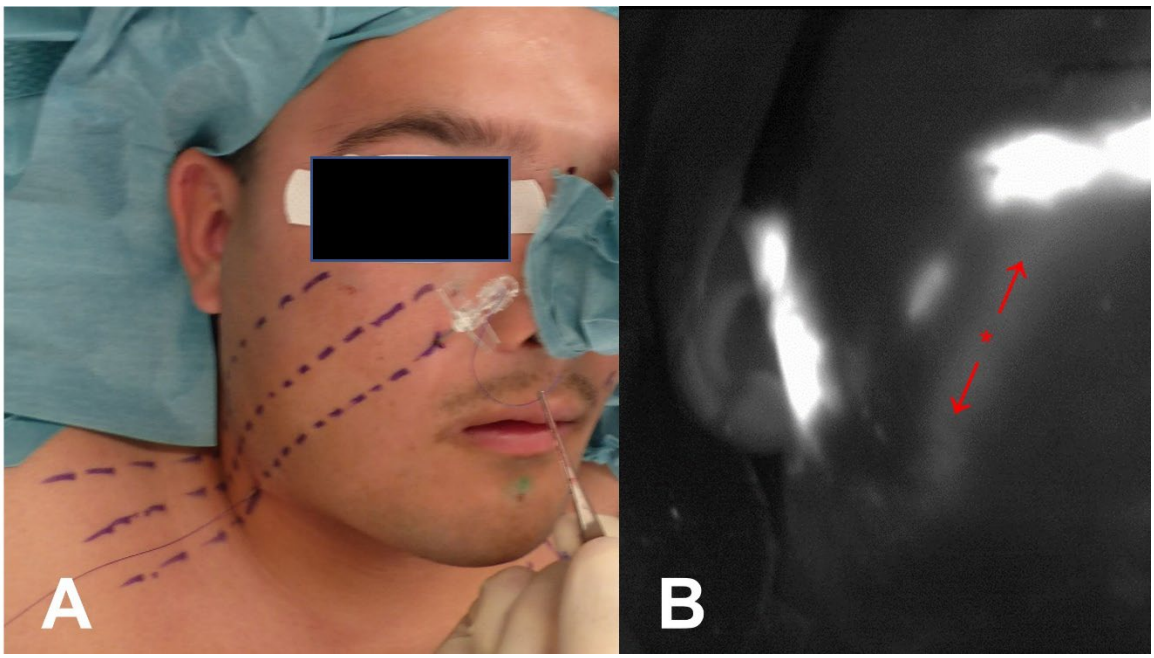

Figure 1. *A (left): Thread lymphangioplasty with 3-0 polydioxanone threads (PDS II) in a patient with lymphedema of the face. The threads are tunneled along the cheeks with a hollow puncture needle. B (right): Flow of ICG dyed lymph along the implanted polydioxanone thread (←*→), visible in ICG lymphangiography, immediately after thread implantation. The ICG contrasted-lymph spontaneously drains along the artificial channel and can be massaged along the implanted thread, as with a natural lymphatic collector.*

4. Subdermal Dissection

Regarding subdermal dissection: Yamamoto has shown in his paper (8) that by mere subdermal dissection (without implantation of any biomaterial of thread) new lymphatic pathways developed in 35.3% of the patients, whereas no statistically significant volume reduction took place after these operations. This means that mere surgical trauma promotes traceable neo-lymphangiogenesis. Certainly, no defined channels remain after this surgery for a long time, since subcutaneously dissected tissues quickly reunite and heal after a few days (as surgical experience shows), if not kept open by an implanted thread or biomaterial inlay.

The reference to Yamamoto's findings is important since it shows that any subcutaneous dissection promotes detectable lymphangiogenesis in 35.3% of the patients. Since subdermal dissection is involved in both classical thread lymphangioplasty and **BioBridge™** implantation, during implantation of the threads, also in these procedures 35.3% of lymphangiogenesis may be due to the "Yamamoto effect" = the mere subdermal dissection.

The criticism by P/K, that classical thread lymphangioplasty was merely due to the Yamamoto effect, cannot be acknowledged because (1) the rate of neo-lymphangiogenesis in this technique has simply not been studied so far, (2) there is a significant volume reduction in thread and tube lymphangioplasty (see the following paragraph: 5. Historical Techniques), which did not occur in the patient where mere subdermal dissections were performed.

Yamamoto's findings imply two further interesting conclusions: (1) lack of any lymphangiogenesis does not necessarily lead to lack of a therapeutic success; and (2) a product promoting lymphangiogenesis does not necessarily lead to a limb volume reduction or to therapeutic success.

5. Historical Techniques – Criticism and Misunderstandings

"The authors validate throughout this paper the claims of success made in historic papers but without providing specific data or criteria. While this is challenging, this lacks scientific rigor because how one author in 1913 defines success could be quite different from another author in 1965 or some other year. Is it limb volume reduction? (by how much is considered successful?), What is the duration of efficacy? (6 months? one year?), complications rate? (0%? 50%?) At the time of many of these papers longevity of treatment was not front of mind (life expectancy in the United States was 51 years in 1913 vs 77 years today).

Indeed, the reviewed papers (ranging from 1908-1987) are not as consistent in providing measurements and data as one wishes today. Therefore, a modern metanalysis did not seem to make sense and would not even have been possible. Matters are nevertheless neither as haphazard nor as insecure as P/K try to put it. Nor does life expectancy have any impact on that question. The longest follow-up reported so far is a one of a patient after 24 years (lymphangioplasty of lymphedematous legs with silk threads). In this patient, the legs remained "shapely and quite normal" (9), even 24 years after the procedure. By all historic authors success is defined as a decrease of circumference of the limbs and/or an improved soft tissue quality and/or and improved range of motion. Exact criteria in terms of cut-off measurements are, unfortunately, not given. Rather, usually, a "complete" or "partial remission" is addressed. Complications are not reported, save for very rare infections and threads protruding out of the wounds (3). To give some examples of the more recent papers on lymphangioplasty:

- in the study by Gorman/Navarre (1956) (10), lymphangioplasties with Tevdec threads were performed in 9 patients. In 88% (= 8) of these patients either a progressive decrease in circumference and softening of the extremity was noted or a continuing softening of the extremity, while the reduction in limb circumference did not last. The follow-up was between 2 and 13 months. Exact measurements are unfortunately not given.

- Silver/Puckett (1976) (3) (this paper is quoted by Paukshto [1]) performed lymphan-

gioplasties with Teflon threads in 16 patients. The average reduction of circumference of the limbs was 1.2cm with a duration of efficacy ranging from several months to 5 years (average 13 months)

- Kaufmann et al. in 1983 (11) made lymphangioplasties with sterilized plaited hair in 11 patients. Three of them had a "complete and persistent remission", four a partial remission, and four no therapeutic effect. The follow-up was up to 3 years. No exact measurements are provided.

These are the only rudimentary clinical studies on the subject. All other papers are case reports:

- Ransohoff in 1945 (12) treated two cases of lymphedema of the hand by lymphangioplasty with nylon threads. The lymphedema disappeared completely that way (reduction of circumference of 3.8-5cm in one case; success documented by photographs).

- Grobmyer et al. in 1968 (13) also used lymphangioplasty with nylon threads in lymphedema of the hand. Decrease of midpalmar circumference by 3.1cm, photo documentation.

- Zieman in 1951 (14) treated lymphedema of (1) the leg (2) the arm (3) the prepuce and (4) the male genitals by lymphangioplasty with nylon threads. Decrease of circumference (leg, midthigh level) by 16 inches, of the arm by 3-4 inches and reduction of the penis circumference by 3 inches (immediate results, no follow-up).

We may supplement a case from our clinic: 55 year-old female patient with secondary lymphedema. Lymphangioplasty with polydioxanone threads (2-0, two strands medially, two laterally, ranging from foot to groin) (*Fig. 2*). Initial leg volume 10,631ml. Three months postoperatively 9,893ml (decrease by 738ml = -6,9 %), less feeling of tension and better tissue quality. LeQOLis score decreased from 25 points preoperatively to 15 points postoperatively (*Fig. 3*). We were unable to obtain similar results by implanting 10 Bio-Bridge™ threads in lymphedematous lower extremities. A lymphangioplasty with Bio-Bridge™ showed either rudimentary drainage or no effect in the cases treated by us.

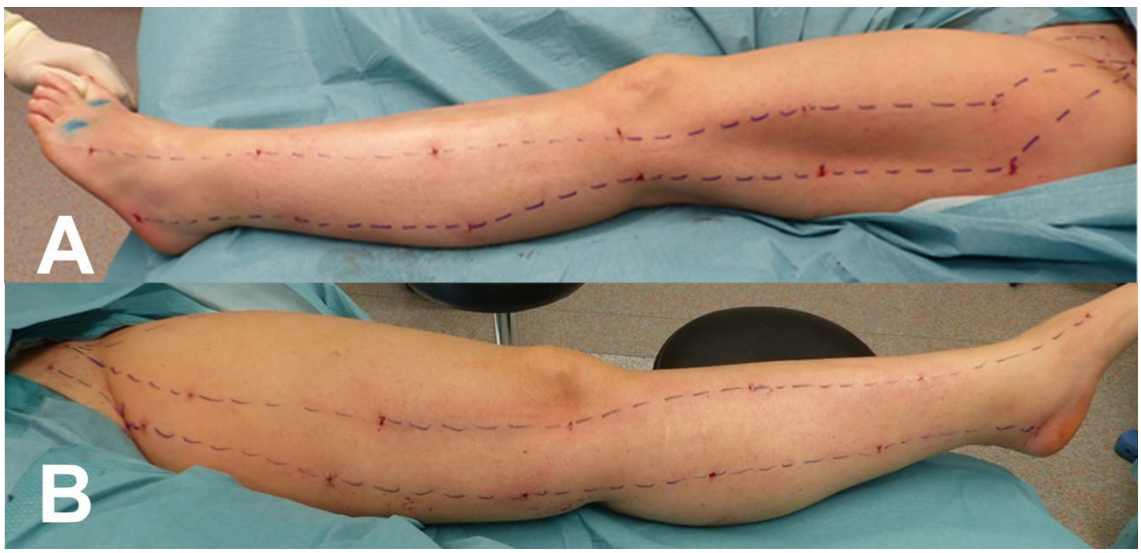

Figure 2. *The pathways (A- external; B-internal) depicting where the polydioxanone threads were subcutaneously tunneled.*

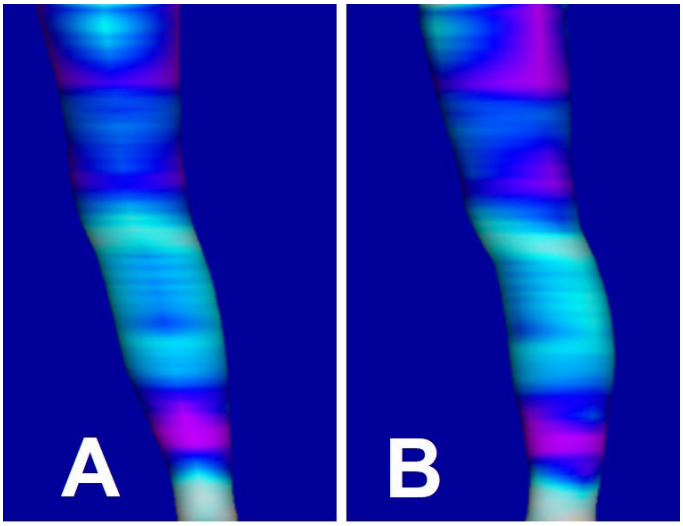

Figure 3. *Decrease in volume and circumference in the same patient over time (color coded: violet: 0.4cm circumference, blue: 0.3cm, and turquoise: 0.2cm). Measurement of volume and subsequenrt graphic imaging was obtained with contactless optoelectronic body scanner (Perometer 400MT, Pero-Systems, Wuppertal, Germany).*

Note that lymphangioplasties with silicone tubes, as stated in our paper, have good results as well. The papers on this topic referred by us have a more rigorous scientific approach, providing exact measurements and data.

To sum up neither in thread nor in tube lymphangioplasties just "some rudimentary level of temporary lymphatic drainage" occurs, as P/K claim.

"One must ask if any of these simple techniques indeed do have merit, why have none of them been adopted and used today in the treatment of lymphedema? This is a fundamental question that has not been answered in this paper. One might conclude that these earlier techniques simply do not work or create risk of other complications that have been known (such as silk threads inducing foreign body reactions)."

It is indeed difficult to answer the question why thread and tube lymphangioplasties are not standard techniques and have only been performed by some individuals, although they are safe and virtually risk-free techniques. Speculating on this question is, however, beyond the scope of our paper. We just wanted to point to the fact that these techniques do have merit and effect and that modern investigations on this topic are highly desirable. Even in the past, thread lymphangioplasty was not widely spread and only used by some clinicians. Tube lymphangioplasty is still being performed with success. Papers on this topic continue to be published. According to the historic literature, complications are scarce (infections, protrusion of material, as mentioned above). Using nylon and other modern suture materials for thread lymphangioplasty (since 1945) was an attempt to minimize foreign body reactions. Using absorbable threads (as polydioxanone) would further reduce the risk, prevent foreign body reactions and capsule formation.

6. Criticism: Control Groups Treated with Thread Lymphangioplasty

"To criticize the numerous preclinical studies conducted using existing and established lymphedema animal models for not comparing **BioBridge™** to a suture or other material – which are not being used clinically today – does not seem fair. These studies, con-

ducted by independent and leading researchers in US, Spain, Taiwan, and Japan, each evaluated BioBridge™ as a therapeutic target against a surgical control group because the control group in these models are well established and were used to quantify the therapeutic benefit of the treatment. If the authors wish to conduct such comparison studies they can, but it does not seem appropriate to criticize all the other studies that have been published in peer-reviewed journals as having a problem. There are a number of different surgical threads, how many of them should be tested?"

We are certain that the numerous preclinical studies comply with the highest scientific standards. It can however not be denied that they have a bias by completely ignoring the historical predecessor technique (thread lymphangioplasty) which does have a drainage effect as well. Taking this into account may have led to other study designs, e. g. control groups of patients treated with classical thread lymphangioplasty. To put it very simply: If someone invents a new, let's say, toothbrush which is "a new twist to an old idea" (1), it should be tested in comparison to conventional toothbrushes which have been successfully used for decades, rather than in comparison with a group of people not brushing their teeth at all. This is however, what has been done in almost all studies using BioBridge™. That thread lymphangioplasty is not clinically used in standard therapy is not really relevant for answering the question which material yields the best drainage effect.

The question how many surgical threads would have to be tested, when not even a single one has been so far, seems to be merely rhetoric. It would be advisable to use a thread with a similar absorption time as BioBridge™ and with a smooth surface like nylon threads successfully used for thread lymphangioplasty so far. That's why we opted for polydioxanone threads.

7. Chicago Study

"The authors state that "An ongoing study in Stanford and Chicago is examining the therapeutic benefits of LVAs alone versus LVAs plus lymphangioplasty with BioBridge™, in a group of approximately 80 patients". Actually, the prospective study in Stanford and Chicago is examining the therapeutic benefits of VLNTs alone versus VLNTs in combination with BioBridge™."

This was indeed a typo, we are grateful for this correction. We are well aware that Professor David Chang of Chicago uses pedicled lateral thoracic VLNT flaps for his study. One of the authors (M.W.) has assisted one of Professor Chang's operations of such a VLNT flap in a study patient of his BioBridge™ study.

8. Metaanalysis by Drobot et al

P/K criticize the following: "In addition, "According to a recent metanalysis, such combined BioBridge™ lymphangioplasties lead to an average excess limb volume reduction of 1-10.7% [47]". But the study analyzed in [47] did not use the BioBridge™ and presented results related to silicone tubing treatment only."

This statement is definitely not true: the quoted paper by Drobot et al. (15) studied nanofibrillar collagen scaffolds (which they abbreviate as NCSs = BioBridge™) and silicone tubes (abbreviation STs). In NCSs (= BioBridge™) they observed an "average excess limb volume reduction of 1% to 10.7% and clear evidence of lymphangiogenesis on imaging." In contrast, "ST implantation showed an average limb volume reduction of 700 to 887 mL and limb circumference reduction of 3.1 to 8 cm". These are the very measurements we referred to in our paper.

9. Handley-Lexer Method

P/K: "Additionally, the authors state that "To date, BioBridge™ has only been implanted subcutaneously. The effect and benefit of BioBridge™ used in the sense of a subfascial lymphangioplasty according to Handley-Lexer still needs to be investigated." Actually, there are clinical cases where BioBridge™ has been implanted in the deep lymphatic region in the surgical treatment of lymphedema. Also, there are clinical cases of head and neck lymphede-

ma treatments."

We did not claim that BioBridge™ has never been implanted in the deep lymphatic region. Rather, our statement was made in the context of lymphedema therapy of the extremities. We wanted to suggest that, in extremities, a higher drainage rate might be obtained, if BioBridge™ was routinely implanted in a way that it reached the deep lymphatics (as was done in the Handley-Lexer method of deep plane lymphangioplasty). A comparison between a subcutaneous implantation and a subfascial one in extremities would therefore be worthwhile.

P/K: "Specifically regarding BioBridge™, the current price in the US is $3,000 per 5-pack, not $1,500 and BioBridge™ is a registered trademark (® not ™)." We gratefully acknowledge this correction.

SUMMARY

We acknowledge the correction of a typo in our reference to the Chicago study, the price of a pack of BioBridge™, and the use of the registered trade mark sign. As for the rest, we do not agree.

P/K repeatedly reproach us a "lack of scientific rigor" for a study meant as a modest review of divergent historical studies which can still inspire modern clinicians and researchers (as they inspired P/K to design BioBridge™). We wanted to stimulate further critical thoughts and research beyond the marketing of a specific product, proposing a classification for a number of seemingly different techniques that follow the same principle. Indeed, scientific experimental proofs of some of our claims have yet to be made, we never denied that.

We are far from reproaching anything to P/K, but would like to encourage a comparison of different lymphangioplasty techniques, in order to find out the best indication for each technique and thus reach the best result for individual patients, also in countries where BioBridge™ is not accessible or affordable.

What could be a stronger argument for its use than if it was proven "with scientific rigor", that a BioBridge™ thread, in a statistically significant way, provides capillary drainage and promotes lymphangiogenesis more than an unaligned collagen thread or an ordinary absorbable surgical thread?

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