Venous valvular reflux in veins not involved at the time of acute deep vein thrombosis

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Purpose: The aim of this study was to determine whether, in lower extremities with documented episodes of acute deep venous thrombosis (DVT), incompetence develops in veins that were not the site of thrombosis.

Methods: Patients were monitored with serial duplex ultrasonography at 1 day, 1 week, 1, 3, 6, 9, and 12 months, and then annually after detection of acute DVT. The following venous segments were analyzed: common femoral, greater saphenous, proximal superficial femoral, deep femoral, popliteal, and posterior tibial. The incidence of reflux development in both thrombosed and uninvolved segments was determined. Reflux was categorized as either transient or permanent.

Results: A total of 227 limbs in 188 patients were serially studied. Mean follow-up was 19.9 months (range 1 to 88 months). Overall, 403 of the 1423 segments (28.3% ± 2.3%) developed reflux during the study, of which 118 (29.3% ± 4.4%) had no prior or concurrent history of thrombosis. Considering only the segments that developed incompetence, the percent without prior thrombosis at each level was as follows: common femoral vein (40.0%), greater saphenous vein (53.1%), deep femoral vein (20.6%), proximal superficial femoral vein (23.9%), popliteal vein (8.9%), and posterior tibial vein (31.9%). Valvular insufficiency developing in segments uninvolved with thrombus was more likely to be transient (40.2%) than was the reflux in thrombosed segments (22.6%). This difference was statistically significant ($p < 0.05$).

Conclusions: Permanent venous valvular damage can occur in the absence of thrombosis after DVT. Reflux in uninvolved venous segments has a different anatomic distribution and is more likely to be transient than the incompetence associated with thrombosis.
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The histologic changes in the venous system after deep vein thrombosis (DVT) have been well documented.[1-5] Soon after thrombus becomes adherent to the venous endothelium, there is an ingrowth of inflammatory cells that ultimately results in fibrous intimal thickening. When this process involves the valve cusps, they often become shortened, thickened, and permanently adherent to the vein wall.

Whether this is the sole mechanism by which valves become permanently incompetent after acute DVT is unknown. In 1986, we instituted a prospective natural history study of venous disease on the basis of frequent, serial duplex ultrasonography.[6,7] We found that in most cases, the development of reflux in a venous segment is indeed preceded by thrombosis and that the likelihood of development of reflux is directly related to the lysis time for most venous segments.[6,7] However, it has been suggested that valvular reflux may also occur in veins not involved with thrombi.[6,8] If this is the case, the frequency and clinical significance of this form of venous insufficiency are unknown.

This study was undertaken to establish the incidence and anatomic distribution of venous reflux among those segments without detectable thrombosis after DVT and to determine whether this incompetence is permanent or transient.

METHODS

Between December 1986 and August 1994, consenting patients with acute DVT were enrolled in

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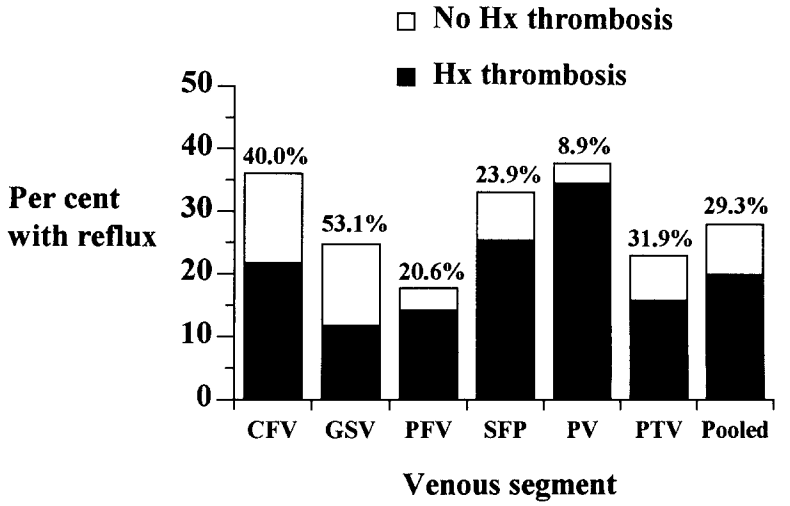

Fig. 1. Percent of segments that developed reflux for individual and pooled venous segments stratified according to history of thrombosis. Percent of refluxing segments without prior thrombosisis indicated above each column.

Table I. Classification of the venous segments which developed reflux into "transient," "permanent," and "unknown" categories

			History of thrombosis			*No history of thrombosis*		
Segment	*No.*	*No. reflux*	*Transient*	*Permanent*	*Unknown*	*Transient*	*Permanent*	*Unknown*
CFV	221	80	7	35	6	13	17	2
GSV	197	49	6	12	5	9	12	5
DFV	190	34	4	19	4	2	4	1
SFP	201	67	6	36	9	6	8	2
PV	208	79	13	46	13	2	5	0
PTV	406	94	17	33	14	9	15	6
Pooled	1423	403	53	181	51	41	61	16

The segments are further stratified according to prior or concurrent history of involvement with thrombus.

a prospective study of the natural history of lower extremity venous thrombosis. The study protocol consisted of venous duplex scanning at 1 day, 1 week, 1 month, every 3 months for the first year, and annually thereafter. Exclusion criteria included the presence of chronic venous disease, a prior history of DVT, debilitating medical comorbidity, and short life expectancy. Between January 1991 and August 1994, the uninvolved legs in patients with unilateral DVT were also scanned at each visit.

Duplex scanning was performed with either an Ultramark 8 or 9 duplex scanner (Advanced Technology Laboratories, Bothell, Wash.). At each examination the entire lower extremity venous system was scanned. For the purposes of this study, reflux and thrombosis (either occlusive or nonocclusive) were documented in the following venous segments: (1) the common femoral vein (CFV) just cephalad to the saphenofemoral junction; (2) the greater saphenous vein (GSV) just caudal to the saphenofemoral junction; (3) the deep femoral vein (DFV) just caudal to the saphenofemoral junction; (4) the proximal superficial femoral vein (SFP) just caudal to the saphenofemoral junction; (5) the popliteal vein (PV) both above and below the knee joint; and (6) both posterior tibial veins (PTV).

All scans were obtained with the patient in the 15-degree reversed Trendelenburg position. A 5 MHz linear-array B-mode transducer with a 5 MHz pulsed-wave Doppler flow detector were used for most examinations; a 10 MHz probe was used to obtain images of some of the PTVs. Reflux was elicited with both the Valsalva maneuver and manual compression cephalad to the segment studied and

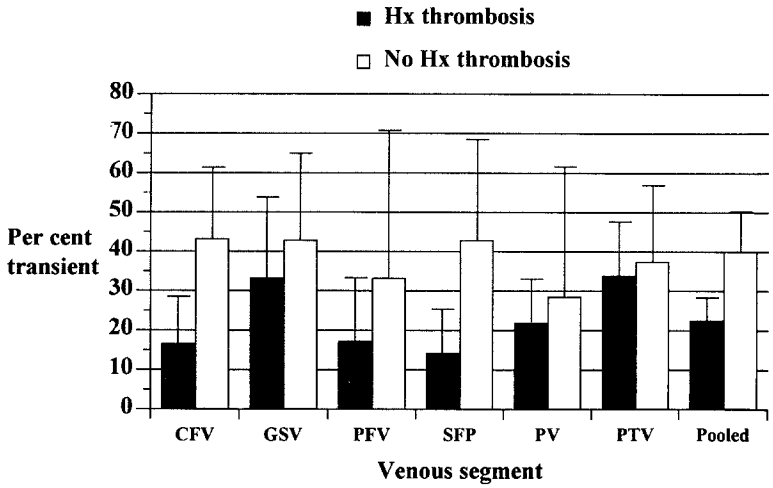

Fig. 2. Percent of reflux development that was transient for individual and pooled venous segments stratified according to history of thrombosis. Difference was statistically significant for pooled segments ($p < 0.05$, chi-square test). *Error bars* indicate 95% confidence intervals.

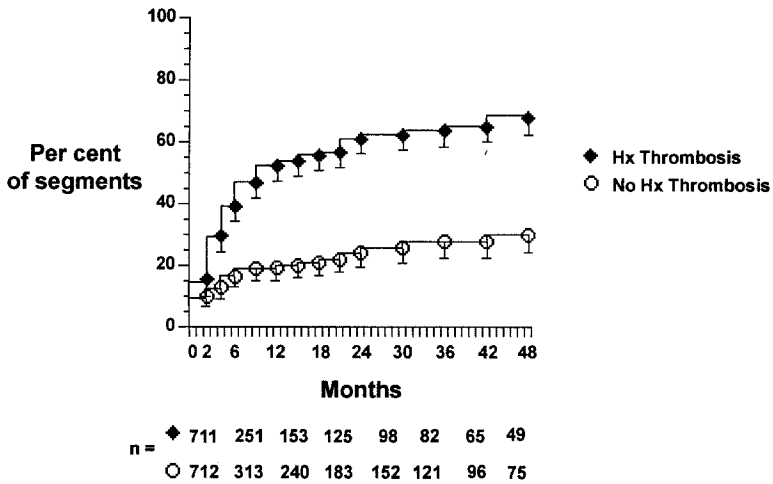

Fig. 3. Cumulative incidence of reflux detection in thrombosed and nonthrombosed venous segments (pooled). *Error bars* indicate 95% confidence intervals.

was defined as reversal of flow on the Doppler spectral waveform persisting longer than 2 seconds. Nonocclusive thrombosis was defined as the presence of flow in an incompletely compressible vessel with or without visible thrombus. Occlusive thrombosis was defined as the absence of flow in an incompressible vessel.

Because one of the goals of this study was to examine the causes of valvular reflux, segments that were incompetent at the first examination were not considered for analysis. Thus, to detect reflux development during the study, a minimum of two examinations were required. Extremities were excluded from analysis if more than two consecutive examinations were missed, and individual segments were similarly excluded if the diagnosis was unclear for more than two consecutive visits. The development of reflux was determined for each venous segment and was subgrouped depending on whether thrombosis preceded the development of incompetence. The cumulative incidence of reflux in both thrombosed and uninvolved segments was calculated by use of the life-table method. No attempt was made to differentiate between occlusive and nonocclusive

thrombosis. All proportions were presented ± 1.96 times the standard error, which will yield upper and lower 95% confidence interval bounds. When appropriate, comparisons were evaluated for statistical significance with the chi-square test.

For incidence determinations, the first occurrence of reflux was considered an endpoint. The reflux was then classified as either permanent or transient. Segments with "permanent" reflux were defined as those that were incompetent at both the last examination and for at least two consecutive examinations. All other occurrences of reflux were termed "transient," except those in which a segment was found to be incompetent at the last visit only. These were categorized as "unknown." A similar analysis was performed on the uninvolved legs in patients with unilateral DVT who were evaluated after January 1991.

RESULTS

Patient population. From December 1986 through August 1994, 202 consenting patients (246 legs) with acute DVT met entry criteria for the study and underwent at least two examinations. Fourteen of these patients (19 legs) missed more than two consecutive examinations and were excluded. The remaining 227 legs in 188 patients included 95 right and 132 left sides. Mean follow-up was 19.9 months (range 1 to 88 months). The mean patient age was 51.3 years with a range of 11 to 88 years. There were 111 men and 77 women. Oral anticoagulation was prescribed by the treating physician for 77.8% of the patients. Risk factors for DVT included bed rest in 36.7%, surgery in 34.0%, malignancy in 29.3%, a family history of DVT in 10.6%, prolonged travel in 4.8%, congestive heart failure in 4.8%, pregnancy in 1.6%, and use of oral contraceptives in 1.1% of the patients.

Several segments were excluded on the basis of either incompetence on the first examination or an unclear diagnosis on more than two consecutive examinations. Of 227 lower extremities with acute DVT, 221 CFV, 197 GSV, 190 DFV, 201 SFP, 208 PV, and 406 PTV segments were available for analysis.

Reflux in uninvolved segments. A total of 403 of the 1423 venous segments analyzed (28.3% ± 2.3%) developed reflux during the study. One hundred eighteen of the 403 segments (29.3% ± 4.4%) had no prior or concurrent history of thrombosis. The incidence of reflux for each of the venous segments analyzed is shown in Fig. 1. The incompetent segments are stratified according to whether they were involved with thrombus. The anatomic distribution of thrombus- and nonthrombus-associated reflux were significantly different ($p < 0.05$, chi-square test). For each level the percent of incompetent segments that were uninvolved with thrombosis was as follows: CFV (40.0% ± 10.7%), GSV (53.1% ± 14.0%), DFV (20.6% ± 13.6%), SFP (23.9% ± 10.2%), PV (8.9% ± 6.3%), and PTV (31.9% ± 9.4%). The largest difference observed was between the PV and the proximal GSV. For the former, the vast majority (91.1%) of segments that developed reflux had a history of involvement with thrombus, whereas for the latter, a history of thrombosis was noted in about one half of the segments.

Persistence of reflux. Table I shows the number of segments for which reflux was categorized as either transient, permanent, or unknown for each level. The data are stratified according to whether the segment had been involved with thrombus. This relationship is depicted graphically in Fig. 2, which shows the percent of incompetent segments for which the reflux was transient for both the pooled data and for the individual levels. Again, the proportions are subgrouped according to involvement with thrombus. Excluding the unknowns from analysis, the overall (pooled) incidence of transient incompetence was significantly higher ($p < 0.05$, chi-square test) for the uninvolved segments (40.2% ± 9.5%) than for the segments with prior or concurrent thrombosis (22.6% ± 5.4%). For each level, veins that had been thrombosed had lower proportions of transient reflux than uninvolved segments, but the differences were not statistically significant except for the pooled data.

Rate of reflux development. The life-table analysis of reflux development in thrombosed and nonthrombosed venous segments is shown in Table II. The rate of reflux development for each level was highest during the first 6 to 12 months after the diagnosis of DVT, regardless of whether the segment was involved with thrombus. After 12 months, these rates were lower, but not negligible. For the thrombosed segments, the rates of reflux development were remarkably similar, with the exception of the PTV, which had a lower cumulative incidence of reflux. Cumulative incidences were more disparate in the nonthrombosed venous segments, ranging from 11.1% ± 8.5% for the DFV to 49.3% ± 16.4% for the CFV at 36 months. Fig. 3 shows the life-table analysis of the pooled segments. Overall, the relative risk of reflux development in thrombosed compared with nonthrombosed segments was 2.27 (95% CI = 2.11 to 2.45) at 4 years.

Table II. Cumulative incidence of reflux detection in thrombosed and nonthromboseed venous segments at 6, 12, 24, and 36 months after diagnosis

Segment	No. thrombosed	No. nonthrombosed	6 months		12 months	
			Thrombosed	Nonthrombosed	Thrombosed	Nonthrombosed
CFV	106	115	41.7 ± 11.2	28.8 ± 9.6	53.1 ± 11.8	30.5 ± 10.0
GSV	47	150	52.6 ± 16.7	20.0 ± 7.5	56.0 ± 16.7	20.0 ± 7.5
DFV	71	119	37.5 ± 14.1	3.0 ± 3.3	57.0 ± 15.5	8.1 ± 6.5
SFP	112	89	47.8 ± 11.3	19.7 ± 9.9	63.7 ± 11.8	25.2 ± 11.9
PV	156	52	45.2 ± 9.6	13.4 ± 11.1	60.0 ± 9.8	13.4 ± 11.1
PTV	219	187	25.8 ± 6.4	13.6 ± 5.8	37.2 ± 8.4	17.7 ± 6.8

All nonthrombosed segments were competent at the initial examination. The data are presented as the percent of segments that developed reflux ± the 95% confidence intervals.

Reflux development in legs without DVT. Between January 1991 and August 1994, 52 patients with uninvolved legs contralateral to an extremity with DVT were enrolled in the study; six were excluded because of inadequate follow-up. The mean follow-up for the remaining group of 46 patients was 10.3 months (range 1 to 36 months). Table III shows the number of segments at each level that developed reflux during the study. Overall, 14 of 305 segments studied (4.6% ± 2.3%) developed reflux. Of the 11 incompetent segments for which the reflux could be categorized as either permanent or transient, seven (63.6%) were transient.

DISCUSSION

The results of this study indicate that reflux development in segments without detectable thrombosis is not uncommon after acute DVT. This observation merits further consideration because approximately two thirds of patients with DVT will ultimately have development of the postthrombotic syndrome.[9] An improved understanding of the events that occur in the lower extremity venous system after acute thrombosis may encourage more specific therapeutic efforts directed toward distinct pathologic processes.

We believe that the standing cuff deflation technique with duplex scanning is the gold standard for determining venous incompetence with anatomic specificity in the lower extremity. Descending venography has its limitations because of difficulty in assessing the more distal venous circulation and because of streaming of hyperbaric contrast that often results in false-positive results in the proximal venous circulation.[10] The standing cuff deflation technique was recently compared with the supine methods (Valsalva's maneuver and manual compression) for the detection of reflux by duplex scanning.[11] When Valsalva's maneuver and manual compression were combined, the specificity ranged from 88% to 100%, and the sensitivity ranged from 67% to 88% (except for the PTV, which had a sensitivity of 30%). On the basis of this study, we began using the standing method exclusively in August 1994. However, the vast majority of examinations dating back to 1986 were performed with the supine methods. We believe that these methods are sufficiently accurate (when Valsalva's method and manual compression are combined) that these data should not be excluded. Therefore, for the sake of consistency, all reflux documented in this report was detected by use of the supine methods. Because of the low sensitivity of these techniques for detecting reflux in the calf veins, we acknowledge that many of the PTV segments may have, in fact, been incompetent at the beginning of the study. Alternatively, we may have dramatically underestimated the development of reflux in both involved and uninvolved PTV segments during the study.

It is possible that the "transient" reflux detected in this study was an artifact of the testing method used. When compared with standing methods, the supine methods have a mean specificity of 92%.[11] Therefore one expects that approximately 8% of the reflux detected with supine methods is erroneous and would be expected to be categorized as "transient" on serial examinations. However, because the prevalence of transient reflux was greater than 8% (22.6% and 40.2% in involved and uninvolved segments, respectively), we believe that a significant fraction of the transient reflux detected is authentic. Furthermore, if transient reflux were entirely an artifact, one would expect this "artifact" to occur with equal frequency regardless of whether there had been a history of thrombosis in that segment. Because this was not the case, it is more likely that most of the transient reflux detected in this study was not an artifact of the testing method used.

24 months		*36 months*	
Thrombosed	*Nonthrombosed*	*Thrombosed*	*Nonthrombosed*
65.3 ± 12.1	36.2 ± 12.0	70.1 ± 12.1	49.3 ± 16.4
60.9 ± 7.4	22.2 ± 8.5	60.9 ± 7.4	27.2 ± 10.3
64.5 ± 15.9	11.1 ± 8.5	64.5 ± 15.9	11.1 ± 8.5
68.5 ± 12.0	28.7 ± 13.1	68.5 ± 12.0	28.7 ± 13.1
69.6 ± 10.1	19.0 ± 14.8	74.3 ± 10.4	19.0 ± 14.8
45.9 ± 9.4	24.9 ± 8.7	49.2 ± 9.9	27.1 ± 9.4

The high frequency of incompetence detected in veins without thrombosis raises several questions: (1) Is reflux development in uninvolved segments a true phenomenon, or are we merely witnessing the effects of missed thrombosis? (2) If this is a real occurrence, what is its mechanism? (3) Is it clinically relevant? (4) What further studies are needed to better define this process?

It is possible that this report's high rate of reflux development in uninvolved segments actually reflects a failure to detect thrombus during the acute phase or the occurrence of thrombosis with rapid lysis between examinations. For venous segments below the inguinal ligament, duplex scanning is least sensitive for detecting thrombi in the calf veins.[12] If the segments that developed reflux without apparent thrombosis actually had missed thrombosis, one would expect this to occur more frequently in the PTV than in the above-knee veins. However, this was not the case. The cumulative incidence of reflux in nonthrombosed segments was higher in the CFV than in the PTV segments, and similar in the GSV and SFP segments. The anatomic distributions of reflux development for thrombosed and nonthrombosed segments were dramatically different. Because these differences are not explained by anatomic differences in the sensitivity of the duplex scanner, they more likely reflect a different mechanism to explain the valvular dysfunction.

Reflux may have developed as a result of thrombosis with complete lysis of a segment between examinations. However, the incidence of reflux in uninvolved segments was highest in the early months after DVT, and this is the time period when examinations were performed most frequently. Five examinations were performed during the first 3 months. Because the median lysis time for segments developing reflux has been shown to be greater than 6 months for most veins,[7] it is unlikely that thrombosis with complete lysis between visits was a significant contributing factor.

It is also possible that valves were damaged by isolated valve-pocket thrombi that were not detectable by the duplex scanner. However, in thorough histologic studies of isolated valve-pocket thrombi, thrombus adherence to valve cusps and valvular damage were unusual.[1,2] In fact, the concentration of plasminogen activators is highest in the endothelium of the cusps, which likely serves to protect the valves. Furthermore, if this were an unrecognized cause of the reflux in uninvolved veins observed in our study, one would expect the subsequent ratio of permanent to transient incompetence to be similar to that after thrombosis. However, there was a significant difference in the subsequent permanence of reflux between the thrombosed and nonthrombosed segments. This finding further supports the argument that there are separate mechanisms to explain the development of incompetence in involved and uninvolved segments.

Incompetence in thrombosed veins is believed to develop as a direct effect of the thrombus with resultant damage to valves. Transient reflux in these veins may develop during the lytic process as thrombus becomes nonocclusive. During this stage, there is flow in the vein, but the valve cusps may become temporarily trapped until the thrombus is more completely lysed. The mechanism by which uninvolved veins become incompetent is unknown. It is unlikely that the mechanism is a systemic one because venous incompetence was uncommon in the legs contralateral to the site of thrombosis. How then does the presence of thrombus exert local effects on valves in uninvolved venous segments? Possible mechanisms include direct endothelial injury, perhaps by the local release of inflammatory mediators, and venous dilation such that the valve cusps no longer coapt properly. Venous incompetence in patients with primary varicose veins develops as a result of dilation and often occurs in a descending fashion. The veins in these patients may be more susceptible to the effects of pressure because of a reduction in venous wall elastin content and decreased smooth muscle cell contractility in response to catecholamines and endothelin.[13,14] If venodilation is important in the postthrombotic leg, it may be related to venous hypertension, especially in segments lying caudal to obstructed or incompetent veins, or it may be related to changes in compliance of the venous wall. Prospective studies are needed to assess the changes in venous diameter that occur when uninvolved segments become incompetent,

Table III. Reflux development in uninvolved legs contralateral to sides with DVT

Segment	*No.*	*Total reflux (%)*	*Transient*	*Permanent*	*Unknown*
CFV	42	5 (11.9)	3	1	1
GSV	45	3 (6.7)	2	1	0
PFV	43	1 (2.3)	1	0	0
SFP	42	1 (2.4)	1	0	0
PV	43	0	0	0	0
PTV	90	4 (4.4)	0	2	2
Pooled	305	14 (4.6)	7	4	3

Forty-six patients were monitored for a mean of 10.3 months. Reflux is categorized as either "transient," "permanent," or "unknown."

and to determine the rates of reflux development in segments caudal to involved veins.

Studies are also necessary to document the effect of this type of valvular reflux on the rate of subsequent development of the postthrombotic syndrome. In the absence of these data, there is evidence to suggest that the occurrence of reflux in this setting may be clinically significant. First, despite the fact that this form of reflux is more often transient than the incompetence associated with thrombosis, the reflux was still permanent in more than half of the segments. Second, insufficiency in the PTV and the superficial system has been shown to be particularly important in the genesis of the postthrombotic syndrome,[9,15-17] and our data indicate that reflux development in nonthrombosed PTV and GSV segments is not infrequent. Meissner et al.[7] have demonstrated that the likelihood of reflux development in thrombosed veins is associated with the lysis time, with the exception of the PTV. Because insufficiency in thrombosed PTVs has no apparent relationship with recanalization times, there must be another mechanism to explain the development of reflux in these important segments. Third, the cumulative incidence of reflux in uninvolved segments continues to rise over time for at least 48 months after acute DVT. Similarly, the cumulative incidences of lipodermatosclerosis and ulceration increase for several years after diagnosis of DVT.[18-20] The often-delayed onset of these symptoms in many patients is probably related to both reflux development in uninvolved segments and recurrent thrombosis.[21] A reduction in this ongoing loss of valvular function that occurs months to years after the initial acute event would likely have a significant impact on the morbidity of DVT.

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The Lifeline Foundation of the Society for Vascular Surgery and the International Society for Cardiovascular Surgery, North American Chapter, desires to stimulate laboratory research in the area of cardiovascular surgery. A resident research award has been established to achieve this goal. The award will consist of a $5000 stipend. In addition, the awardee will receive 1-year complimentary subscriptions to the JOURNAL OF VASCULAR SURGERY and *Cardiovascular Surgery*. The Society will select a single awardee each year. The Research and Education Committee of the Lifeline Foundation will be responsible for the selection process.

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