Arterial Stiffening Influence of Sympathetic Nerve Activity
Evidence From Hand Transplantation in Humans

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Abstract—Studies in animals and humans suggest that sympathetic activity exerts a stiffening influence on large and middle-sized artery walls. We sought to obtain further evidence on this issue by measuring radial artery distensibility in an allotransplanted and thus denervated hand using the contralateral artery as control. In 2 men, blood pressure was measured by a semiautomatic device (Dinamap). Diastolic diameter, systo-diastolic diameter excursion (ultrasound Wall Tracking system), and distensibility (Reneman formula) of both radial arteries were measured at a level corresponding to 4 cm below the suture of the transplanted hand 40 days after surgery and every 4 weeks for the next 6 months. After surgery, systo-diastolic diameter excursion and distensibility were much greater in the transplanted radial artery than in the contralateral vessel, reaching values similar to the contralateral ones after 4 months, when signs of reinnervation of the transplanted hands had appeared. Radial deinnervation was accompanied by an increased arterial distensibility, which provides further evidence of the sympathetic stiffening effect on arterial wall in humans. (Hypertension. 2005; 45:608-611.)

Key Words: denervation ■ sympathetic nervous system ■ transplantation

Sympathetic nerve activity exerts a “tonic” stiffening influence on arterial wall.1,2 This has been shown in animals in which chemical sympathectomy was accompanied by an increase in carotid artery distensibility.3 It has also been shown in humans in whom anesthesia of the brachial plexus and anesthesia of the low spinal cord and lumbar sympathectomy were all followed by an increase in the distensibility of the radial or the femoral artery, reflecting the stiffening effect neural influences exerted on the vessel wall.4

Our hospital started a program of allotransplantation of the hand 2 years ago. This gave us a chance to determine what happens to arterial distensibility in transplanted organs and to make use of another human “model” on which to study the relationship between sympathetic tone and arterial distensibility, which could be measured at various times after the surgical intervention in the radial artery below the transplantation line, using the values obtained from the contralateral vessel as control. This article reports the results obtained in 2 patients.

Methods

We studied 2 men (patient 1, age 35 years; patient 2, age 31 years) who underwent allotransplantation of the right hand, which had been lost in a previous car accident. Both patients underwent a routine pretransplantation investigation and morphological and functional testing of the forearm stumps to ensure immunologic and mechanical donor–recipient compatibility. They were administered treatment with monoclonal antibodies anti-CD25 (Baxilimab, Simulect), FK506 (tacrolimus, Prograf), mycophenolate mofetil (Cell Cept), and prednisone immediately after surgery to prevent graft rejection. Maintenance therapy was unchanged throughout the study duration. The post -treatment program of rehabilitation (started as the swelling subsided) consisted of physiotherapy, electrostimulation, and occupational therapy. Pain, touch, and T° sensations, as well as ability to perform active movements, were examined weekly by conventional clinical tests. Sweat function was examined by application to the skin of laboratory blotting papers, also on a weekly basis. Radial artery distensibility was measured 40 days after the surgical procedure and then every 4 weeks for the next 6 months. Measurements were made in the wrist 4 cm below the suture and at the same wrist level in the contralateral vessel. Patients consented to the study after explanation of its nature and purpose. The study protocol was approved by the ethics committee of our Institution.

Evaluation of Radial Artery Distensibility

Radial artery distensibility was measured by a B-M mode echotracking device based on Doppler shift (Wall Track System; PIE Medical, Maastricht, the Netherlands) and on a transducer operating at a frequency of 7.5 MHz.6,7 The transducer was mounted on a stereotaxic arm oriented perpendicularly to the longitudinal axis of the vessel under B-mode guidance. After switching to A-mode, the back-scattered echoes from the anterior and posterior radial artery walls were visualized on a screen and the corresponding radiofrequency signal was tracked by electronic tracers to allow the digitized signal of the internal diameter variations to be derived at 50 Hz. The spatial resolution was 300 μm.8,9 Blood flow velocity was measured...
at the same site of the diameter measurement by 8-MHz probe positioned with an angle of 40° to 60° from the principal axis of the artery. Blood flow was calculated as the product of flow velocity and arterial diameter. Blood pressure was measured from the brachial artery at the same time of the ultrasound evaluation via a semiautomatic device (Dinamap 1846 SX/SXP; Critikon, Chatenay Malabry Cedex, France) and radial artery distensibility was derived according to the following formula:

$$\text{Dist} = \frac{2(\Delta D/D_d)}{\Delta P}$$

where Dist is distensibility, Dd is the diastolic diameter of the vessel, $\Delta D$ is the systo-diastolic diameter change, and $\Delta P$ is the corresponding pulse pressure. A single operator made radial artery measurements with an intraobserver variability of 4%. Heart rate was measured by the palpatory method (30 seconds) after each blood pressure measurement. No measures of longitudinal distensibility were obtained because of technical limitation of methodology used.7,8

**Results**

In patient 1, blood pressure and heart rate were normal at the initial examination and did not show any consistent change in the follow-up period (Figure 1, left panels). As shown in Figure 2 (left panels), in the radial artery contralateral to that of the hand undergoing allotransplantation, diastolic diameter, systo-diastolic diameter change, distensibility, and blood flow remained stable from the initial examination to the end of the follow-up period. In contrast, in the radial artery of the transplanted hand, although diameter and blood flow also did not change, systo-diastolic diameter change and distensibility were all greater than in the “control” artery after surgery, with a subsequent progressive reduction to values similar to the “control” ones after $\approx 4$ months. Similar results were obtained in patient 2 (Figures 1 and 2, right panels). At the weekly examinations, the transplanted hand of both patients showed the ability to perform active movements after $\approx 3$ months from surgery. This was also the case for detection of skin stimuli and sweat.

**Discussion**

In the 2 patients included in the study, allotransplantation of the right hand was associated with a similar diastolic diameter, a greater diameter excursion from diastole to systole, and a much greater calculated distensibility of the radial artery below the transplantation level as compared with the contralateral control vessel. All abnormal values, however, showed a progressive reduction in the weeks thereafter and returned to levels similar to the contralateral ones in $\approx 4$ months, ie, after the time when the transplanted hand showed the ability to perform active movements to detect touch, pain, and temperature stimuli and to sweat, thereby exhibiting signs of reinnervation.9–10 Thus, although there is a limitation with the number of included subjects, because of the fact that this surgical procedure is exceptionally rare, our data suggest that transplantation is characterized by a temporary marked re-
The reduction in the ability of the arterial wall to resist the distension caused by intravascular pressure as a result of a marked increase in arterial distensibility. Based on previous animal and human data on the stiffening influence of ongoing sympathetic activity on large and medium arteries, this is likely to be caused by loss of sympathetic innervation, with sympathetic reinnervation of the vessel wall being conversely responsible for return of arterial distensibility to normal.

As discussed in previous studies in animals and humans, the stiffening effect of sympathetic activity on the vessel wall (and thus the increased arterial distensibility when sympathetic influences are removed) may be produced by contraction of smooth muscle because the contracted muscle has a greater elastic modulus than the relaxed one. It may also be produced, on a more chronic basis, by growth of less distensible connective tissue for which sympathetic influences are trophic factors. The participation of the sympathetic nervous system in the alterations of arterial distensibility in a post-transplantation organ does not exclude the involvement of other factors, given the complex alterations in the local milieu brought about by organ transplantation, although our data allow us to exclude or consider unlikely a number of them. After 40 days, the transplanted hand still showed some edema, which subsided entirely over the subsequent follow-up period. This may have increased radial artery distensibility, because Bank et al have reported that inflating a water-filled cuff around the brachial artery increases the diameter excursion of the enclosed vessel, presumably because of an increased distensibility caused by muscle relaxation. However, this was seen for major reductions of transmural pressure caused by increases in outside pressure that are beyond those produced by the small residual edema of the hand seen in our patients. Furthermore, an increase in interarterial fluid content and tissue pressure could also have the opposite effects, i.e., it could mechanically restrain the ability of the vessel to distend in response to intravascular pressure. Thus, it is unlikely that edema per se is responsible for the initial elevation and subsequent reduction of radial artery distensibility. It is also to be remarked that, probably because of the complex milieu brought about by hand transplantation, no blood flow changes were observed in the transplanted or the control arm.

Figure 2. Radial artery diastolic diameter, systo-diastolic diameter excursion, distensibility, and blood flow during the 6 months after hand transplantation in the 2 patients of Figure 1. T indicates data from the transplanted radial artery; C, data from the contralateral intact or control vessel.
Although not quantified, the transplanted hand certainly underwent muscle atrophy because of inactivity. However, this also cannot be held responsible for the post-transplant increase in arterial distensibility, because we have seen that inactivity and muscle atrophy by prolonged enclosure of a fractured forearm in a cast reduces rather than increases radial artery distensibility, which only regains its normal value weeks after cast removal and rehabilitation procedures.\textsuperscript{14}

Organ transplantation requires a complex medical treatment, part of which consists of immunosuppressive agents that can effect vascular structure and function. However, it is unlikely that this played a role in the changes of arterial distensibility that was seen in the transplanted hand, because no changes were seen in the contralateral hand, which was obviously also exposed to the drug(s) effect.

Finally, hand transplantation certainly also altered endothelial function. However, these changes most likely consisted of a reduction in nitric oxide secretion after surgery (despite the absence of any blood flow reduction), with a gradual and possibly progressive incomplete recovery thereafter. Because nitric oxide has a relaxing and antifibrotic effect on vascular smooth muscle, its reduction should have favored an early arterial stiffening rather than making the artery more distensible, as was observed.\textsuperscript{15,16}

Our study has limitations and clinical implications. The fundamental limitation is that the evidence of sympathetic reinnervation was only clinical, ie, recovery of sweating response to $T^0$ changes, and thus was qualitative rather than quantitative. This was determined in part by the constraint posed by the ethics committee, who wanted us to avoid maneuvers that could even temporarily interfere with organ perfusion, such as return of reflex or central sympathetic vasoconstriction. The clinical implication relates to whether the increase in radial artery distensibility that accompanies transplantation has favorable or unfavorable clinical implications. An increase in vessel distensibility is regarded as clinically beneficial because it results into a reduction in pulse pressure (an independent cardiovascular risk factor)\textsuperscript{17} and endothelial trauma, with a reduced atherogenesis.\textsuperscript{18} It is not inconceivable, however, that when the increase in distensibility is as abrupt and large as the one seen in the radial artery after transplantation, the resulting marked increase in systo-diastolic vessel excursion may lead to mechanical damage of the vessel.

References

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Hypertension. 2005;45:608-611; originally published online February 7, 2005;
doi: 10.1161/01.HYP.0000157368.09939.88

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/45/4/608

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