

## **PARTICIPANTS**

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## **PRESENTATION**

**Dr. M. Mark Melin:**

Hello, I'm Dr. Mark Melin, I'm a vascular surgeon and we're going to discuss my personal journey to understanding lymphedema and phlebolymphe<sup>d</sup>ema.

### **Disclosures:**

An Honorarium has been provided by Tactile, I'm a member of the Speakers Bureau for Tactile, and Google images and Tactile images have been utilized for this presentation.

In medical school we were all taught that the Classic Starling Principle that Dr. Starling developed in 1896. This microvascular fluid exchange model discusses hydrostatic pressures which push fluid through the artery and the capillaries into the interstitium???, where the vast majority is then reabsorbed by the veins. We can see in this image that Dr. Starling demonstrates again that net fluid movement is out of the arteries and subsequently reabsorbed in the post-capillary venules.

As a practicing vascular surgeon, I typically evaluated varicose veins in an isolated fashion, looking at the classic CEAP standing for Clinical Etiology Anatomical ???Physiology clinical classifications. In the clinical classification, Class 1 stands for Telangiectasias, Type 2 is the type ordinary Varicose Veins, Type 3 is the presence of edema, Type 4 is the development of hyperpigmentation and skin changes such as eczema, Class 5 is a healed venous ulcer and class 6 is the presence of a venous ulcer.

In my early practice as a vascular surgeon, I had an underappreciation of the degree of lymphedema impact on the patients that I served, especially with advanced venous disease. And it wasn't typically until patients presented in the very advanced phases of lymphedema that I would begin to recognize the presence of significant interstitial edema and advanced lymphedema stages. As I evaluated more data, I became aware of the importance of recognizing lymphedema in association with venous disease, now known as phlebolymphe<sup>d</sup>ema. Phlebolymphe<sup>d</sup>ema begins in the C3 status and is now been definitively demonstrated by near infrared imaging to exist with lymphatic dysfunction in late stages of C3, C4, C5, and C6. This is representing a new dawn in the era of lymphedema management, and it's important to recognize that lymphedema is closely linked with advanced vascular venous disease. But the average medical student still only receives 30 minutes of education on lymphatics and venous dysfunction.

The glycocalyx is a gel-like impermeable layer that lines all blood vessels down to the five-micron level. There's approximately 60 to 100,000 miles of arteries, veins and lymphatics in our body. The importance of the recognition of the glycocalyx is that it alters the Classic Starling understanding and prevents reabsorption of interstitial fluid into the veins. The role of the healthy glycocalyx is four-fold. It improves endothelial function, as the little hairs of the glycocalyx move, it results in sheer force that can release nitric oxide, it decreases permeability and therefore does not allow fluid reabsorption into the veins as the Classic Starling Model described, it is very important in the terms of coagulation, it inhibits platelet adherence and has an important impact on coagulation regulatory factors. The importance of preventing inflammation by

preventing leukocyte adhesion subsequently can increase the risk of chronic venous disease.

In the Revised Starling Principle, we note that the glycocalyx prevents reabsorption of lymphatic fluid into the vein and now we recognize that 100 percent of all lymphatic fluid must enter the lymphatics to be returned to the venous system. The clinical implications as described by Michael and Mortimer and Rockson describe that all chronic lymphedema indicates an inadequacy of failure of lymphatic drainage. This now has a significant implication for how we treat lymphatic and venous disease in that we have to treat both the lymphatic as well as the venous disease to achieve maximal patient outcomes. Near infrared imaging, a science advanced by Dr. Eva Sevick-Muraca, has demonstrated that lymphatic dysfunction exists within advanced venous disease. By the introduction of ??? green into the subdermal lymphatic collection system, we can note in the initial panel that there's normal function, however in the patient that has congenital lymphatic disorder, there's significant dermal backflow. When this was performed in patients that had C6 disease with open venous ulcers, it demonstrated significant dermal backflow and with the use of an advanced pneumatic compression device there was significant clearing of the subdermal lymphatic collection. This is also noted in the patient that had C4 disease in the lower panels. Phlebolymphe~~de~~ma disease progression is again now recognized both in near infrared imaging, which we can correlate with clinical and physical findings and have a significant impact on how we now should treat patients with a recognition.

This slide demonstrates the progressive spiral of lymphatic dysfunction. With advanced phlebolymphe~~de~~ma the lymphatic system is overloaded resulting in compromised immune response. This increases the risk of skin infection and cellulitis. With the development of cellulitis, the lymphatic function is further compromised and can be even further damaged. This can result in skin fibrosis and subsequent progressive lymphatic damage and the vicious cycle continues. The cost of cellulitis and skin infections was recently published in "JAMA Dermatology" in 2019. This was a retrospective cohort analysis of U.S. national readmission rates and utilized 2014 nationwide readmission database. In this cohort, 9.8 percent of almost 450,000 cellulitic admissions were associated with non-elective readmissions within 30 days. This resulted in a total cost of more than 500 million dollars for all caused non-elective readmissions and the readmissions for skin and subcutaneous infections cost more than 100 million dollars. Obviously, this is a significant economic burden. The economic burden directly related to venous leg ulcers was published by Dr. O'Donnell, et.al. in the "Journal of Vascular Surgery," in 2014 and this demonstrates in a real contemporary vascular practice a total cost of approximately \$10,500 over the course of 120 days of cost. The total cost was threefold higher if the ulcer failed to resolve. Nearly two-thirds of the admissions were for treatment of cellulitis with intravenous antibiotics that were resistant to the typical cares of outpatient treatments. Again, the overall burden from an economic value, as well as from a societal value for treatment of venous leg ulcers is significant. Most of this is related to the undiagnosed aspect of the associated phlebolymphe~~de~~ma. Another study that demonstrates the economic burden of cellulitis infections in venous leg ulcers demonstrated healthcare system spending for a single episode of cellulitis including four days of hospitalization was approximately \$16,000. If we evaluate total cost per year for a venous leg ulcer, it's approximately \$15,700 and can more than double to \$30,000 to \$35,000 for those venous leg ulcers that fail to heal. Dr. Wade Farrow who developed the Farrow Wrap, wrote an excellent study in 2010 regarding the under diagnosis and under treatment of phlebolymphe~~de~~ma within the wound clinic environment, he stated that simple compression concentrates proteins creating a pro-inflammatory environment. The proteins and the pro-inflammatory cytokines can subsequently lead to tissue fibrosis. This can then result in breakdown of skin integrity resulting in bacteria rapidly propagating into the subdermal protein-rich lymphatic fluid. This subsequently can result again in that cycle of cellulitis, decreased function of the lymphatics and subsequent progressive fibrosis and damages lymphatics. Successful treatment of phlebolymphe~~de~~ma requires appropriate drainage of the protein-rich lymph fluid that is within the subdermal collection, and again, we have demonstrated based on near-??? data and based upon our understanding of phlebolymphe~~de~~ma that this requires treatment of the lymphatic system and not simply treatment of the venous insufficiency. In the 2015 "Journal of the American Medical Association Dermatology" study that evaluated cancer and non-

cancer patient treatments of lymphedema, with utilization of an advanced pneumatic compression device, Flexitouch had a significant impact on reduction in rates of cellulitis by almost 80 percent, a 54 percent reduction in the rate of inpatient hospitalizations, a 40 percent reduction in the rate of outpatient hospital visits. And this was summated in an overall reduction of total cost of 37 percent. A New York study performed in 2015 also demonstrated that utilization of Flexitouch had a significant reduction of cellulitis episodes and a significant reduction in overall number of venous leg ulcers. In the 2018 "Journal of Vascular Surgery" study, Flexitouch was compared to other advanced pneumatic compression devices in the scope of conservative therapy. It's important to note that when we discuss Flexitouch therapy, it is not a standalone therapy and should be utilized in the setting of care through a lymphedema clinic with a physical therapist or an occupational therapist. When we compare Flexitouch with conservative therapy to conservative therapy alone, there's a significant cost reduction of approximately 69 percent. When conservative therapy and simple pneumatic devices are compared to conservative therapy plus Flexitouch, there is an 85 percent cost reduction. And when we compare other advanced pneumatic compression devices used in the scope of conservative therapy, compared to conservative therapy with Flexitouch, we see again a significant reduction overall cost of 53 percent.

This slide demonstrates that venous and lymphatic disease is again intimately associated in terms of dysfunction as the venous disease becomes more progressive. Physicians recognize C2 disease as typically type ordinarir??? varicose veins. In C3 we recognize the onset of edema, in C4 we recognize skin changes and subsequent fibrosis, in C5 we recognize a healed ulceration and C6 is a current active venous leg ulceration. The importance of recognizing phlebolymphe~~de~~ma existence within the C3 to C6 patients allows improved patient outcomes when appropriate treatment of lymphedema is performed.

#### Conclusions

In conclusion, venous and lymphatic anatomy and disease states are under taught as part of the U.S. medical system, each medical student now receiving less than 30 minutes of education in years one and two. The recognition of the glycocalyx has resulted in a revision of the 1896 Starling Principle and we now understand that 100 percent of lymphatic interstitial fluid must return through the lymphatic system and no fluid is returned through the venous circulation. This also implies that all chronic edema is a result of inadequate lymphatic drainage. The development and advancement of near infrared imaging has helped us to understand and correlate chronic lymphatic dysfunction with advanced venous disease. Lymphatic dysfunction and phlebolymphe~~de~~ma are associated with an increased risk of cellulitis, chronic inflammation and progressive lymphatic damage. And we know this to be a vicious circle, that until we treat the underlying lymphatic dysfunction is difficult to arrest. Venous leg ulcers and cellulitis are associated with an increased rate of hospitalization, outpatient care and medical resource utilization. Flexitouch Plus, when used as part of a dual therapy, through a certified lymphedema clinic that utilizes manual lymphatic drainage and complete congestive therapy, has been now clinically proven in multiple studies to be economically advantageous by decreasing cellulitis, hospitalizations, and outpatient visits. Thank you.

#### Dan Carlson:

Dr. Melin, on behalf of Tactile Medical, thank you so much for your presentation and congratulations on your multiple talks at the American Vein and Lymphatic Society Annual Congress last weekend. Really appreciate all of your knowledge and sharing with us today. For those of you who took the time out of your busy schedules to join this webinar, we really appreciate you joining us. And as we're waiting for calls to come in through the phone system, we're going to turn to some of the questions that came in through the Q&A widget online. If you do think of questions after today's webinar, please get those to your Tactile Medical product specialist as we will get those to Dr. Melin and follow up via email after the fact. So one of the questions that came in through the Q&A widget during the lecture, the question says, does the study presented on the slide comparing the cost of treatments include the cost of the pump and is that the cost savings presented?

**Dr. M. Mark Melin:**

Dan, thank you for the question. Again, I want to thank everybody that took time out of their busy clinic day to spend time with us. One of our big promotions is trying to do venous education, lymphatic education, and then the combined phlebolympheidema education. And being down at ABLs this last weekend was really humbling; a lot of fabulous people, Kent ???, Steve Dean???, they really opened up some significant doors for some of us who had come down there to present and it was a really great opportunity. In regards to that particular study, that was published in the "Journal of Vascular Surgery" in 2018 and it's a health economic study where they data mined and one of the unique things about Tactile is because they do all the servicing, all the billing, all the charging, they can associate every order with an MPI number. So they know exactly the billing process in working with the pairs to get the lymphedema pumps to patients. So really to equalize everything, because the other companies don't have access to that data, the cost of the pumps was pulled out of that study and that way it's more of an altruistic view so you can see what the results are of the different pumps on simply the medical care. There's other data that's been published in papers that have shown that to cover the cost of the pump can take somewhere around .7 of a year and even there's data that shows 6/10 of a year or 6/10 of 12 months to actually cover the cost of the pump. And I think it's really important to remember, unlike an oil change in your car, this is a one-time cost. Once it's purchased, this pump is going to be useful on a daily basis for multiple years. So, I think if we're going to amortize it like a house mortgage, it accelerates how quickly the house is paid off for because of the benefits in terms of downhill cost for lymphedema cares markedly decrease. So that's a really insightful question, the person that asked that, and I hope that clears it up a little bit.

**Dan Carlson:**

Yeah, thank you Dr. Melin, I think that's a fantastic answer and a good way to think about this, it's very much an investment and managing and preventing those costs annually, so thank you for that. Next we're going to turn to a question that came from VCU Medical Center, Dr. Michael Amendola who first says thank you for presenting and it's actually a two-part question, so one is do you know of any medical therapies that affect the lymphatic return and then two, what imaging studies are you currently using for lymphedema diagnosis or is it a strict clinical diagnosis?

**Dr. M. Mark Melin:**

Michael, excellent question. Let me start with the imaging studies first. The classical imaging studies of course that we don't do anymore would be lymphangiography. We try to avoid putting dyes into the lymphatic system; usually they're already damaged. It won't change your outcomes at this point unless you're thinking about doing a lymphatic reconstruction. When I was down at ABLs this last week, and I saw Dr. Peter Neligan speak, and just a gifted plastic surgeon out of the State of Washington, he showed these fascinating pictures of MRIs of the lymphatic system which are a reconstruction in 3D, and he's using this more so to be able to do planning for reconstructive surgery and also just purely diagnostic. Sometimes he'll run into big lymphatic malformations that will change how he does his surgical procedure. And then he's doing intraoperative injection of fluoroscopy to be able to further image, he's doing his reconstructive methods. The classic one we all think about is lymphoscintigraphy. I have decreased my overall ordering of lymphoscintigraphy only because as I treated more and more patients with phlebolympheidema, the diagnosis has just become so apparent, especially based on the studies that Eva and Aldrich and Rasmussen have done down in Houston, that it's shown that when you do micro dosing of endocrine??? in green, if you have stasis dermatitis changes in the skin you know by default automatically there's lymphatic dysfunction and lymphedema as well. So, every patient I see now that is a late-stage C3, a C4, C5, C6, we just know every one of those patients has associated lymphedema. So, I've stopped studying those folks from a lymphatic

standpoint, I still of course get all those folks ??? superficial and deep venous reflux and look for was there any symptomatic DBT before. In terms of medical treatment, there's really good evidence, if you're looking at straight venous leg ulcers, there's been people, I used to use a lot of trental, pentoxifylline, be dosed one table three times a day, I've read a lot of the medical treatment using daflon or the ???, the United States version that is called Vasculera. In Europe there's been 40 plus studies that have now been done, ten of those I believe were RCTs. Very good robust data that's come out of Europe in terms of benefit for flavonoids and specifically the daflons or what are called micro purified flavonoid fractions, and the reason it's called that is that to get it small enough to get good bio-absorbability is one of the important things. The unique thing about Vasculera is they add an alkaloid analyzing agent just because of the citrus component because these are all coming from the rinds of oranges. So I do think there's really good robust data that supports using a flavonoid and it takes about three months to really have an impact so I think we also have to just let patients know it's going to take a little bit to have an impact, but I am using this quite liberally on all my patients now.

**Dan Carlson:**

Alright, great way of covering the two-parter there. And Dr. Melin, as you were providing that answer, a thank you came in from Dr. Amendola as well, so thank you. Let's turn next to a question from the University of New Mexico from Dr. Mark Langfeld. How much does obesity contribute to leg edema with or without venous disease?

**Dr. M. Mark Melin:**

Mark, it's a great question. It can get really complex. Clearly obesity, because of the impact upon the abdominal domain, can have a huge impact on the retroperitoneal space and increase lymphatic dysfunction. So, I think we've all now become accustomed with the phrase obesity-related lymphedema disease. And then of course, I think the people we have to really tease out of that group are the ones that are not obese because of a caloric issue, but the ones that have lipedema that then is complicated or weaponized by our caloric unrestricted state in the United States. So, I think it's also really important to diagnose the patients with lipedema. Steve Dean and Karen Herbst have taught me so much about this and if you don't know much about lipedema, I would tell you there's a great open access article from 2016 that Karen Erbs<sup>o</sup>stein, ??? Don Buck wrote and I hand that out to all my patients. We have to tease out the lipedema patients because if we try to calorie restrict them and try to get them to exercise, they might lose fat on the torso and up but they're not going to be able to lose it from the buttocks on down; it gets super frustrating for them. And it ends up fat shaming them. So, if it's pure caloric excess, I'm getting those folks involved obviously with a bariatrician and nutrition services, getting them into an exercise program. And oftentimes that will help us significantly in terms of management of the lymphatic dysfunction. Once we get them to a point where they've got open ??? rations and weeping lymph??? excess, then almost all those patients have a primary lymphedema component that even after shedding the weight, they're still going to be dealing with the long-term issue and I think we have to be more aggressive with those folks that they've gotten to that point. That was a really excellent question, thank you for asking that Mark.

**Dan Carlson:**

Alright Dr. Melin, thank you very much for the answer and again completely echo. Having heard Dr. Herbst and Dean speak often about that interestingly, always referring to obesity very much as kind of a chicken and the egg effect of both a cause and an effect of lipedema, so great answer on that one. I want to turn next to a question that came in through the Q&A widget. As you're thinking about risk factors, what do you look at in a swollen leg that increase the patient's chance for a VLU?

**Dr. M. Mark Melin:**

So, if we're worried about VLU in swelling, we kind of have to go back to history, so has the patient had a superficial bout of phlebitis, has there been a DBT, has there been a pulmonary embolis, does the patient have a cable filter, has it been removed? Has the patient had iliac stints before or significant abdominal trauma, vein harvest for a heart bypass, any prior malignancies, any current malignancies which of course increases their hyper coagulability status? Has there been groin surgery in the past, has there been a lymph node resection? Obesity as we just talked about, diabetes and tobacco can certainly play into making these conditions worse. Liver disease, renal disease, people certainly on dialysis. In cardiac disease CHF can certainly make all of this worse. I think the other really important thing that Tom O'Donnell brought out, I think a med student co-wrote this with him at ??? and it just came out in the "Journal of Vascular Surgery" about a year ago is that we can't forget about what's going on between the ears. In our patient population that's depressed, and certainly the patients coming into our wound clinic, we have a high percentage of patients that are depressed, it's hard for them to simply just brush their teeth much less take care of these really complex wounds. And so when we're trying to guide them on how to take care of their wounds and you're saying look, I want you to pull on your compression socks, do this A, B, C, D, E, F, G on your wound, and I want you to do a pump on your legs and I want you to take this medication, I want you to exercise, I want you to eat less, it's completely overwhelming. So, I think we have to be really sensitive and pick up on this issue. If somebody's got depression, we're not going to get adherence rates until we help guide them through that. And I do think if you work in a wound clinic, it's important to pick up on this and get the primary doc involved and get this patient some help because that's going to improve your outcomes in the wound clinic. It's an excellent question, I'm glad somebody asked that.

**Dan Carlson:**

And I think it's a really important part of your answer Dr. Melin what you mentioned about the psycho-social elements of it and really getting those patients treatment for that part and making sure that they're empowered to take care of themselves in a chronic condition like this. So, thank you for a fantastic answer. Turning next to, a really good question came in, 'cause you've spoken so often about the importance of incorporating the lymphedema therapist into your practice as a vascular specialist, so the question is what advice would you offer to vascular specialists for working more closely with certified lymphedema therapists?

**Dr. M. Mark Melin:**

So, I would, honestly I'd tell you don't do what I've done most of my career where I simply was getting a piece of paper from a therapist, I was signing it and I was saying just get it taken care of without really totally comprehending what was going on. I have really worked hard to team build and all of us want this because we all want good outcomes for our patients, so I would tell you put a face to the signature, go visit the lymphedema therapist, see what they do, understand their philosophies, understand their trainings, understand what lana??? Is, all the associations they do and the professionalism they have. Usually they've been doing this for a long time, they're very, they're like health coaches, so they will augment your outcomes if you understand what they do and building this relationship I think goes a long way towards it. So they care just as much about getting patients healed and keeping them healed as we do and they are facilitators. So ultimately, in building this relationship, and I don't order a lymphedema pump without ordering a therapist, so it's called dual therapy because a pump with a patient without a therapist is not going to have good outcomes. So I purposely will order the therapist first so I don't forget to order the therapist and then I'll take the measurements and order the pump at the initial consult if it's appropriate. And the lymphedema therapist will really offload your practice. I think in our busy practices we don't have the time to sit here and be the

excellent health coaches that we really would like to be in our heart and souls, and so building this bonding relationship and really empowering and enabling the lipedema therapist will maximize your outcomes. People will notice, family practice will notice, internal medicine will notice; it'll boost your clinic in many ways and it'll set you apart. So, I would tell you, don't make the mistake I did. Do it sooner and don't wait until you're halfway through your career.

**Dan Carlson:**

Fantastic, thank you Dr. Melin. Again, I think that speaks back to and having reference to ABL5 earlier, I think more physicians thinking like you and incorporating the lipedema therapist into the venous practices, really, really important for getting the best care for these patients with mixed venous and lymphatic disease. So thank you. A question came in on the Q&A Widget again stating, what characteristics and history do you look for in distinguishing if lymphedema is primary or secondary and then how do you code for that?

**Dr. M. Mark Melin:**

Yeah another really good functional question because this really then comes down to what are we doing at the time that we see the patient because if we're going to get our patient covered to see the lymphedema therapist to get their garments, to get a lymphedema pump, we have to have the right documentation, we have to have the right coding, and that all then goes back to taking a really good history and making sure that it gets into the documents. So, the first thing I would tell you is there's a template that exists within Tactile. They've been very altruistic on this; it is not brand specific. If you don't have this template, we're Epic based and it's in our system. I know it can go into almost any system. I would incorporate that in because that's your checklist that helps remind you what you need to pick up on a physical examination and document to help your patient get the treatments they need. So, I also referenced before a paper by Drs. Mortimer and Rockson that was 2014 about the changes in how we understand lymphedema and it's figure 3 or 4 that talks about phenotypic and genotypical types of things to differentiate primary from secondary. One of the things we know now is that there are many, many more patients that have primary lipedema that may show up right at birth called congenital and may show up like, for a woman, after onset of menses until about age 30, for a man before age 30, that's called lymphedema praecox. And then after age 30 or 40 it's called lipedema tarda. All those are primary lymphedemas. Clearly we're seeing more and more patients show up in their 50's, 60's, 70's, where there's almost like a tipping event and the analogy I use is the patient that had a knee replacement, never had an infection, never had an issue with the knee, orthopedic surgeon did a fabulous job, no DBT's, no deep venous insufficiency, nothing, and yet their leg's still swollen four years later. And these patients, more likely than not, are primary lymphedema tarda. So when it comes to the documentation piece, as you do your accurate documentation to note the lymphedema existence, and then when it comes time to code it, it's coded as QA2.0 and I always then write after that diagnosis primary lymphedema tarda to indicate that that's that. And we have multiple papers now in purviewed literature that would support that viewpoint. There's a lymphoscintigraphy study that just came out last year, there is Drs. Mortimer and Rockson's paper that came out, there's that genetic paper that Dr. Michael Feldman had wrote out of Chicago. So there's multiple papers I think we can utilize to justify that diagnosis. That's the diagnosis that helps our patients ultimately get the treatments from the therapist for their compression wraps, for their physical therapy, occupational therapy, and for ??? lymphedema pump. So good question; I'm glad somebody asked that.

**Dan Carlson:**

Alright, thank you Dr. Melin, very comprehensive answer. I was looking at both the physical findings and family history and getting to that correct diagnosis, so thank you very much for that. At this time, we do not have any additional questions coming in over the phone or through the Q&A Widget so we'd like to conclude today's webinar. Thank you again Dr. Melin for sharing your expertise and thank you to all of you across the

country that joined us for this webinar. Again, if you do have questions that come up after the fact, please get those to your Tactile Medical Specialist so that we can follow up on email. Thank you again and have a fantastic day.