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# TOE-BRACHIAL INDEX RISE IN LYMPHEDEMA PATIENTS WITH MULTILAYER BANDAGE

**J-E. Trihan, S. Mestre, I. Quéré, D. Lanéelle, A. Perez-Martin**

Vascular Medicine Unit, Cholet Hospital, Cholet, France (JET); Department of Vascular Medicine, Angers University Hospital, Angers, France (JET); CHU de Montpellier – Department of Vascular Medicine, Hopital Saint-Eloi, Montpellier, France (SM, IQ); UA11 INSERM – UM Institut Desbrest d'Épidémiologie et de Santé Publique (IDESP), Montpellier , France (SM, IQ, AP-M); Vascular Medicine, Côte de Nacre University Hospital, Caen, France (DL); UNICAEN, INSERM 1075, COMETE, Caen, France (DL); Vascular Medicine, Nîmes University Hospital, Nîmes, France (AP-M)

*ABSTRACT*

*Multilayer compression bandaging (MLB) remains the primary treatment in lymphedema in association with manual lymphatic drainage. However, MLB can be contraindicated in patients with advanced lower extremity artery disease (LEAD). Presently, the prevalence of LEAD in lymphedema patients remains unknown. The goals of this study included i) to estimate the prevalence of LEAD, defined by toe-brachial index (TBI) less than 0.7, and ii) to measure the evolution of TBI after 30 min of MLB. A cross-sectional study was performed during a 3-month period on patients presenting with lower extremity lymphedema. Demographic data, basal TBI (T=0min) and TBI after 30 min of MLB at rest (T=30min) were recorded. Twenty-four patients with a total of 29 lymphedema limbs were included with a mean age of 62 years-old [Inter-quartile range (IQR) = 48 – 68] and 65.5% presenting with primary lymphedema. Non-symptomatic LEAD, defined as TBI < 0.7, was found in 8 lymphedema limbs (27.6%). Advanced age, severe stages, and longer duration of lymphedema were associated with LEAD in univariate analysis. Median TBI increased significantly between T=0min and T=30min of MLB: 0.81 [IQR: 0.68 – 0.93] and 0.96 [IQR: 0.82 - 1.12] respectively (p= 0.004). Distal localization of lymphedema was associated with a decrease in TBI at T=30min in univariate analysis. Subclinical LEAD was found in over a quarter of lymphedema limbs and was more frequent in patients with advanced age, severe stages, and longer duration of lymphedema. Based on these findings, subclinical peripheral artery disease may be widely underestimated in lymphatic pathologies.*

**Keywords:** Lymphedema; toe-brachial index; compression bandaging; lower extremity artery disease (LEAD); peripheral artery disease (PAD)

Primary or secondary lymphedema can be a significant burden with reported prevalence of 200 million people worldwide with a majority secondary to filariasis in developing countries (1). It is a chronic disease caused by an impairment of lymphatic drainage with normal capillary function leading to chronic inflammation and reactive tissue fibrosis (2). First-line treatment usually involves manual lymphatic drainage (massage technique that stimulates lymphatic contractility), skin care, weight control, exercise and compression therapy commonly using multilayer compression bandaging (MLB) (3). In parallel, severe ischemia of at least one lower limb (defined by

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toe pressure of 30 mmHg or less) is an absolute contradiction for multilayer bandaging as recommended by international expert consensus (4). To our knowledge, prevalence of lower extremity artery disease (LEAD) among lymphedema patients remains unknown and there are no data available about arterial response to multilayer bandaging in lymphedema. This study evaluated (i) prevalence of LEAD (defined by toe brachial index (TBI) of less than 0.7) among patients followed for lower extremity lymphedema, and (ii) microcirculatory responsiveness to multilayer bandage at rest.

## *MATERIALS AND METHODS*

### *Patients*

A cross-sectional study was conducted from April 1st to June 30th 2018 in Saint-Eloi Montpellier University Hospital, a French national reference center for lymphology. Consecutive adult patients hospitalized for intensive decongestive therapy were included. For a patient with bilateral lymphedema, each limb was included separately. Enrolled patients were followed at our lymphedema reference center where all patients undergo lymphoscintigraphy at least once to confirm the diagnosis.

Exclusion criteria included: refusal to participate in the study, skin infection or chronic ulcer on the study lower limb, toe pressure of 30mmHg or less, uncertainty about lymphedema diagnosis, life expectancy of less than 24 hours, cardio-vascular instability, patients receiving reinforced protection, persons deprived of liberty by a juridical or administrative decision, and adults under protective legislative measures.

The following demographic data were obtained from electronic medical records: age, gender, tobacco habits, history of hypertension, dyslipidemia, diabetes, severe to terminal chronic kidney failure (defined by creatinine clearance of less than 30 mL/min/1.73m$^2$), body mass index, lymphedema history (primary/secondary, times since onset of symptoms, localization), usual lymphedema treatment (manual lymphatic drainage, compression therapy using multilayer bandage or stocking, and if so, pressure level). If no clinical sign of lymphatic stasis was found above the knee, lymphedema was considered as distal and conversely, it was considered as proximal if no sign of lymphatic sign was found below the knee. A patient could have both proximal and distal lymphedema. Secondary lymphedema was confirmed if we could find at least one of the following in the medical history before the onset of the first lymphedema clinical sign: local cancer treatment (i.e. surgery, radiotherapy) of the affected limb, general cancer treatment (i.e. chemotherapy), history of trauma to the affected limb or infection (repeated erysipelas, filariasis). Otherwise, the patient was considered to have primary lymphoedema. For lymphedema staging, we followed the 2020 International Society of Lymphedema staging system including stage 0, 1, 2, late 2 and 3 (5).

After written information regarding this study was provided, no patient was opposed to anonymously participation in this study. Written consent from the participants was not required to participate in this study as all testing were considered as routine care, in accordance with national legislation and institutional requirements. All procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2000.

### *Pressure Measurements*

All measurements were performed by 2 trained vascular physicians (JET, SM). Patients were in decubitus position, at rest in a room between 20 and 22° Celsius.

Diagnosis of LEAD was confirmed if TBI was less than 0.7 at rest. Toe blood pressures were measured by photo-plethysmography, using a semi-automatic measure device (SysToe®, Atys Medical, Soucieu-en-Jarrest, France). Pressure measurement was conducted according to the manufacturer's instructions and as described in the literature (6). Pressure cuff (adapted to the toe size) was placed at the base of the big toe, and the Laser Doppler probe (with the inflation cuff) at the top of the toe. The cuff was inflated at 200

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mmHg and was then automatically and linearly deflated. Systolic blood pressure was read automatically by software when the plethysmographic probe detected the return of blood perfusion.

Systolic humeral blood pressures were measured in both arms with an automatic device (Carescape Dinamap V100, GE Healthcare Systems, Chicago, Illinois, USA) with patient in a supine position after at least 10 minutes of rest. Blood pressure cuffs were adapted to the patient's weight and height (10-cm or 12-cm cuff).

We carried out serial measurements of TBI following the same protocol. Each measurement included humeral systolic blood pressure (SBP) on the right arm, then on the left arm, and then photoplethysmographic toe pressure(s). If patient presented with bilateral lower limb lymphedema, we arbitrarily measured blood pressure on the right toe first, then on the left toe. Each patient had at least 2 consecutive measurements of toe pressure and the mean value was selected. If values differed by at least 20% (calculated from the highest value), two additional measurements were taken, highest and lowest values were excluded and the selected value was the mean of the two remaining measurements. TBI was then calculated by dividing the mean toe pressure by the highest value of the right and left arm SBP as recommended by international guidelines (7).

The first TBI (baseline) was performed with the patient at rest in decubitus position for at least 5 min, without compression therapy. The study physician installed a two-layer bandaging if toe pressure was greater than 30 mmHg. For both layers, we used a short-stretch elastic bandage (Kit Biflex® short-stretch, Thuasne, Levallois-Perret, France) with fitting indicator for pressure graduation, from the base of the toes to mid-thigh, with a bandage coverage by 1/2 of the width. All bandages were used in strict respect of the manufacturer's instructions which guarantee an effective interface pressure between 36 mmHg and 44 mmHg.

The second TBI measurement was carried out 30 minutes after the multiple layering with the patient kept in decubitus position.

*Statistical Analysis*

Statistical analysis was conducted in R 4.0.2 software (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org), using R studio interface. Because this cohort was not derived from random selection, all statistics are deemed to be descriptive. There were no missing data. Continuous variables are expressed as means and standard deviation (SD) analyzed by the Student t-test. When normality could not be confirmed (using Shapiro test), variables were expressed as median and inter-quartile range (IQR), defined by the first and the third quartile. Categorical variables are expressed as numbers and percentages, which were compared by the $\chi 2$ test or the Fisher exact test if necessary. Difference among TBI means was tested using the Mann-Whitney-Wilcoxon test because the number of subjects was <30. For association with LEAD (TBI < 0.7), the Fisher test was used for binary variables with results expressed as Odds ratio (with 95% confidence interval) and the Mann-Whitney-Wilcoxon test was used for quantitative or ordinal variables with results expressed as W-statistics. For association with TBI evolution at T=30min (continuous variable), non-parametric Spearman correlation test was used for continuous variables (expressed as rho coefficient) and the Mann-Whitney-Wilcoxon test was used for binary variable with results expressed as W-statistics. A value of $p < 0.05$ was chosen as statistically significant in the two-tailed analysis.

*RESULTS*

*Patients*

Twenty-four patients were included with a total of 29 limbs (*Table 1*). A majority of patients were women with primary lymphedema and distal localization. Most patients were at low cardiovascular risk as a minority of patients presented with hypertension, dyslipidemia, diabetes, or were active smokers. Six patients (25%) had body mass index > 30 kg/m$^2$. No patient presented with clinically significant arterial claudication.

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**TABLE 1**
**Characteristics of Included Patients**

| Patient characteristics | Value (n= 24) |
|---|---|
| Age (years; **median [IQR]**) | 62.00 [48.00 - 68.00] |
| *Sex* | |
| **Female** (%) | 22 (75.9) |
| **Male** (%) | 7 (24.1) |
| Body mass index (kg/m$^2$, median [IQR]) | 25.0 [22.3 – 27.9] |
| Hypertension (%) | 7 (22.1) |
| Dyslipidemia (%) | 4 (13.8) |
| Diabetes (%) | 3 (12.5) |
| Active smokers (%) | 3 (10.3) |
| Tobacco use (pack-year, median [IQR]) | 20 [17.5 – 30) |
| Chronic Kidney Disease (< 30 mL/min/1.73m$^2$) (%) | 0 (0) |
| **Lymphedema characteristics** | **Value (n=29)** |
| ***Territory*** | |
| Left lower limb (%) | 14 (48.3) |
| Right lower limb (%) | 15 (51.7) |
| ***Localization*** | |
| Proximal (%) | 5 (17.2) |
| Distal (%) | 17 (58.6) |
| Proximal & distal (%) | 7 (24.1) |
| ***Type*** | |
| Primary (%) | 19 (65.5) |
| Secondary (%) | 10 (34.5) |
| ***Stage*** | |
| Stage 1 (%) | 2 (6.9) |
| Early stage 2 (%) | 11 (37.9) |
| Late stage 3 (%) | 12 (41.4) |
| Stage 4 (%) | 4 (10.3) |
| Duration of lymphedema (years; median [IQR]) | 17 [5 – 24] |
| ***Treatment*** | |
| Patients using compression therapy daily (%) | 26 (89.7) |
| **Patients using multilayers** compression therapy daily (%) | 11 (42.3) |
| Manual lymphatic drainages (%) | 19 (65.5) |
| ***Hemodynamics*** | |
| Toe pressure at rest (mmHg, median [IQR]) | 100 [80 – 138] |
| **TBI (no unit, median** [IQR]) | 0.81 [0.68 – 0.93] |
| **TBI < 0.7 (%)** | 8 (27.6) |

*Lower Extremity Artery Disease (LEAD)*

Regarding prevalence of lower extremity artery disease (LEAD), 8 lymphedema limbs (27.6%) from 7 patients had low TBI (< 0.7) with a median value of 0.645 [IQR= 0.635 – 0.655]. No patient presented with severe LEAD, defined by TBI < 0.4. We attempted to determine which parameters were associated with low TBI on univariate analysis (*Table 2*). Unfortunately, multivariate analysis could not be achieved due to the low number of cases (n=8). Among cardiovascular risk factors, only age seemed associated with low TBI without reaching significance (p=0.07) (*Table 2*). However, more severe stages of lymphedema (stages 3 and 4) were associated with LEAD (p=0.01). Low TBI was detected in none of the stage 1-lymphedema limbs, 1 (9.1%) of the early stage 2- lymphedema limbs, 4 (33.3%) of the late stage 2- lymphedema limbs and 3 (75.0%) of the stage 3 lymphedema limbs. Longer duration of lymphedema was also associated with low TBI (p=0.03).

*Toe-Brachial Index Responsiveness to Multilayer Bandaging*

Among the 29 lower limbs included, MLB induced a significant rise in TBI (p=0.005). Mean TBI was 0.81 [IQR: 0.68 – 0.93] before MLB (T=0min) and 0.96 [IQR: 0.82, 1.12] after 30 min of MLB (T=30min) (p=0.004) (*Fig. 1*). Four lower limbs (13.8%) showed a decrease of TBI at T=30min. Among these 4 limbs, one had basal TBI < 0.7 and showed a very low decrease in TBI: -0.01. The other 3 limbs had basal TBI of 0.81, 0.93 and 0.96; and showed a decrease in TBI of -0.04, -0.11 and -0.05 respectively. In univariate analysis, only distal localization of lymphedema was significantly associated with TBI decrease at T=30min (p= 0.01) (*Table 3*). Duration of lymphedema showed modest inverse correlation (Rho = -0.44) without reaching significance (p= 0.06). Multivariate analysis could not be done due to insufficient statistical power.

Among limbs with low TBI (< 0.7) at baseline, only one showed low TBI at T=30 min of MLB (*Fig. 1B*). Median TBI increase was + 0.17 [IQR: 0.09 – 0.26]. Regarding limbs with normal TBI value at baseline, median TBI increase was 0.12 [IQR: 0.04 – 0.22].

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**TABLE 2**
**Parameters Associated with Low Toe-Brachial Index at Baseline in Univariate Analysis**

| Variables | Odds ratio (IC 95%) or W-statistics ∫ | p-value |
|---|---|---|
| ***Patients characteristics*** | | |
| Age | 46 | 0.07 |
| Sex | 2.46 (0.27-21.0) | 0.36 |
| Hypertension | 0.36 (0.01-4.06) | 0.63 |
| Dyslipidemia | 0.49 (0.00-4.03) | 0.55 |
| Diabetes ∫∫ | - | - |
| Active smokers | 6.14 (0.28-411.0) | 0.17 |
| Tobacco use (in pack-year) | 66 | 0.11 |
| ***Lymphedema characteristics*** | | |
| Territory (Left vs. right lower limb) | 0.91 (0.13-6.36) | 0.99 |
| Type (Primary vs. Secondary) | 0.20 (0.00-2.05) | 0.20 |
| Localization (Proximal vs. Distal / Both) | 0.01 (0.00-2.81) | 0.28 |
| Stage | 35.5 | 0.01 |
| Duration of lymphedema | 40 | 0.03 |
| Compression therapy daily | 0.75 (0.03-49.6) | 0.99 |
| Manual lymphatic drainages | 0.41 (0.06-3.01) | 0.39 |

∫ The Fisher test was used for binary variables, with results expressed as Odds ratio (with 95% confidence interval) and the Mann-Whitney-Wilcoxon test was used for quantitative or ordinal variables with results expressed as W-statistics.
∫∫ Statistical testing was not possible with the diabetes variable as only one patient had diabetes.

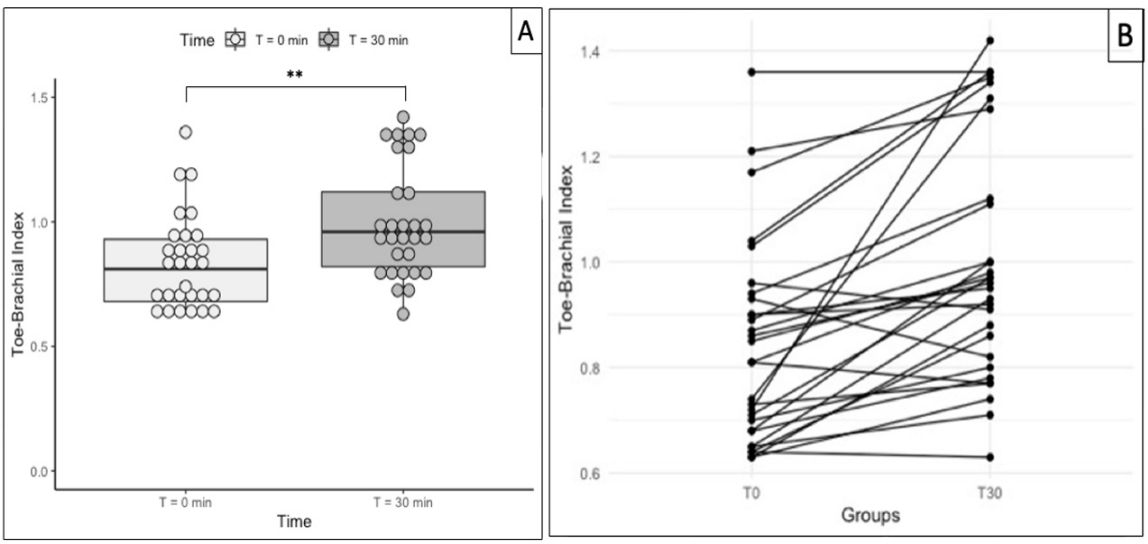


***Fig. 1:*** *A) Boxplot of toe-brachial index (TBI) change secondary to multilayer compression bandage (baseline and 30-min after). B) changes in individual TBI measurements from baseline to 30 minutes after multilayer compression bandage. Significance level: **: p<0.01.*

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**TABLE 3**
**Parameters Associated with the Toe-Brachial Index Change Secondary to Multilayer Compression Therapy in Univariate Analysis**

| Variables | Univariate analysis | |
|---|---|---|
| | Spearman's Rho coefficient or W-statistics ∫ | p-value |
| ***Patients characteristics*** | | |
| Age | Rho = 0.05 | > 0.2 |
| Sex | W = 521 | > 0.2 |
| Body Mass Index | Rho =- 0.16 | > 0.2 |
| Hypertension | W = 503 | > 0.2 |
| Dyslipidemia | W = 509 | > 0.2 |
| Diabetes ∫∫ | W = 498 | > 0.2 |
| Active smokers | W = 479 | > 0.2 |
| ***Lymphedema characteristics*** | | |
| Territory (Left vs. right lower limb) | W = 502 | > 0.2 |
| Type (Primary vs. Secondary) | W = 476 | > 0.2 |
| Localization (Proximal vs. Distal / Both) | W = 384 | 0.01 |
| Stage (Stages 1 & 2 vs. stages 3 & 4) | W = 406 | 0.09 |
| Duration of lymphedema | Rho = - 0.44 | 0.06 |
| Compression therapy daily | W = 483 | > 0.2 |
| Manual lymphatic drainages | W = 502 | > 0.2 |

∫ The non-parametric Spearman correlation test was used for continuous variables (expressed as rho coefficient) and the Wilcoxon test was used for binary variables with results expressed as W-statistics

*DISCUSSION*

Our results showed high prevalence of sub-clinical LEAD based on TBI measurement < 0.7 in lymphedema patients, and multilayer compression bandage induced increase in TBI at 30 min.

Study on the burden of LEAD in lymphedema patients is scarce in the literature. On this subject, Moffatt and colleagues reported LEAD prevalence of 1.93% among the 259 patients with chronic edema included in an international prospective cohort (8). However, diagnosis of LEAD was based on standardized patient questionnaire. It is reasonable to assume that in fact, only symptomatic LEAD was reported insofar as most LEAD diagnoses are based on suggestive clinical signs. In our study, LEAD was much more frequent in lymphedema patients (27.6%), but no patients showed any clinical signs of LEAD (arterial claudication, non-healing ulcers or gangrene, etc), a finding potentially implying that subclinical LEAD is more frequent in lymphedema patients.

A recent large-scale study highlighted an association between chronic edema and peripheral arterial occlusive disease (PAD), diabetes, and heart failure/ischemic heart disease in the U.K. population (8). In this study, in a questionnaire-based study of 2541 patients receiving nursing care, Moffatt and al. found that PAD was present in 5.5% of chronic edema patients compared to 1.9% of non-chronic edema patients. However, data collection through questionnaire results in memorization bias and possible comprehension bias (patients may not have understood the pathology when they were diagnosed with LEAD) which could have led to underestimation of LEAD prevalence.

There are discrepancies in the literature regarding the TBI cut-off value (9), which ranges from 0.60 to 0.75, but TBI is generally considered as abnormal when it is < 0.70 (10–13). Even if 27.6% of our lymphedema limbs had TBI < 0.7, it is worth noting that none had TBI < 0.6, indicating mild LEAD. It is also

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concordant with the fact that no patient had clinical signs of LEAD.

The physiopathology of edema has changed in recent years. Despite the traditional understanding of the Starling model, it is now thought that in the physiological state there is an outflow of fluid in the capillary bed, with no significant reabsorption at the venous end, implying that the interstitial excess capillary filtrate and macromolecules are taken up mostly by lymphatics. Hence, edema arises when capillary filtration exceeds lymphatic drainage (14,15). In lymphedema patients, lymphatic drainage is irremediably altered, inducing chronicity and skin alterations (16). In our study, we used toe pressure rather than ankle pressure to diagnose LEAD as ankle pressure measurement can be challenging and biased in lymphedema patients due to thickened skin, renitent edema, and increased depth of the anterior and posterior tibial arteries. In the future, it would be interesting to compare diagnostic accuracy between TBI and ankle brachial index in detection of LEAD in a large cohort of patients with lymphedema / chronic edema.

Regarding toe pressure rise secondary to MLB, it is consistent with the literature. For many years, Fromy and colleagues have studied the microcirculatory changes induced by cutaneous pressure. They have established that pressure stimulation allows for microvascular vasodilatory reflex in the human skin (17). This reflex is nerve-mediated (17–19) and can be altered in patients with diabetes (20) or advanced age (21). In our study, the results suggest that this microvascular vasodilatory reflex is preserved in lymphedema patients and may indicate that the fibrosis and loss of elastic tissue that characterize lymphedema does not prevent reflex hyperemia. This raises the possibility that the subcutaneous arteriole is not narrowed by being surrounded by so much excess collagen and can dilate. Only 4 lymphedematous limbs with MLB showed a decrease in TBI at 30min. They presented with distal localization and trended toward older lymphedema with severe stages. Only one patient with baseline TBI <0.7 has a very small decline in value (-0.01). This shows that it is possible to apply compression in the context of chronic edema even with associated LEAD, but that appropriate assessment criteria and clinical monitoring must be in place. Further studies are needed to determine whether the pressure-induced microvascular vasodilatory reflex is altered in patients with distal, ancient, advanced stages lymphedema.

*Limitations*

Several limitations in this study should be addressed. First, the study was retrospective, and exhaustive bias control could not be ensured. The number of included patients was modest (n=29 limbs) and so results should be interpreted with caution pending conclusive replication. However, to our knowledge, this study was the first to evaluate subclinical LEAD in lymphedema patients. Study on a larger number of patients in needed. Second, the prognosis value of low TBI in lymphedema was not evaluated in this work since no patient follow-up was performed. Third, TBI measures were performed by a single trained vascular physician for each patient and inter-individual reproducibility could not be evaluated. However, due to semi-automatic measuring TBI reproducibility could be considered as satisfactory.

*CONCLUSION*

Sub-clinical lower extremity artery disease, defined by toe-brachial index < 0.7, was present in over a quarter (27.6%) of lymphedema patients. Patient age, severe stages, and longer duration of lymphedema were associated with LEAD in univariate analysis. Pressure-induced vasodilatory reflex is preserved in most lymphedema patients, but may be altered in distal, older, and severe-stage lymphedema. More studies are needed to confirm the burden of subclinical LEAD in lymphedema patients and the prognosis value of altered pressure-induced vasodilatory reflex.

*CONFLICT OF INTEREST*

All authors declare no financial conflicts

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of interest relevant to this article.

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**Jean-Eudes Trihan, MD**
**E-mail: j.eudes.trihan@gmail.com**
**phone +33 5 49 44 31 17**
**fax: +33 5 49 44 36 92**



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