



CARDIO VASCU-GROW™ AND PERIPHERAL VASCULAR DISEASE

1. Summary

Lower extremity peripheral vascular disease (PVD) occurs in the blood vessels of the legs and feet. PVD is a progressive disease that involves the narrowing of the leg arteries due to a gradual buildup of plaque. PVD of the lower extremities results in reduced blood flow in the legs, is a major cause of diminished ability to walk and in advanced cases can lead to leg amputation. The primary symptom of lower extremity PVD is a type of leg pain that occurs when a patient is active (e.g., while walking) called intermittent claudication. The pain is caused by inadequate oxygen supply to the legs. In severe cases, patients may experience pain even at rest and pain due to tissue loss or gangrene. Diabetics are at special risk for PVD.

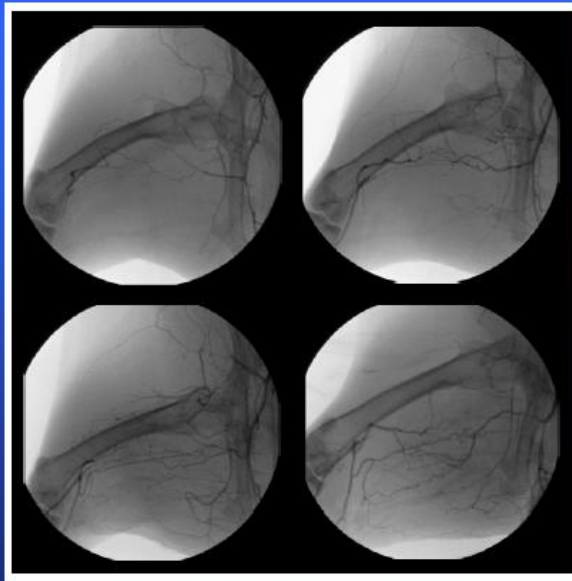
The diffuse nature of PVD often makes it difficult to treat. Estimates of prevalence of PVD in the U.S. range from 8-14 million patients with hospitalization of about 250,000 patients annually. Treatment options include angioplasty, stenting and other catheter-based procedures to dissolve clots. Surgery is often necessary to remove plaque from blood vessels to prevent an embolism from forming or to allow better blood flow through a blocked artery. Bypass grafts are another surgical alternative. In general, surgical procedures carry higher risk and longer recoveries but offer better and longer lasting outcomes. There is a significant need for better therapies. Growing new blood vessels that may improve the blood supply to the legs and feet to decrease pain and prevent tissue loss is very promising research. **Cardio Vascul-Grow™** has been demonstrated to stimulate the growth of new blood vessels when injected near a blocked coronary artery, leading to a significant increase of blood flow around the blockage in the heart. It is possible that a very similar biological process can be duplicated in the legs of PVD patients.

2. Results from CVBT's Current Animal Studies

CVBT has collaborated with the American Cardiovascular Research Institute (Norcross, GA) on two animal efficacy PVD studies. Intramuscular injections of either 10 or 100 ug/kg **Cardio Vascul-Grow™** were given 3 times a week for a 2-week period into ischemic rabbit hindlimbs. Increased blood flow into the leg muscle was observed and new blood vessel growth was noted in the **Cardio Vascul-Grow™**-injected limbs. (See Figures 1 and 2 below.)

Hindlimb Angiograms

Baseline Control
(Day 5)
(25 ± 0.4 vessels)



Vehicle Control
(Day 20)
(46 ± 4 vessels)

60 µg/kg
(Day 20)
(63 ± 5 vessels*)

600 µg/kg
(Day 20)
(63 ± 7 vessels*)

*p<0.05 vs. vehicle control

Figure 1. Effect of Cardio Vasu-Grow™ in Stimulating New Blood Vessel Growth in Rabbit Ischemic Hindlimbs. Hindlimb angiograms are shown that were performed either 5 days (baseline control) or 20 days after the animals were subjected to a surgical procedure resulting in hindlimb ischemia. At both the 60 ug/kg and 600 ug/kg total dose of **Cardio Vasu-Grow™**, a statistically significant increase in the number of blood vessels was observed in the ischemic leg muscles that were injected with **Cardio Vasu-Grow™** compared to animals treated with the placebo vehicle control.

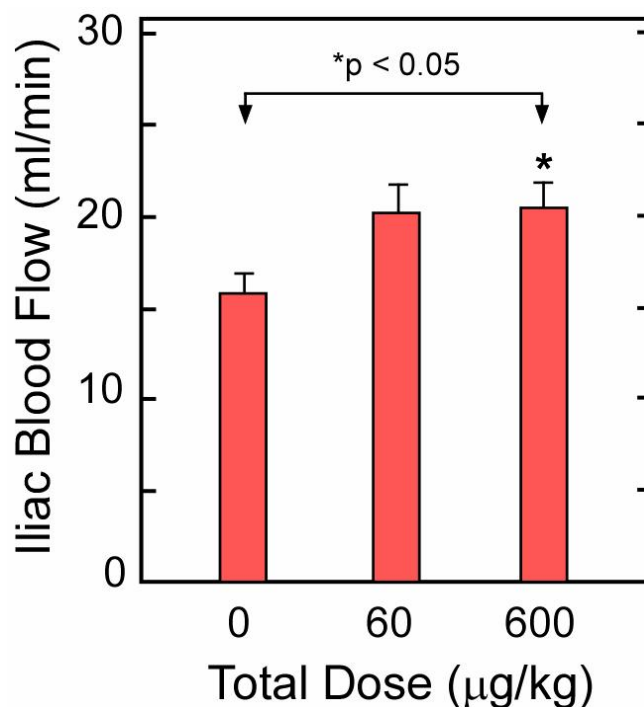


Figure 2. Cardio Vasu-Grow™ Increases Iliac Basal Blood Flow. The basal blood flow through the iliac arteries supplying blood to ischemic rabbit hindlimbs is plotted vs. the total intramuscular dose of Cardio Vasu-Grow™ given over two weeks. The higher dose causes a statistically significant increase in basal iliac basal blood flow.

3. Summary and Conclusions

These studies demonstrate that **Cardio Vasu-Grow™** can cause a statistically significant increase in new blood vessel formation and basal iliac blood flow in an animal model of peripheral vascular disease. As estimates of the prevalence of this disease range from 8-14 million patients in the United States alone, this could be a very significant new medical indication for CVBT's drug if approval is eventually granted. CVBT is aggressively pursuing the development of **Cardio Vasu-Grow™** for peripheral vascular disease. Toxicity studies to support an Investigational New Drug (IND) application to the U.S. FDA are currently ongoing as well as preparation of clinical protocols for Phase I studies in diabetic patients.