

ArtAssist[®]

THE ARTERIAL ASSIST DEVICE[®]

with *endo/shear*[™]
for arteriogenesis

▶ History & Literature Review

Fast Facts - To Keep You On Track

History

In the earliest stages of research, ACI Medical observed significant increases in arterial blood flow while testing a device that applied rapid, high-level compressions to the lower limb.

Excited by these findings, ACI Medical identified the following goals:

1. Determine the mechanisms of action that produced this phenomenon;
2. Define the optimum stimulus for maximizing blood flow to ischemic tissues;
3. Measure the physiological effects on arteriopathic patients;
4. Study the clinical effects on patients with intermittent claudication;
5. Determine its clinical utility for limb salvage in patients with critical limb ischemia

ACI Medical has worked with academic centers across the world to reach these goals.

Literature Review

The following are summaries of the most important published literature on the ArtAssist[®] device.

All references can be obtained at ACIMedical.com/ArtAssist

Studies organized by subject:

- 1. Physiological & Optimization**
- 2. Intermittent Claudication**
- 3. Limb Salvage & Critical Limb Ischemia**
- 4. Arteriogenesis & Collateralization**



1. Physiological & Optimization Studies

Reference 3. Intermittent Calf and Foot Compression Increases Lower Extremity Blood Flow

A.R. Eze, A.J. Comerota, et al. Temple University School of Medicine, Philadelphia, PA, USA. *Am J Surg* 1996; 172:130-5

Investigations at Temple University showed that rapid, high pressure intermittent pneumatic compression (IPC) not only increased popliteal artery flow (using duplex imaging) but also significantly increased foot skin perfusion using laser Doppler fluximetry.

We learned the importance of compressing both foot and calf regions in that they both contributed to enhancement of popliteal arterial flow and cutaneous flow at the foot.

Reference 5. Intermittent Foot and Calf Compression: Effects on Arterial Blood Flow and Value in the Treatment of Intermittent Claudication

A.N. Nicolaides and K.T. Delis. Presented at the 24th Annual Symposium on Current Critical Problems, New Horizons & Techniques in Vascular and Endovascular Surgery; November 1997

A randomized controlled study performed by Nicolaides and Delis found that after 5 months of treatment (Group 1 used the ArtAssist® device and 75 mg/day of aspirin and Group 2 took the same amount of aspirin alone), only Group 1 showed significant increases in initial and absolute claudication distances, resting ABI, post exercise ABI and resting popliteal artery volume flow (vFI).

One year follow-up showed that the benefits gained by Group 1 were well-sustained; most likely due to arteriogenesis.

Reference 9. Acute Effects of Intermittent Pneumatic Compression on Popliteal Artery Blood Flow

N. Labropoulos, et al. Department of Surgery, Loyola University Medical Center, Maywood, IL, USA. *Arch Surg* 1998; 133:1072-5.

Labropoulos, et al found that, when investigating acute effects on normal limbs, there was significant increase in popliteal blood flow. Furthermore, they observed a significant increase in the time averaged velocity, most notably due to a dramatic drop in the peripheral vascular resistance, which allowed peak systolic and end diastolic flow velocities to increase. No immediate change in artery diameter was observed.

Reference 12. Optimum Intermittent Pneumatic Compression Stimulus for Lower-limb Venous Emptying

K.T. Delis, A.N. Nicolaides, et al. Irvine Lab for Cardiovascular Investigation and Research Academic Vascular Surgery, Imperial College School of Medicine, St. Mary's Hospital, London, UK. *Eur J Vasc Endovasc Surg* 19, 261-9 (2000).

Understanding that reduction in venous pressure was an important mechanism of action, investigators performed an optimization study that measured invasive foot vein pressures. They determined the optimal stimulus that was then incorporate into the device used in future clinical testing and the commercial device: foot, followed by calf compression to 120 mmHg in 330 msec rise time and fall time with 3 second pressure hold, 3 times per minute.

Reference 15. Rapid intermittent compression increases skin circulation in chronically ischemic

legs with infra-popliteal arterial obstruction

P.S. van Bemmelen, et al. Division of Vascular Surgery, State University of New York, Stony Brook. VASA 2000; 29:47-52.

(In reference also to van Bemmelen's studies on page 6) van Bemmelen, et al continued their research with the optimized device and showed the significant increase in skin circulation using laser Doppler fluximetry in patients with infra-popliteal disease. He also showed angiographic evidence of another mechanism of action: arteriogenesis – the formation of collateral arteries that takes place after several months of use of the ArtAssist® device. Further work on rabbits showed that collateralization is indeed an important, long-term mechanism of action.

Reference 22. Effects of intermittent pneumatic compression of the calf and thigh on arterial calf inflow: A study of normals, claudicants, and grafted arteriopathies

K.T. Delis, A.N. Nicolaides, et al. Imperial College School of Medicine, St. Mary's Hospital, London, UK. Surgery; 2000, vol. 129, no. 2, p. 188-195.

At St. Mary's Hospital in London, investigators found that thigh and calf combination IPC therapy produced significant increases in volume flow, mean velocity and end diastolic velocity, while the pulsatility index decreased. The same was also true with separate IPC therapy (thigh only or calf only), though the results were less pronounced.

Reference 35. Haemodynamic effect of intermittent pneumatic compression of the leg after infrainguinal arterial bypass grafting

K.T. Delis, et al. Regional Vascular Center, Surgery and Department of Academic Cardiology, St. Mary's Hospital, Imperial College School of Medicine, London, UK. Br J Surg 2004; 91:429-34.

At St. Mary's Hospital in London, Delis, et al found that IPC of the foot and calf was most effective in enhancing mean velocities, peak systolic velocities, end diastolic velocities when applied together with a one second delay. They concluded that IPC therapy could reduce the risk of bypass graft thrombosis.

Reference 56. Integrity of venoarteriolar reflex determines level of microvascular flow enhancement with intermittent pneumatic compression

M. Husmann, et al. Div. of Angiology, University Hospital Bern, Div. of Angiology, University Hospital Zurich, Department of Vasc Surgery, Athens Medical Center, Marousi, Athens, Greece, and Imperial College School of Medicine, Zurich. J Vasc Surg 2008; 48:1509-13.

A joint study between Swiss and Greek academic institutions found that, since patients with PAD had their VAR abolished when using the IPC device, skin blood flow was augmented.

2. Intermittent Claudication Studies

Reference 39. Effect of Intermittent Pneumatic Compression of Foot and Calf on Walking Distance, Hemodynamics and Quality of Life in Patients with Arterial Claudication, A Prospective Randomized Controlled Study with 1-Year Follow-up

K.T. Delis and A.N. Nicolaides. Imperial College, Faculty of Medicine, St. Mary's Hospital, London, UK and Mayo Clinic, Division of Vascular Surgery, Rochester, MN, USA. *Annals of Surgery* March 2005; Vol. 241, no. 3:431-4.

A randomized controlled trial by Delis and Nicolaides showed that foot and calf IPC emerged as an effective, high-compliance, complication-free method for improving the walking ability and pressure indices in stable claudication, with a durable outcome. All patients' quality of life was surveyed with the short-form 36 Health Survey Questionnaire. Those who underwent foot and calf IPC showed significant improvements.

Reference 40. Rapid foot and calf compression increases walking distance in patients with intermittent claudication: Results of a randomized study

G. Ramaswami, et al. Dept of Surgery, New York Methodist Hospital, LSU School of Medicine, UC San Diego, VA Hospital Bronx, NY. *J Vasc Surg* May 2005; vol. 41, no. 5; 794-801.

Ramaswami's RCT on Veterans Administration Hospital patients with intermittent claudication also showed that the significant increases in pain free walking distance were sustained after one year.

Reference 41. Improvement of the walking ability in intermittent claudication due to superficial femoral artery occlusion with supervised exercise and pneumatic foot and calf compression: A randomized controlled trial

S.K. Kakkos, et al. Imperial College of Science, Technology and Medicine, London, UK. *Eur J Vasc Endovasc Surg*. August 2005; Volume 30: 164-175.

This was a three-arm RCT of ArtAssist® compression, supervised exercise and unsupervised exercise done by Kakkos, et al. They showed almost tripling of pain free walking distances and increased ankle pressures in intermittent claudication patients in the ArtAssist® device group and supervised exercise group while no benefits were observed in the unsupervised exercise group.

Reference 63. Using intermittent pneumatic compression therapy to improve quality of life for symptomatic patients with infrapopliteal diffuse peripheral obstructive disease

Chang ST, Hsu JT, Chu CM, Pan KL, Jang SJ, Lin PC, Hsu HC, Huang KC. *Circ J*. 2012;76(4):971-6. Epub 2012 Feb 4. Division of Orthopedic Surgery, Chia-Yi Chang Gung Memorial Hospital, 6 Sec. West Chai-Pu Road, Pu-TZ City, Chai-Yi Hsien, Taiwan. cst1234567@yahoo.com.tw

This Taiwan-based controlled study of 31 patients with skin lesions due to PAD documented changes in walking distance, quality of life, and TcPO₂. The study group showed significant increases in walking distance compared to the control group. Quality of life also increased significantly for study patients. Distal TcPO₂ measurements were improved for the study group. Study patients for this trial benefited from ArtAssist® device IPC therapy despite their poor prognoses.

Reference 65. Randomized study on the effects of different strategies of intermittent pneumatic compression for lower limb claudication

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A. Berni; L. Tromba; L. Falvo; F. Tartaglia; M. Sgueglia; S. Blasi; P. Polichetti. "Sapienza" University of Rome, Italy, Department of Surgical Sciences. *G Chir* Vol. 30 - n. 6/7 - pp. 269-273. Giugno-Luglio 2009.

This Italy-based study compared the efficacies of various IPC regimens (e.g. Group 1: control, Group 2: 1 hour T.I.D. for four months, Group 3: 2 hours once per day for four months, and so on). The highest results came from Group 3, where therapy compliance was 83%. Benefits gained from IPC therapy lasted about one year after the end of treatment.

3. Limb Salvage & Critical Limb Ischemia Studies

Reference 26. Limb salvage using high-pressure intermittent compression arterial assist device in cases unsuitable for surgical revascularization

P.S. van Bemmelen, et al. Dept of Vasc Surg and Podiatry, VA Med Ctr, Northport, NY and Div. Vasc Surg, SUNY at Stony Brook. *Arch Surg*. 2001; 136:1280-1285.

Van Bemmelen, et al were the first to examine the possible impact of ArtAssist® device compression in limb salvage of critically ischemic limbs. Patients that used the device at least 2.4 hours per day showed improved arterial pulsatility and limb salvage compared to those that used the device for only about an hour per day. This study set the stage for additional limb salvage trials by Louridas and Esan.

Reference 42. Hemodynamic effects of intermittent pneumatic compression in patients with critical limb ischemia

N. Labropoulos, et al. Department of Surgery, Loyola University Medical Center, Maywood, IL. *J Vasc Surg* October 2005; Vol. 42, No. 4: 710-716.

Labropoulos, et al measured arterial flow in the popliteal artery, medial gastrocnemial artery, genicular collateral artery and skin blood flow of the foot in patients with critical limb ischemia shown by arteriography. Flow was increased significantly in all measured vessels and cutaneously even in end stage ischemic disease.

Reference 44. A randomized, placebo-controlled limb salvage trial using the ArtAssist® pneumatic compression device

George Louridas, MD. Section of Vascular Surgery, University of Manitoba, Winnipeg, Canada, 2006. Presented at the Winnipeg Vascular & Endovascular Symposium April 2006.

Louridas performed a pilot study to determine if ArtAssist® compression was efficacious in preventing amputations in critically ischemic limbs that were unsuitable for surgical revascularization. Encouraging results supported the larger RCT using a placebo device. With a 24 month follow-up, the ArtAssist® device group had an 86% limb salvage rate in non-renal failure patients compared to a 32% limb salvage rate for the control group.

Reference 57. Enhanced cell therapy strategy to treat chronic limb-threatening ischemia

D. Eton and H. Yu. Baptist Cardiac and Vascular Institute, Miami, Dept of Surgery, University of Miami Miller School of Medicine, Miami and Miami Veteran's Administration. *J Vasc Surg* 2010; 52:199-204.

In Miami, Drs. Eton and Yu explored an adjunct therapy strategy with the ArtAssist® device and the modified dosage of granulocyte-colony stimulation factor (G-CSF). The ischemic patients studied showed remarkable

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clinical, hemodynamic and angiographic improvement. Further study is ongoing.

Reference 59. Sequential compression biomechanical device in patients with critical limb ischemia and nonreconstructible peripheral vascular disease

S. Sultan, et al. Dept. Vasc and Endovasc Surgery, Western Vascular Institute and Dept. Vasc and Endovasc Surgery, Galway Clinic, Galway, Ireland. *J Vasc Surg* 2011; 54:440-7.

In a Galway study, Sultan, et al found that patients who suffered rest pain and/or tissue loss due to CLI yielded a 94% limb salvage rate over a period of 3.5 years. In addition to enhancing limb salvage, therapy with the ArtAssist® device non-operatively reduces the length of hospital stay for non-reconstructable patients and is a more cost-effective solution than amputation.

4. Arteriogenesis & Collateralization Studies

Reference 32. Angiographic improvement after rapid intermittent compression treatment [ArtAssist®] for small vessel obstruction

P.S. van Bemmelen, et al. Dept. of Surgery, Div. of Vascular Surgery, SUNY at Stony Brook, NY. *Ann Vasc Surg* 2003; 17:224-228.

A patient prepared for below-knee amputation instead underwent treatment with the ArtAssist® device and developed extensive collateral arteries in the calf. This resulted in limb salvage and the subsiding of rest pain (only a modified transmetatarsal amputation was needed). This study by van Bemmelen et al encourages physicians to compare their patients' arteriograms after therapy with the IPC device.

Reference 48. Long-term intermittent compression increases arteriographic collaterals in a rabbit model of femoral artery occlusion

P.S. van Bemmelen, et al. Dept. of Surgery and Pathology, Temple University, Philadelphia, PA, USA. *Eur J Vasc Endovasc Surg* 34, 340-346 (2007).

Each of the New Zealand rabbits in this study by van Bemmelen, et al showed larger and more numerous collateral arteries in experimental limbs after 10 weeks on a modified ArtAssist® device.

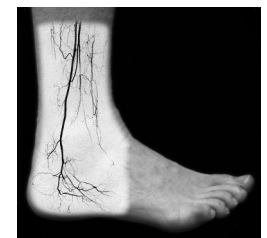
Reference 60. Impact of a single session of intermittent pneumatic leg compressions on skeletal muscle and isolated artery gene expression in rats

B.T. Roseguini, et al. Department of Biomedical Sciences, University of Missouri, Columbia, MO. *Am J Physiol Regul Integr Comp Physiol*. 2011 Dec; 301(6)R1658-68. Epub 2011 Sep 28.

Roseguini, et al at the University of Missouri, in an effort to understand exactly what happens at the molecular level, found that IPC is able to facilitate arteriogenesis by stimulating gene expression of growth factors.



Before



After 4 months' ArtAssist device treatment

van Bemmelen, et al., *Ann Vasc Surg* 2003

In Summary...

- ▶ The ArtAssist® pneumatic compression device is a home-use medical treatment for patients with peripheral arterial disease.
- ▶ Recommended usage is 3 to 6 hours per day for 90 days - the time required to establish collaterals.
- ▶ The mechanisms of action, including arterial collateralization (arteriogenesis), have been well-identified.
- ▶ The device parameters of pressure, timing and compression locations (foot, ankle & calf) have been optimized for PAD.
- ▶ The ArtAssist® device is shown to be effective in increasing pain-free walking distance in claudicants for a sustained period in five independent controlled trials.
- ▶ The ArtAssist® device has been shown to prevent amputations in critically ischemic limbs in three independent studies.
- ▶ This treatment modality is well-tolerated, has no known adverse reactions and represents a cost-effective therapy, especially for patients unable to undergo surgical revascularization.

ArtAssist[®]

THE ARTERIAL ASSIST DEVICE[®]

with *endo/shear*[™]
for arteriogenesis

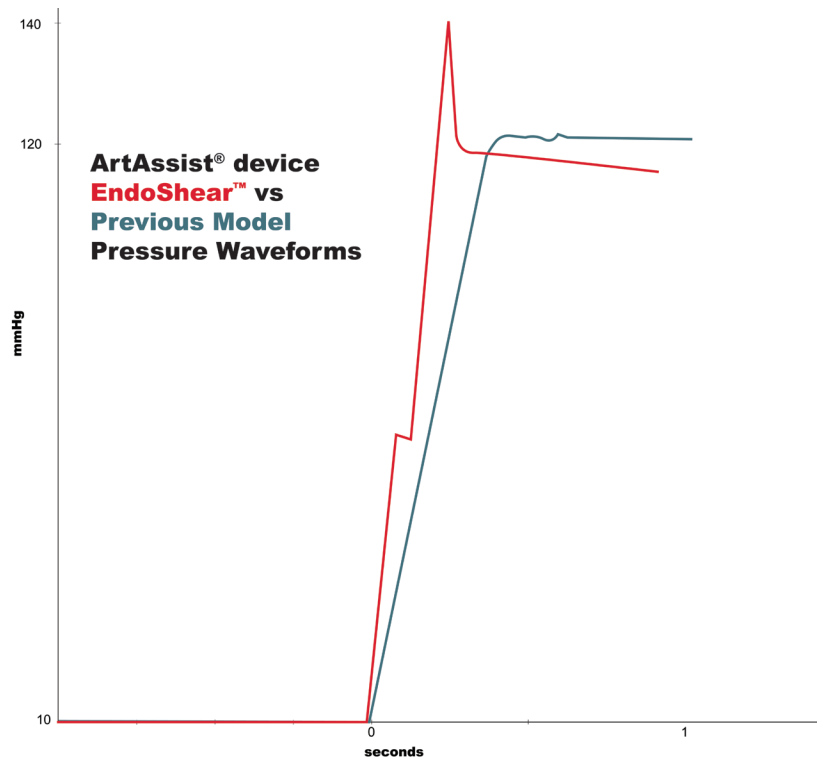
Increased endothelial *shear stress*
promotes *collateral artery growth*

Functionality

- Optimized for collateral artery growth
- Higher endothelial shear stress means higher chance of long-term benefits
- Multiple compression sequence delivers compression & decompression in well under 300 milliseconds
- New adaptive technology senses how much air should inflate cuffs, providing consistent therapy
- FDA 510(k) compliant & patent pending

Ease of use

- 7 lbs. lighter than previous model
- Readily available for patients. See contact information on last page



Arteriogenesis has arrived.[™]

For Prescriptions & Expert Information

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Physician Commentary

“The ArtAssist® device has incorporated the important elements and the optimization of the hemodynamics. Namely, the high-pressure inflation, the rapid inflation, the sequence in between foot and calf, and then the repetition at three times each minute.”

- Anthony Comerota, MD, Vascular Surgeon

“[With the ArtAssist® device] we have a double-mechanism that produces such a major increase in the arterial flow...if you have an increase in the arterial flow, the endothelium is stimulated, it produces nitric oxide and on the long-term, we get a fantastic collateral circulation...that explains why people, after two or three months of using it, can double and triple their claudication distance.”

- Andrew N. Nicolaidis, MS, FACS, Professor of Vascular Surgery

“The ArtAssist® was designed based on research of instantaneous blood flow measurements, which I did with ultrasound and laser...During the use of the device, the patient should start to notice less pain because there’s an immediate increase in the blood flow to the leg and foot. After doing this for a period of three months, the effect of repeated flow increases is similar to muscle training because there is a lasting increase in the natural bypass arteries

formed around the blockage.”

- Paul S. van Bemmelen, MD, Vascular Surgeon



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