

# Clinical implementation of the Humacyte human acellular vessel: Implications for military and civilian trauma care

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## ABSTRACT:

The incidence of wartime vascular injury has increased and is a leading cause of mortality and morbidity. While ligation remains an option, current resuscitation and damage control techniques have resulted in vascular repair being pursued in more than half of wartime injuries. Options for vascular reconstruction are currently limited to autologous vein or synthetic conduits, choices which have not changed in decades, both of which have problems. Autologous vein is preferable but requires time to harvest and may not be available. Synthetic grafts are poorly resistant to infection and associated with thrombotic complications. Recognizing this capability gap, the US Combat Casualty Care Research Program has partnered with academia and industry to support the development and clinical introduction of a bioengineered human acellular vessel. This human acellular vessel has the potential to be an off-the-shelf conduit that is resistant to infection and incorporates well into native tissues. This report reviews the rationale of this military-civilian partnership in medical innovation and provides an update on the clinical use and ongoing study of this new vascular technology. (*J Trauma Acute Care Surg.* 2019;87: S44–S47. Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.)

**LEVEL OF EVIDENCE:** Therapeutic, level III.

**KEY WORDS:** Vascular trauma; vascular conduit; trauma surgery.

Vascular injury is a significant contributor to loss of life and limb in the civilian and military setting.<sup>1</sup> The incidence of vascular trauma in combat has increased from a rate of 2% to 3% during the Vietnam War to more than 15% in the wars in Iraq and Afghanistan.<sup>2,3</sup> The increased rate is multifactorial and partly due to force protection measures that reduce the incidence of lethal torso and head injuries, and the use of modern extremity tourniquets to control extremity hemorrhage. More effective damage control resuscitation strategies used within a data-driven, military trauma system also means that more injured service members are surviving to have vascular injury treated.<sup>2–4</sup>

The operative approach to vascular injury has been transformed since World War II when ligation (and often amputation) was the dictum.<sup>5</sup> Reports from the recent wars show that some type of revascularization is now pursued in more than half of cases, and that early limb salvage is nearly 90%.<sup>2,3,6,7</sup> While the principles of vessel ligation and of “life over limb” are still important, modern damage control resuscitation and use of temporary vascular shunts have allowed pursuit of life and limb in a greater number of complex cases.<sup>8–10</sup> At the same time, research has shown that the ischemic threshold of the limb is less than the traditional “6-hour” rule and that reperfusion should be restored

within 3 hours or less if quality or functional limb salvage is to be expected.<sup>11–13</sup>

This transformation has occurred in an era in which training opportunities in open vascular surgery have decreased significantly.<sup>14,15</sup> Subspecialization and reliance on endovascular approaches have meant that today's surgeon has less experience exposing, preparing, and sewing saphenous vein conduit.<sup>15</sup> Now more than ever, there is a need for an “off the shelf,” infection-resistant vascular conduit that can be quickly used by nonspecialized surgeons to treat vascular injury. This report reviews one such technology resulting from a military-civilian partnership in medical innovation.

## EXISTING CONDUIT OPTIONS

Autologous vein—most frequently the great saphenous—is the preferred and most often used conduit in the management of wartime vascular injury. In the setting of extremity trauma this most commonly involves interposition graft replacement of the injured artery.<sup>2,3,16,17</sup> Studies from the military trauma system and the Combat Casualty Care Research program show that saphenous vein is an effective conduit in this setting with good patency rates and tissue incorporation, although thrombosis and infection occur in 10% to 20% of cases.<sup>2,3,16,17</sup>

Despite favorable outcomes associated with vein, its use is precluded in a number of cases. For example, saphenous vein may be damaged and unusable in situations where both lower extremities are injured (i.e., complex blast or penetrating injuries).<sup>18,19</sup> In austere environments, where quick, damage control operations are the rule, the time and resources required to surgically identify, remove, and prepare the saphenous vein may be a limiting factor. The time needed to harvest and prepare the saphenous vein is particularly problematic in multiple casualty situations in which a number of operations need occur in a short period.<sup>20</sup> Finally,

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the surgical wound created to remove the vein is not insignificant and itself becomes infected in 5% to 10% of cases.<sup>6-8</sup>

When saphenous vein is not available, synthetic grafts including expanded Polytetrafluoroethylene (ePTFE) (i.e., Gortex) and Dacron are common alternatives. Synthetics are used in 6% to 7% of military cases and have been found to be less durable and resistant to infection than autologous vein.<sup>16,17,21,22</sup> Registry data and anecdotal observations have shown that synthetic conduit is poorly incorporated in large soft tissue wounds in which surrounding tissue viability is questionable, and in which a greater degree of contamination exists. Poor incorporation and susceptibility to contamination can lead to long-term graft infection, with or without anastomotic disruption, and thrombosis. In the military experience, synthetic conduit has been shown to have lower patency than saphenous vein, with studies showing thrombotic complications in nearly 50% of the cases.<sup>16,17</sup>

Other less-common conduit options include xenogeneic tissues, such as bovine carotid artery and cryopreserved cadaveric vessels. Although interesting and useful in some situations, large scale availability and use of these conduits—especially for the acute phase of injury management—have been limited by the ability to efficiently and reproducibly procure, ship, and safely store these products. The experience of these xenogenic conduits is almost entirely in the realm of elective or semielective chronic vascular disease conditions, and there are no reports of their use in the acute management of wartime vascular injury. The clinical data available for these types of conduits comes from small studies which suggest lower patency than autologous vein and higher risk of structural complications, such as stenoses and or aneurysm formation. Postimplantation immune response has also been reported in patients in whom cryopreserved vessels have been used, possibly leading to graft durability issues.<sup>23</sup>

## THE IDEAL VASCULAR CONDUIT

The ideal material for vascular reconstruction would combine the favorable safety, efficacy, and durability profiles of autologous vein, with the expediency and predictable sizing (i.e., diameter and length) of an “off-the-shelf” product. Such a conduit would eliminate the technical expertise and time required for vein harvest as well as associated wound complications. A perfect conduit would also have physical characteristics that make it easy to handle and sew, and biologic properties allowing it to become incorporated by the host patient. The military's medical research program has responded to this requirement in vascular injury management and made this type of enhanced conduit a top priority. As with other research and innovation efforts, the military has partnered with civilian academia and private industry to develop a new product with many of the features of an ideal vascular conduit. Leveraging scientific breakthroughs in the field of regenerative medicine and the enterprising nature of private industry, this effort has resulted in the growth of novel human acellular vessels (HAV) that hold promise in addressing this high-priority gap in combat casualty care.

## THE HAV

Humacyte is developing the HAV, which is a bioengineered, sterile, nonpyrogenic acellular tubular vessel composed

primarily of human collagen and other extracellular matrix components. The HAV has “off-the-shelf” availability and reproducible sizing of synthetic grafts and studies have shown it to have favorable resistance to infection.<sup>24</sup> Findings also show that the HAV is extensively remodeled by the host or recipient patient when the conduit is used for arteriovenous access creation. In these studies, HAV sections were taken during routine procedures and subjected to histological analysis which revealed the HAV is permissive to infiltration of host cells, modifying into a multi-layered living structure mimicking the native vasculature. This evolution of HAV into a living tissue lends the capacity to heal and respond to changes in the host, notably without invoking an overt immune response.

The HAV is being studied in Phase II and Phase III clinical trials for use in arteriovenous access creation for hemodialysis, and vascular repair and reconstruction (including peripheral arterial disease and vascular trauma). In hemodialysis the HAV has received regenerative medicine, advanced therapy designation, an expedited approval pathway designated by the Food and Drug Administration for exceptionally promising medical advances that treat serious conditions under the 21st Century Cures Act. The HAV is being developed in close collaboration between the Department of Defense (DoD) and Humacyte for its use in vascular repair and reconstruction.

Figures 1 to 3 demonstrate the use of an HAV in the setting of a civilian gun-shot wound to the superficial femoral artery. The patient had sustained multiple injuries and a temporary vascular shunt inserted to sustain flow to his extremity as a damage control maneuver. The HAV was used as a conduit for definitive repair, sutured in place using a standard vascular technique.

## CLINICAL STUDIES AND CHALLENGES

Humacyte has initiated seven clinical trials using the HAV. Four clinical studies in end-stage renal disease, two in peripheral arterial disease and one in vascular trauma. Arteriovenous access creation in end-stage renal disease is in two ongoing Phase III



**Figure 1.** An operative image of the superficial femoral artery with a shunt in place. The injury was following a gunshot wound.



**Figure 2.** The same patient in Figure 1, following shunt removal and the implantation of a HAV.

clinical trials, one study compares the HAV to ePTFE and the other compares HAV with autologous fistulae. The use of HAV in vascular trauma is being explored in a Phase II open-label clinical trial. Additionally, the HAV has been made available by Humacyte for compassionate use in two cases. In both cases, the HAV was used for vascular repair.

Conducting clinical studies in vascular trauma presents a number of unique challenges. Performing a traditional randomized, prospective study is fraught with technical and logistical hurdles. Vascular trauma can occur in almost any anatomical location, making randomization of comparable injuries nearly impossible. As patency and rate of complications have been reported to differ based on injury location, this is a critical challenge to address.

For this reason, new guidance on the use of real-world evidence coupled with the use of vascular trauma registries, such as the American Association for the Surgery of Trauma Prospective Observational Vascular Injury Treatment registry, could be useful in developing alternative methods to compare the profile of the HAV to historical cases receiving standard of care.<sup>22</sup>

Moreover, the collection of long-term patency and complications is not the standard of care, creating a dearth of long-term data.

The prevalence of subjects becoming lost to follow-up is higher in trauma studies as well, again contributing to difficulties in the collection of long-term data even in a clinical trial setting. Analysis of published studies using autologous vein have demonstrated that the outcome at 30 days is highly predictable of the long-term outcome in terms of patency and complication rates,<sup>16,25-27</sup> with fewer than 2% of patients exhibiting complication in the long-term that were not present within 30 days.<sup>26,27</sup> Thus, the use of 30-day timepoints may well serve as an intermediate assessment, which when couple with long-term postmarketing studies, could generate a robust dataset for further analysis.

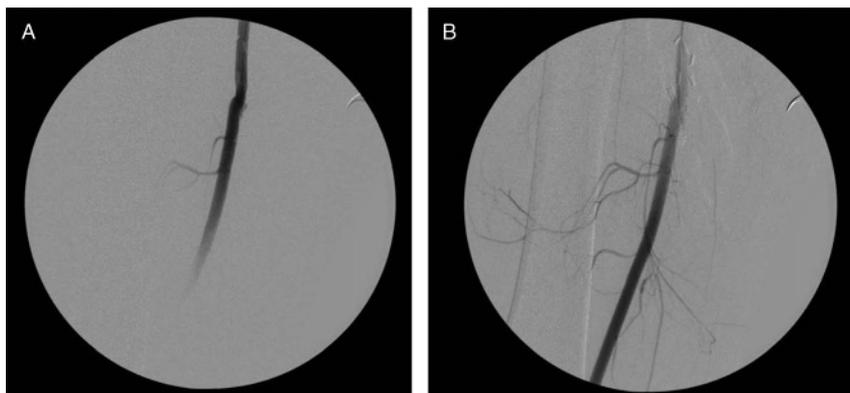
## CONCLUSION

The HAV is a pioneering regenerative medicine technology, which addresses an unmet need in the treatment of vascular trauma. The HAV is currently being developed for use in end-stage renal, disease, peripheral arterial disease and vascular trauma. However, the clinical need for vascular repair material is much more expansive. Cardiovascular disease remains a leading cause of morbidity globally. Congenital cardiovascular disorders, oncologic surgery and organ transplant, all rely heavily on the use of autologous vein, with limited alternatives available.

Novel technologies like the HAV are among the first generation of regenerative medicine advances aiming to generate artificial biological structures used to repair or replace damaged tissues and organs. The HAV shows promise in resistance to common complications associated with current alternative conduit materials, with the added benefit of being modified by the host and incorporated as a living tissue. The clinical trial design and regulatory pathways for these nontraditional therapies present challenges, the answers to which may sculpt the future landscape of how such biologics are clinically tested and approved.

## AUTHORSHIP

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**Figure 3.** (A) A completion angiogram of the left superficial artery demonstrating the proximal anastomosis. (B) A completion angiogram of the left superficial artery demonstrating the distal anastomosis.

## DISCLOSURE

J.M. and J.H.L. are employees of Humacyte Inc. The remaining authors declare no conflicts of interest. The views and opinions expressed in this article are those of the authors and do not reflect the official policy or position of the US Air Force, US Department of Defense, or the US Government.

## REFERENCES

1. Eastridge BJ, Mabry RL, Seguin P, et al. Death on the battlefield (2001–2011): implications for the future of combat casualty care. *J Trauma Acute Care Surg.* 2012;73(6 Suppl 5):S431–S437.
2. White JM, Stannard A, Burkhardt GE, Eastridge BJ, Blackburne LH, Rasmussen TE. The epidemiology of vascular injury in the wars in Iraq and Afghanistan. *Ann Surg.* 2011;253(6):1184–1189.
3. Patel JA, White JM, White PW, Rich NM, Rasmussen TE. A contemporary, 7-year analysis of vascular injury from the war in Afghanistan. *J Vasc Surg.* 2018;68(6):1872–1879.
4. Bailey JA, Morrison JJ, Rasmussen TE. Military trauma system in Afghanistan: lessons for civil systems? *Curr Opin Crit Care.* 2013;19(6):569–577.
5. DeBakey ME, Simeone FA. Battlefield injuries of the arteries in World War II: an analysis of 2,471 cases. *Ann Surg.* 1946;123(4):534–579.
6. Perkins ZB, Yet B, Glasgow S, Marsh DWR, Tai NRM, Rasmussen TE. Long-term, patient-centered outcomes of lower-extremity vascular trauma. *J Trauma Acute Care Surg.* 2018;85(1S Suppl 2):S104–S111.
7. Sharrock AE, Tai N, Perkins Z, White JM, Remick KN, Rickard RF, Rasmussen TE. Management and outcome of 597 wartime penetrating lower extremity arterial injuries from an international military cohort. *J Vasc Surg.* 2019. pii: S0741-5214(18)32673-9.
8. Fox CJ, Gillespie DL, Cox ED, Mehta SG, Kragh JF Jr., Salinas J, Holcomb JB. The effectiveness of a damage control resuscitation strategy for vascular injury in a combat support hospital: results of a case control study. *J Trauma.* 2008;64(Suppl 2):S99–S106; discussion S106-7.
9. Rasmussen TE, Clouse WD, Jenkins DH, Peck MA, Eliason JL, Smith DL. The use of temporary vascular shunts as a damage control adjunct in the management of wartime vascular injury. *J Trauma.* 2006;61(1):8–12.
10. Gifford SM, Aidinian G, Clouse WD, Fox CJ, Jones WT, Zarzabal L, Michalek JE, Propper BW, Burkhardt GE, Rasmussen TE. Effect of temporary shunting on extremity vascular injury: an outcome analysis from the Global War on Terror Vascular Injury initiative. *J Vasc Surg.* 2009;50(3):549–555.
11. Burkhardt GE, Gifford SM, Propper BW, Spencer JR, Williams K, Jones L, Sumner M, Cowart J, Rasmussen TE. The impact of ischemic interval on neuromuscular recovery in a porcine (Sus Scrofa) survival model of extremity vascular injury. *J Vasc Surg.* 2011;53:165–173.
12. Hancock HM, Stannard A, Burkhardt GE, Williams K, Dixon P, Cowart J, Spencer JR, Rasmussen TE. Hemorrhagic shock worsens neuromuscular recovery in a porcine model of hind limb vascular injury and ischemia/ reperfusion. *J Vasc Surg.* 2011;53(4):1052–1062.
13. Alarhayem AQ, Cohn SM, Cantu-Nunez O, Eastridge BJ, Rasmussen TE. Impact of time to repair on outcomes in patients with lower extremity arterial injuries. *J Vasc Surg.* 2019;69:1519–1523. pii: S0741-5214(18)32221-3.
14. Burkhardt GE, Rasmussen TE, Propper BW, Lopez PL, Gifford SM, Clouse WD. A national survey of evolving management patterns for vascular injury. *J Dermatol Surg.* 2009;6(5):239–247.
15. Rasmussen TE, Woodson J, Rich NM, Mattox KL. Vascular trauma at a crossroads. *J Trauma.* 2011;70(5):1291–1293.
16. Watson JD, Houston R 4<sup>th</sup>, Morrison JJ, Gifford SM, Rasmussen TE. A retrospective cohort comparison of expanded polytetrafluoroethylene to autologous vein for vascular reconstruction in modern combat casualty care. *Ann Vasc Surg.* 2015;29(4):822–9.
17. Woodward EB, Clouse WD, Eliason JE, Peck MA, Bowser AN, Cox MW, Jones WT, Jenkins DH, Smith DL, Rasmussen TE. Penetrating Femoropopliteal injury during modern warfare: experience of the Balad Vascular Registry. *J Vasc Surg.* 2008;47:1259–1265.
18. Gordon W, Talbot M, Fleming M, Shero J, Potter B, Stockinger ZT. High bilateral amputations and dismounted complex blast injury (DCBI). *Mil Med.* 2018 Sep 1;183(Suppl 2):118–122.
19. Cannon JW, Hofmann LJ, Glasgow SC, Potter BK, Rodriguez CJ, Cancio LC, Rasmussen TE, Fries CA, Davis MR, Jezior JR, Mullins RJ, Elster EA. Dismounted complex blast injuries: a comprehensive review of the modern combat experience. *J Am Coll Surg.* 2016;223(4):652–664.e8.
20. Propper BW, Rasmussen TE, Davidson S, Vandenberg S, Gunst MA, Clouse WD, Burkhardt GE, Gifford SM, Johannigman JA. Surgical response to multiple casualty incidents following single explosive events. *Ann Surg.* 2009;250(2):311–315.
21. Vertrees A, Fox CJ, Quan RW, Cox MW, Adams ED, Gillespie DL. The use of prosthetic grafts in complex military vascular trauma: a limb salvage strategy for patients with severely limited autologous conduit. *J Trauma.* 2009;66(4):980–983.
22. DuBose JJ, Savage SA, Fabian TC, Menaker J, Scalea T, Holcomb JB, Skarupa D, Poulin N, Chourliaras K, Inaba K, Rasmussen TE, AAST PROOVIT Study Group. The American Association for the Surgery of Trauma PROspective observational vascular injury treatment (PROOVIT) registry: multicenter data on modern vascular injury diagnosis, management, and outcomes. *J Trauma Acute Care Surg.* 2015;78(2):215–222; discussion 222-3. Erratum in: *J Trauma Acute Care Surg.* 2015;78(3):657.
23. Madden R, Lipkowitz G, Benedetto B, Kurbanov A, Miller M, Bow L. Decellularized cadaver vein allografts used for hemodialysis access do not cause allosensitization or preclude kidney transplantation. *Am J Kidney Dis.* 2002;40(6):1240–1243.
24. Kirkton RD, Santiago-Maysonet M, Lawson JH, Tente WE, Dahl SLM, Niklason LE, Prichard HL. Bioengineered human acellular vessels recellularize and evolve into living blood vessels after human implantation. *Sci Transl Med.* 2019;11(485):pii: eaau6934.
25. Casey K, Demers P, Demers P, Deben S, Nelles ME, Weiss JS. Outcomes after long-term follow-up of combat-related extremity injuries in a multidisciplinary limb salvage clinic. *Ann Vasc Surg.* 2015;29(3):496–501.
26. Klocker J, Bertoldi A, Benda B, Pellegrini L, Gorny O, Fraedrich G. Outcome after interposition of vein grafts for arterial repair of extremity injuries in civilians. *J Vasc Surg.* 2014;59(6):1633–1637.
27. Keen RR, Meyer JP, Durham JR, Eldrup-Jorgensen J, Flanigan P, Schwarcz TH, Schuler JJ. Autogenous vein graft repair of injured extremity arteries: early and late results with 134 consecutive patients. *J Vasc Surg.* 1991;13(5):664–668.