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New Diagnostic and Therapeutic Approach to Erectile Dysfunction and Peyronie's Disease

César Eisner[1]*, Facundo Lacsi[2] and Matías Caradonti[3]

[1]Shockwave Argentina, Buenos Aires, Argentina

[2]Medical-Academic Department of Health Sciences and Education of the National University of La Rioja, Argentina

[3]Hospital Donación Francisco Santojanni, Ciudad Autónoma de Buenos Aires, Argentina

ABSTRACT

Color Ecodoppler (EC) and fundamentally Two-Dimensional Shear Wave Elastography (2D-Shear Wave Elastography or simply 2D-SWE), currently provide us with diagnostic tools with the ability to objectively demonstrate the condition of blood vessels and tissues level of the penile Corpora Cavernosa (CC) and the Tunica Albuginea (TA), in order to distinguish qualitatively and quantitatively and in a Non-Operator Dependent way the different vascular and tissue mechanisms that cause Erectile Dysfunction (ED) and the Disease of Peyronie (EP), as well as assessing the response to treatment with Low Intensity Focused Shock Waves (LI-ESWT-Low Intensity Extracorporeal Shock Wave Therapy), whose mechanisms of action have been widely demonstrated with innumerable and reliable scientific papers in which last years.

***Corresponding author**
César Eisner, Shockwave Argentina, Buenos Aires, Argentina.

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Introduction

Historically, both the diagnosis of ED and the assessment of the results of the various therapeutic options have been mainly clinical, and beyond the existing complementary studies, even today they are partly assessed subjectively through questionnaires.

Since the beginning of the 21st century, low-intensity focused shock wave treatments (LI-ESWT) applied to Male Sexual Dysfunctions have been implemented with good results in clinical practice, but their acceptance by the medical community did not have an absolute consensus. due to ignorance of the scientific foundations that support them.

Fortunately, the continuous and immense contribution of researchers, the development of new diagnostic technologies and the activities carried out by the ISMST (International Society For Medical Shockwave Treatment) and the ONLAT (Ibero-Latin American Federation of Shockwave Societies and Associations in Medicine) and Tissue Engineering), have contributed to a deeper understanding of the biological mechanisms that underlie the increasingly better results obtained with this type of treatment.

Goals

The objectives of this work are

1. Demonstrate the usefulness of treatments with low-intensity focused shock waves for vascular-fibrogenic Erectile Dysfunction and Peyronie's Disease.
2. To demonstrate the usefulness of Shear Wave Elastography and color Doppler echo without the use of vasoactive drugs in the diagnosis of vascular-fibrogenic Erectile Dysfunction and Peyronie's Disease, as well as in monitoring the results obtained with Wave Treatment Low Intensity Focused Shock.
3. Consider what priority should be given to Treatment with Low Intensity Focused Shock Waves among the various therapeutic options for Erectile Dysfunction and Peyronie's Disease.

Shock Wave Equipment 2d-Swe Equipment

Material and Methods

In relation to ED, in order to achieve efficient therapeutic results, an accurate diagnosis is essential, since not all ED can be treated with LI-ESWT. Ultrasound diagnosis has evolved in recent years allowing the implementation of mpUS (Multiparameter Ultrasound) in all transducers, which includes two-dimensional echography (BE), two-dimensional color echodoppler (CE), power-angio, microvascular, spectral, and Bidimensional Shear Wave Elastography or 2D-Shear Wave Elastography (2D-SWE) simple, simultaneous and superimposed qualitative-quantitative (TriVu), through which better diagnoses are made with a significant increase in sensitivity, specificity, predictive values and AUROC (especially in the differential diagnosis between benign and malignant tumors). In its beginnings, Elastography, an imaging diagnostic method that allows to assess the elasticity (or rigidity) of tissues, began to be used with its Strain (by compression) or Quasistatic modality, assessing the elastic deformation of biological tissues, but qualitatively or semi-quantitatively and operator dependent, so the reliability of the method was initially discredited.

Currently, the 2D-SWE modality allows a qualitative diagnosis (on a color scale that goes progressively from blue (soft) to red (hard), quantitative (in kilopascals or meters/second), and in a Non-Operator Dependent manner, since the system does not assess tissue deformation, but rather measures the speed of transverse attenuation of ultrasound in a given area, where the higher the speed, the greater the stiffness, thus becoming a highly reliable diagnostic method.

For the present work, the monitoring of the images was carried out with an Aixplorer ultrasound diagnostic equipment, version 12, from the French company Supersonic Imagine, with a linear SL 15-4 transducer (up to 15 MHz), which has color Ecodoppler and Elastography. qualitative-quantitative shear wave (2D-SWE), and treatments with an electromagnetic equipment of focused shock waves brand Storz Medical model Duolith SD1 Ultra of Swiss origin.

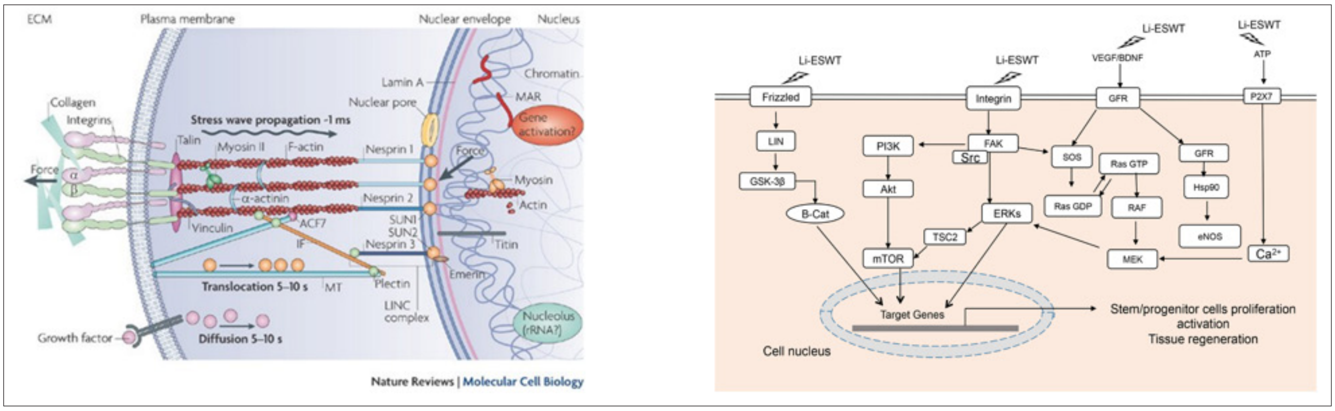
The LI-ESWT action mechanisms are based on mechanotransduction, which is defined as the process by which a physical stimulus (such as a shock wave) generates a biological response.

Through it, the physical stimulus generated by the low-intensity focused shock waves promotes at the cellular level, following the signaling pathways Wnt, ERK, FAK, SRE, ATP and BDNF, among others (Dr.Tom Lue, from the University of San Francisco, USA, January 2019) the nuclear transcription of growth factors (VEGF, TGFß1, eNOS, neurotrophic factors, etc.) and structural proteins (actin, myosin, myelin, etc.) achieving the selective and specific responses necessary for repair the affected tissues, vessels or nerves, trying to restore the anatomical and/or functional eutrophism of the penis, similar to a normal healing process.In this way, the LI-ESWT will promote in CC the replacement of fibrous tissue or with a higher percentage of type I collagen by new muscle fibers and type III collagen (more elastic), recovering erectile function by achieving greater compliance, restoring the penile retraction, penile curvature and correcting VF caused by increased TA stiffness ("venous microleakage").

And in cases of penile varicocele (responsible for a "macro venous leak"), the mechanism of therapeutic action produced by the shock waves will be to generate turbulence that causes the disruption of venous flow and its subsequent recanalization and redirection through smaller vessels. caliber, suitable for generating an efficient veno-occlusive mechanism, as well as reducing fibrosis, which, by increasing tissue pressure on the veins, could be responsible for causing venous dilatations.

Other potential causes of varicocele or phleboectasia are BPH (due to compression of the Santorini periprostatic plexus), obesity (due to increased abdominal pressure) or disorders of the venous walls due to aging.

For all of the above, fundamentally with the use of BE, CS and 2D-SWE we can identify tissue alterations, as well as quantify vascular diameters, CC or TA stiffness, and objectively assess the therapeutic response obtained with LI. -ESWT, since its effects reduce the rigidity of the CC, of the TA and the diameter of the dilated veins.



Mechanotransduction Signaling pathways in the penis [1,2].

Diagnosis

Considering that ED is multicausal, an in-depth questioning of patients should be initially called for to rule out psychogenic or organic, surgical factors (for example: radical prostatectomy), the intake of drugs whose side effects affect erectile function (beta-blockers, antiandrogens, some antidepressants, etc.), or take into account contraindications typical of LI-ESWT, such as the presence of pacemakers, arrhythmias, coagulation disorders, and anticoagulated patients or patients with infections, tumors, or penile prostheses [3-10].

Even so, it will be of fundamental importance to perform a CE (without injection of vaso-active drugs) and a 2D-SWE of the penis to verify the alteration of the intervening mechanisms such as the presence of vascular dilatations in the trunk and roots, or an increase in the rigidity of the CC or the TA, since the therapeutic results of the LI-ESWT will be directly related both to the changes in the images obtained and to the clinical response of the patients [11-20].

CS without the use of vasoactive drugs has the ability to demonstrate the presence of venous dilation both in the trunk and in the penile roots, so observing dilated veins (>1.5 mm) in flaccidity directs us towards the diagnosis of a Venous Leak (VF), given the vascular inability to contribute to an efficient veno-occlusive mechanism.

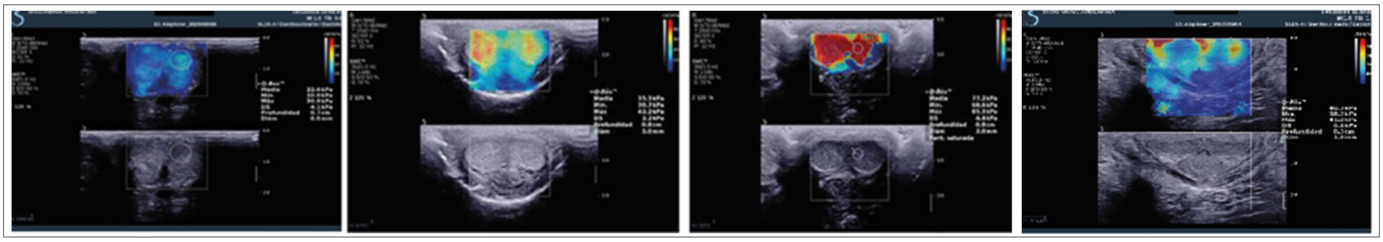
The intention of performing the CE avoiding the injection of vasoactive drugs, is that the hemorrhage generated by the needle when entering the CC, demonstrated with the 2D-SWE to leave fibrosis sequelae that will limit the compliance ("expansive capacity") of the cavernous smooth muscle (producing severe fibrogenic ED, with values generally above 100 kPa).

The hematoma caused in the CC will not be visible on the skin due to the containment of the TA and Buck's fascia. The presence of venous dilatations resulting from an increase in the rigidity of the CC are indicative of a "macro" Venous Leak (responsible for a rapid loss of erection) in a similar way and comparable to the hepatic mechanism, where hypertension portal consequent to parenchymal stiffness due to hepatic fibrosis is determined indirectly by the increase in the caliber of the portal vein (> 15 mm), causing retrograde flow and collateral circulation with perivesicular varicose veins, in the skin of the abdomen (in "jellyfish head"), hemorrhoidal, esophageal, etc. Similarly, fibrosis in penile CCs may produce VF, generating venous dilatations that will determine an inefficient veno-occlusive mechanism. The difference in the diagnostic interpretation of VF using color echo Doppler with vasoactive drugs is that the increase in end-diastolic velocity forced by said vasoactive drugs is considered an indicator of VF (a fact that will always happen when the veno-occlusive mechanism fails). while in flaccidity, the failure of the veno-occlusive mechanism can be directly assessed by the increase in venous diameter. On the other hand, the 2D-SWE has the capacity to qualitatively-quantitatively demonstrate the degree of elasticity of the CC and the TA [21-30].

The loss of said elasticity or, in other words, the increase in the central rigidity of the CC, which in many cases is increased simply by the passing of the years, by the application of intracavernous injections, treatments with finasteride, abrupt sexual maneuvers or spontaneous venous ruptures due to capillary fragility, limits the expansive capacity or compliance of the venous sinusoids due to smooth muscle fibrosis and is therefore the cause of fibrogenic ED. In addition, when an increase in CC stiffness above 25 kPa is observed elastographically, arterial insufficiency due to vascular compression will be suspected, which will increase in direct proportion to the increase in stiffness.

Another cause of ED can be due to loss of the elastic capacity of the TA (composed of 95% type III collagen and 5% elastin), causing a "micro" VF as the subalbugineous vessels cannot be efficiently occluded. In these cases, the increase in rigidity in the CCs will not be central but peripheral, observing in the 2D-SWE an image in the shape of a ring, totally or partially, surrounding the CCs [31-35].
And when the increase in rigidity occurs mainly at the level of the intercavernous septum, in addition to a micro VF, a picture of penile retraction may appear. The increased stiffness of the TA can be attributed to a replacement of type III collagen by collagen type I, less elastic, or to the reduction of the percentage of elastin in its composition.

Therefore, only those patients with what we could call "vascular-fibrogenic" ED, previously diagnosed by CE or 2D-SWE, may be suitable for a successful LI-ESWT, regardless of the presence of other etiopathogenic factors, which simultaneously and in parallel will require their specific treatment. (psychogenic, neurogenic, drug, hormonal, cardiovascular or metabolic) [36-40].



1°) Focal edema 2°) Diffuse fibrosis 3°) Fibrous plaque 4°) Calcified plaque

Treatment

At present, I-PDE5 (sildenafil, tadalafil, vardenafil, avanafil) are the first choice treatment for ED. Its action allows, after erogenous stimulation, firm and sustained erections, since they keep cGMP levels high. cGMP promotes the egress of intracellular Ca+ into the extracellular matrix (ECM), causing muscle relaxation and allowing venous expansion and filling. This action is reversed with the appearance of phosphodiesterase 5 (PDE5). However, if the CC or TA present an increase in their stiffness (evidenced with 2D-SWE) either due to fibrosis, an increase in type I collagen fibers or a decrease in muscle fibers, adequate compliance will not be obtained and therapeutic efficacy will decrease. of the I-PDE5. Not knowing this condition can lead to vascular disorders at the heart or brain level due to overdose [41].

For these reasons, reducing CC rigidity to treat vascular-fibrogenic ED, penile retraction, or penile curvature is one of the proposed objectives to be achieved with LI-ESWT.

Tissue stimulation with low intensity focused shock waves promotes the synthesis of new muscle fibers, the synthesis of type III collagen and the transdifferentiation of fibroblasts into myofibroblasts, allowing an increase in the elasticity of the treated areas to be obtained. We must bear in mind that in cases of PD with fibrous or calcified plaques, the therapeutic objective will not be to eliminate the plaques but to reduce the rigidity of the periplaque tissue, which is truly responsible for the curvature. (In addition, calcified plaques do not have the ability to respond biologically to shock wave stimulation).

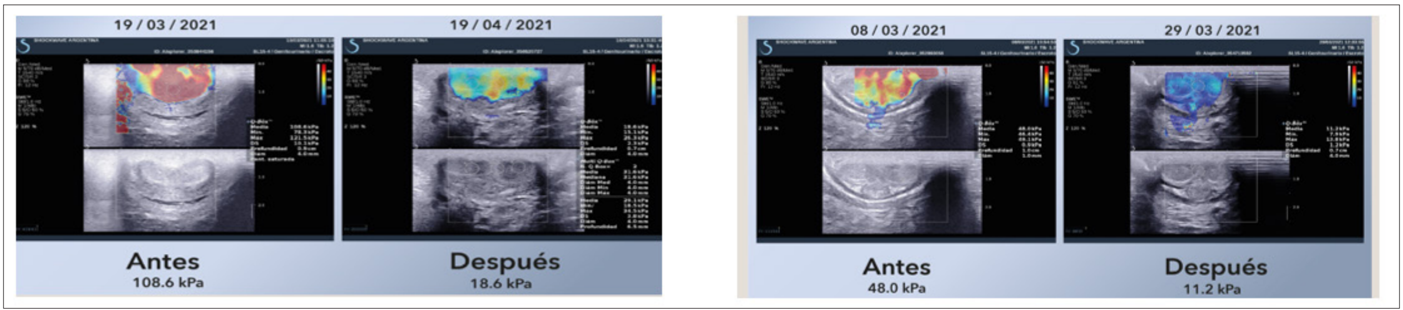
And in cases of VF diagnosed by an increase in venous caliber (> 1.5 mm), LI-ESWT's ability to embolize dilated veins by disrupting venous flow will make it possible to achieve recanalization and redirection of said venous dilatations. Proof of embolization can be determined by venous hypoechogenicity and disappearance of posterior sonic enhancement, color Doppler signal, and spectral waveform [42,43].

In young men or without ED, the mean CC stiffness is below 25 kPa (Trama F. et al. April 2021), while all patients with mean stiffness with values above the ED report ED. 50 kPa, regardless of age or comorbidities (DBT, HTA, Dyslipidemia, etc.). On the other hand, although each answer is individual, in general the application of 6 LI ESWT sessions, at a rate of 3000 waves per session, 1 to 2 times a week, with a frequency of 4 Hz and with an energy of 0.25 mJoules/mm2, manages to reduce the stiffness values of the CC between 5 kPa to 15 kPa average per session (depending on age and the regenerative conditions of each patient), presenting the results obtained with a direct correlation with clinical improvement, either without the use of I-PDE5 or with a better erectile response at low doses, given the lower tissue resistance to vasodilation. These results can be assessed with 2D-SWE throughout the treatment and, obviously, the adjustment of the number of sessions should be estimated from the initial stiffness values [44,45].

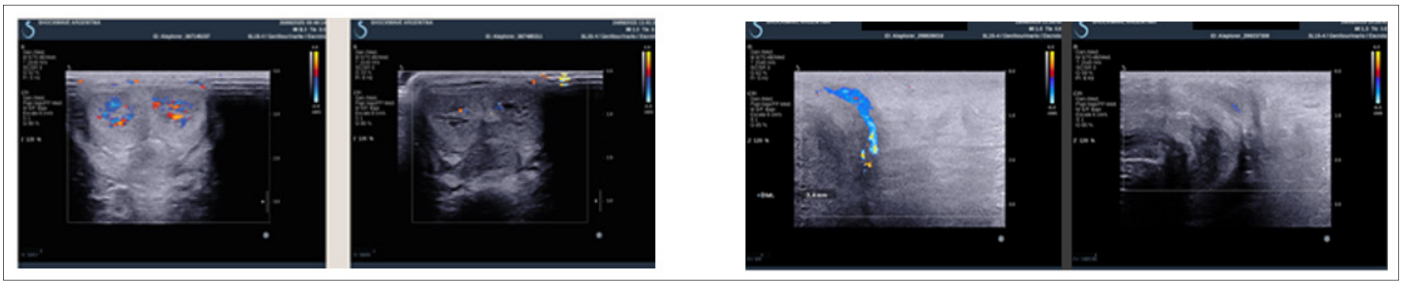
In cases of neurogenic ED Post-RP (radical prostatectomy) with nerve sparing, previous EMG of the CC w/sensory and motor conduction velocity in order to compare the previous state with the final results of the treatment, more extensive protocols are used (12 sessions of 1500 waves each) and with lower energy levels (not greater than 0.15 mJoules/mm2), given the high sensitivity of the treated peripheral nerves. And if increased rigidity is simultaneously observed in CC, TA or FV, its treatment should be after that of Post-RP neurogenic ED.

In these cases, from 30 days after the RP, the sooner the treatment begins, the better results can be obtained.

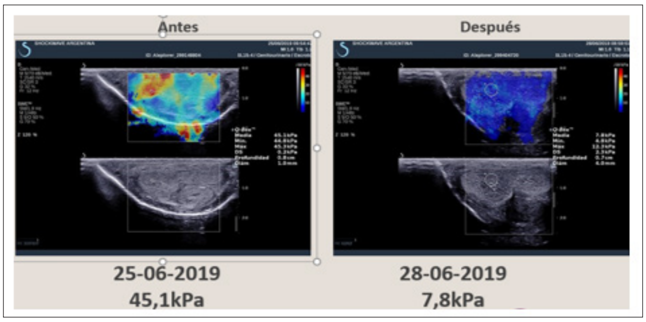
In any case, favorable responses to regenerative therapy have been obtained even after tissue and functional damage have occurred after cavernous nerve injury in operated patients [46-50].



Fibrogenic DE in CC. DE in tunica albuginea



Truncal varicocele (before and after LI-ESWT) Radicular varicocele (before and after LI-ESWT)



Peyronie's disease without plaques (before and after LI-ESWT)

Note the reddish area of upper-right asymmetric stiffness, responsible for the ipsilateral curvature and its resolution post-treatment (blue-soft color).

Results

For the statistical evaluation of this work, 41 male patients who underwent their ED (Erectile Dysfunction) or PD (Peyronie's Disease) treatment of 6 sessions each, between March 2021 and March 2022, were counted.

The types of DE considered were:

- DE F (fibrogenic ED) due to increased tissue stiffness in the center of CCs (with values > 25 kPa)
- Macro VF (vascular venous leak) due to varicocele in the trunk or roots of the CC (with venous diameters > 1.5 mm)
- Micro VF (venous albugineal leak) due to increased (peripheral) stiffness of the BP (with venous leakage through the vessels subalbugineous)
- D. EM (Mixed forms: Fibrogenic ED + Micro FV)
- PE (Peyronie's disease) without plaques. (due to focal edema or diffuse fibrosis)
- AND. P with plates. (fibrous or calcified)

Cases of psychogenic or neurogenic ED, those that were evaluated with other methods (psychodiagnosis or electromyogram of CC with sensory and motor conduction velocity) were not taken into consideration.

The decision to carry out 6 sessions of 3000 waves each, at a power of 0.25 mJ/mm2 and at a frequency of 4 Hz, was based on the empirically estimated average reduction in tissue stiffness (10 kPa, +-5 kPa) until reaching values below 25 kPa, and in monitoring the reduction in venous caliber in cases of varicocele until reaching values of less than 1.5 mm.

For each type of sexual dysfunction, the averages of: cases by pathology, age of the patients, initial value in kPa, final value in kPa, reduction in stiffness in kPa per session, and for cases of macro FV, were considered to be the vascular diameters pre-treatment, post-treatment and average reduction per sesión [51-54].

Of The 41 Patients Evaluated, The Following Were Presented

DEF: 9 (21.95%), Macro FV: 3 (7.31%), Micro FV: 8 (19.51%), DEM: 10 (24.39%), EP s/p: 7 (17 0.07%) and PE c/p: 4 (9.75%).

The Age of the Patients was Between 30 and 76 Years, with the Average Age Per Pathology Being

DEF: 63 years, Macro FV: 50 years, Micro FV: 64 years, DEM: 60 years, EP s/p: 59 years and EP c/p: 66 years.

The Average Initial Values Per Pathology were

DEF: 72.04 kPa, Macro FV: 3.4 mm., Micro FV: 67.87 kPa, DEM: 78.9 kPa, EP s/p: 75.42 kPa and EP c/p: 75.3 kPa

The Average Final Values Per Pathology were

DEF: 14.33 kPa, Macro FV: 0.63 mm., Micro FV: 16.18 kPa, DEM: 19.8 kPa, EP s/p: 23.62 kPa. and EP c/p: 22.37 kPa.

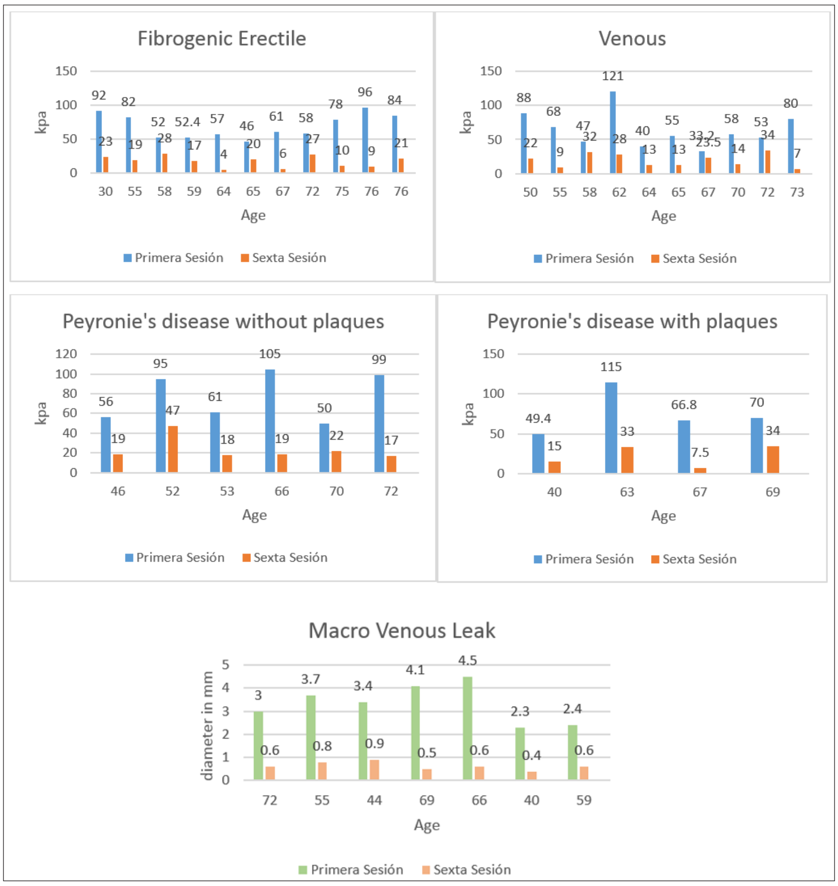
The Average Values of Stiffness Reduction Per Session and Per Pathology were

DEF: 11.54 kPa, Micro FV: 10.50 kPa, DEM: 11.82 kPa, EP s/p: 11.88 kPa and EP c/p: 10.58 kPa.

The mean stiffness reduction value of all forms of ED per session (except Macro FV) was 11.28 kPa.

The average value of stiffness reduction in the PE (with and without plates) per session was 11.23 kPa.

The average value of reduction of the venous diameter per session in the Macro FV: 0.55 mm



Discussion

At present, evidence-based medicine is taken into account, and considering that symptomatic treatments are still being carried out to date or without a prior certainty diagnosis, puts the medical community in the commitment to adjust to these principles.
In addition, having the possibility of carrying out objective, qualitative-quantitative and non-operator-dependent imaging diagnoses, as well as novel therapeutic alternatives that promote natural self-repair mechanisms, points us to a new direction aimed at continuing to improve understanding and results. of ED and PD treatments.

On the other hand, the innumerable investigations initiated since 1985 in relation to the biological mechanisms of action of low intensity focused shock waves, present to date a clear and direct clinical and imaging correlate, as well as certainties regarding their restorative effects. and lack of adverse effects at recommended doses. The limitation of the application of these treatments at the private level can be given by the high cost of the necessary equipment, however, this situation can be resolved at the institutional level.

Conclusion

The abundant evidence of scientific papers presented in recent years strongly supports the application of the LI-ESWT. But before the result of these treatments, obtaining a prior certainty diagnosis with the new diagnostic imaging modalities becomes imperative.

In particular, 2D-SWE has become a medical event, since after BE and CE, it has become a third generation in ultrasound imaging, where for the first time we can quantify tissue stiffness, which also allows us to objectively assess the elastic condition of the CC and TA of the patients before and after the LI-ESWT.

Finally, the demonstration of the therapeutic and statistical results obtained both at the laboratory level and at the clinical and imaging level demonstrated with the LI-ESWT, where favorable responses and absence of adverse effects were obtained in the entirety. of the cases treated, leads us to consider what priority these treatments should have among all the options currently available. Undoubtedly, a greater number of cases will be necessary to consolidate the promising results achieved.

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