Clinical Results With an ePTFE Inflow Conduit for Mechanical Circulatory Support

Tofy Mussivand, PhD,[a,i] Roland Hetzer, MD,[b] Ettore Vitali, MD,[c] Bart Meyns, MD, PhD,[d] Philippe Noirhomme, MD,[e] Reiner Koerfer, MD,[f] Aly El-Banayosy, MD,[f] Ernst Wolner, MD,[g] Georg Wieselthaler, MD,[g] Bruno Reichart, MD,[h] Peter Uberfuhr, MD,[h] Robert Halfmann, MD,[i] and Peer Portner, PhD[j]

Background: Neurologic complication is an adverse event associated with mechanical circulatory support. To decrease the incidence of embolic cerebrovascular accidents (CVA) during support with the Novacor left ventricular assist system (LVAS), an expanded polytetrafluoroethylene (ePTFE) inflow conduit has been developed and introduced clinically.

Methods: Using clinical data from Europe and Canada, we conducted a retrospective analysis of the incidence of embolic CVA with the ePTFE inflow conduit (n = 88) in comparison with the previously used polyester inflow conduits (n = 310, including Vascutek® n = 155 and Cooley® n = 155). We calculated freedom from embolic CVA, risk reduction for embolic CVA, and linearized rates of embolic CVA.

Results: A significant decrease in the incidence of embolic CVA was demonstrated with the ePTFE conduit (ePTFE 10% vs polyester 23%, p = 0.002). Kaplan-Meier analysis of freedom from embolic CVA at 180 days after implantation was 86% for the ePTFE group vs 72% for the polyester group (log-rank test, 0.0185). We also found an associated risk reduction of 55% in CVA occurrence in the ePTFE group when compared with the Polyester group (hazard ratio, 0.445; 95% confidence limit, 0.222–0.890; p = 0.0221). Linearized CVA rates also were decreased at all time intervals after implantation in the ePTFE group.

Conclusions: Preliminary clinical results with the newly introduced ePTFE inflow conduit provide compelling evidence that the ePTFE conduit material significantly decreases thromboembolic complications during mechanical circulatory support with the Novacor LVAS. J Heart Lung Transplant 2004;23: 1366-70. Copyright © 2004 by the International Society for Heart and Lung Transplantation.

Neurologic complications remain one of the most serious adverse events for mechanical circulatory support (MCS) recipients. Although a certain baseline number of neurologic complications can be expected in this extremely moribund patient population, the addition of an artificial blood-conducting pathway and a mechanism to propel the blood certainly are contributing factors. Engineering methodologies are used to limit these risks by addressing the issues outlined by Virchow in his seminal report on pre-disposing factors for thromboembolic complications.[1] Virchow's triad (i.e., vessel-wall abnormalities, abnormal flow, and coagulation state) must all be addressed in the development and clinical use of an effective MCS device. The current study addresses the wall material by replacing the polyester material typically used in this application with expanded polytetrafluoroethylene (ePTFE).

We based the hypothesis that ePTFE would provide a superior material for this application on the realization that the left ventricular assist system (LVAS) inflow conduit, in terms of flow and pressures, is more venous than arterial.[2] ePTFE has been used extensively in vascular grafts, and evidence suggests that the material

From the [a]University of Ottawa Heart Institute, Ottawa, Ontario, Canada; [b]German Heart Center Berlin, Berlin, Germany; [c]Hospital Niguarda ca' Granda, Milan, Italy; [d]Gasthuisberg University Hospital, Leuven, Belgium; [e]Cliniques Universitaires Saint-Luc, Brussels, Belgium; [f]Herz-und Diabeteszentrum NRW, Bad Oeynhausen, Germany; [g]AKH der Stadt Vienna, Vienna, Austria; [h]Ludwig-Maximilians-University Munich, Munich, Germany; [i]World Heart Corporation, Ottawa, Ontario, Canada and Oakland, California; and [j]Stanford University School of Medicine, Stanford, California.

Submitted July 15, 2003; revised September 8, 2003; accepted September 10, 2003.

Three of the authors have a financial interest in World Heart Corporation, the manufacturer of the Novacor LVAS. T. Mussivand and R. Halfmann are employees of the corporation and P. Portner is a consultant.

Presented at the 22nd Annual Meeting and Scientific Sessions of the International Society for Heart and Lung Transplantation, April 10, 2003, Vienna, Austria.

Reprint requests: Tofy Mussivand, MD, Cardiovascular Devices Division, University of Ottawa Heart Institute, 40 Ruskin Street, Room H560, Ottawa, Ontario, Canada K1Y 4W7. Telephone: 613-761-4545. Fax: 613-761-4478. E-mail: tmussivand@ottawaheart.ca

 1053-2498/04/$–see front matter. doi:10.1016/j.healun.2003.09.029

is less thrombogenic,[3] has less platelet activation,[4] and has less complement activation.[5] All of these properties contribute to a decreased inflammatory process.[6] These potential benefits were investigated in Novacor LVAS studies with an ePTFE conduit in the ovine model (n = 8, unpublished data, Oyer PE, et al. 1997-98). These studies demonstrated the elimination of a pseudoneointimal lining. These findings led to the clinical introduction of the ePTFE conduit in Europe and Canada that is reported here.

METHODS

Device

The device used in this study is the Novacor LVAS (World Heart Corporation; Ottawa, Canada, and Oakland, CA, USA), which is an implanted, electromechanically driven, dual pusher-plate pump that has been described previously.[7–9]

Inflow Conduits

The Novacor LVAS was initially introduced with an inflow conduit constructed from a low-porosity polyester material (Cooley®, Meadox Medical; Oakland, NJ). Subsequently, in March 1998, an integrally supported, knitted-polyester inflow conduit (Vascutek®, Sulzer Vascutek Ltd; Renfrewshire, Scotland, UK) was introduced to address the mechanical and mural-flow shortcomings of the Cooley conduit.[2] Most recently, an inflow conduit constructed from ePTFE (Edwards Lifesciences; Irvine, CA) has been used clinically.

After the initial 52 implantations with the ePTFE inflow conduit, modifications were undertaken to enhance overall structural integrity and to improve sealing at the apical cannulation site, without changing the blood interface. Subsequent analysis of outcomes demonstrated no significant differences in embolic cerebral vascular accident (CVA) ($p = 0.569$) between the initial and revised ePTFE configurations, and for the purpose of this analysis, we have grouped them together.

Patients

We retrospectively analyzed 398 patients. All patients had New York Heart Association (NYHA) Class IV heart failure. The Polyester group consisted of 310 patients who underwent implantation with the Novacor LVAS with a polyester inflow conduit (155 with the Cooley® inflow conduit implanted between May 1995 and November 1998, and 155 with the Vascutek® inflow conduit implanted between March 1998 and July 2000). The ePTFE group consisted of 88 patients, including all patients who underwent implantation with the ePTFE inflow conduit in Europe and Canada between April 2000 and January 2003. The ePTFE implantations were conducted at 25 centers (see Appendix I for contributing centers and investigators).

Table 1. Differences in Baseline Patient Characteristics by Group

	Polyester group (n = 310)	ePTFE group (n = 88)	Significance
Mean age (years)	47 (16–75)	51 (14–68)	0.0114†
Cause			
Cardiomyopathy	67%	60%	
Ischemic	25%	36%	0.0019*
Acute myocardial infarction	4%	4%	
Other	4%	–	

*Fisher's exact test. †Student's t-test.
ePTFE, expanded polytetrafluoroethylene.

Table 1 shows patient characteristics for both groups. We noted 2 significant differences between the 2 groups: 1) slightly older patients in the ePTFE group and 2) a greater proportion of patients with ischemia in the ePTFE group.

Data Analysis

We conducted statistical analyses using the SAS System (SAS for Windows Version V.8e, SAS; Cary, NC). We used the Student's t-test and the Fisher's exact test to compare baseline characteristics and overall incidence of embolic CVA. We used the Poisson regression rate ratio to compare the linearized rate of embolic CVA. Kaplan-Meier and log-rank statistics were used to compare freedom from embolic CVA. Cox proportional rate determined the decrease in risk for embolic CVA. We used Kaplan-Meier analysis of freedom from embolic CVA to calculate risk up to 180 days, because previous reports had documented that the greatest risk for embolic CVA occurs within the first 30 days and that 97% of embolic CVAs occur within 180 days after implantation.[2]

We defined an embolic CVA as a cerebral deficit that was sudden in onset, clinically relevant, and persisted for >24 hours.[2] The embolic origin of the deficit was confirmed by conventional diagnostic methods or at autopsy.

RESULTS

We noted a significant improvement in freedom from embolic CVA in the ePTFE group using the Kaplan-Meier analysis (Figure 1). We found a 55% decrease in the risk of embolic CVA in the group that received the ePTFE inflow conduit compared with the Polyester group, using the Cox proportional ratio method (hazard ratio, 0.445; 95% confidence limit, 0.222–0.890; $p = 0.022$).

We also found a significant difference ($p = 0.002$) in the overall incidence of embolic CVA between the ePTFE group with 9 events in 88 implants (10%) and the Polyester group with 73 events in 310 implants (24%). We also conducted ad hoc review of each of the events in the ePTFE group. Each of the clinical

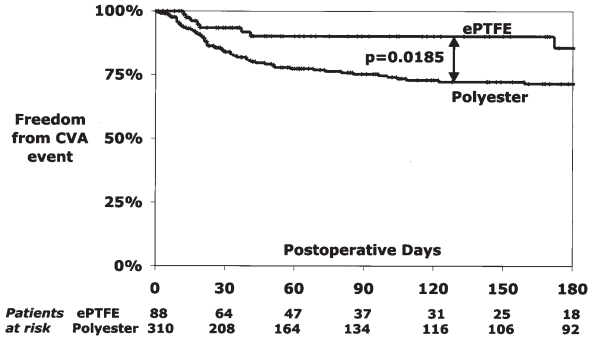

Figure 1. Kaplan-Meier analysis of freedom from embolic CVA in the ePTFE and Polyester inflow-conduit groups. CVA, cerebral vascular accident; ePTFE, expanded polytetrafluoroethylene.

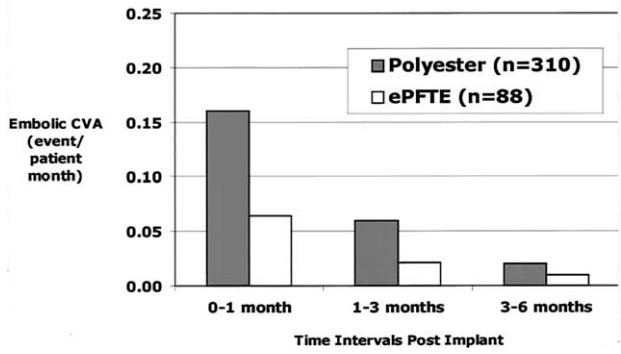

Figure 2. Comparison of linearized rates (events per patient-month) for embolic CVA between the polyester and ePTFE inflow-conduit groups at specific time intervals after implantation. CVA, cerebral vascular accident; ePTFE, expanded polytetrafluoroethylene.

teams were asked whether detailed examination of patient records provided any specific clinical issues that may have been primarily responsible for the events. Based on this review, investigators identified 2 of the 9 events in the ePTFE group as non–device-related. One patient had a previous history of peripheral thromboembolism and 1 had left ventricular thrombus at the time of initial LVAS implantation. Excluding these events would result in a device-related incidence of embolic CVA with the ePTFE inflow conduit of 7.9%.

Because of the recent availability of the ePTFE inflow conduit and a larger proportion of the ePTFE implants currently being used, we noted a significant difference in the mean support time between the 2 groups: 120 days (0–921 days) for the ePTFE group vs 210 days (0–1796 days) for the Polyester group. However, as previously noted, the clinical experience to date clearly has established the first 30 days of support as the period of greatest risk for embolic CVA, with a subsequent temporally diminishing risk.[2,8,10] However, to confirm that the difference in mean support times between groups in this analysis did not skew the results, we also calculated linearized rates (events/patient-month) (Table 2). Again, we noted a significant decrease in embolic CVA for the ePTFE group, with a linearized rate of 0.025 events/patient-month vs 0.034 events/patient-month for the Polyester group (rate ratio, 0.76). Assessing the linearized rate for non–device-related events further decreased the rate to 0.019 events/patient-month (rate ratio, 0.59). In addition, if we separate the linearized rates into specific time intervals after implantation (i.e., first 30 days, 30–90 days, etc.) as shown in Figure 2, the difference between the 2 groups is even more pronounced. With this approach a 50% decrease in the linearized embolic CVA rate is observed between the groups during the greatest risk period of the first 30 days, which is consistent with the 55% risk reduction determined by the Cox proportional ratio. Furthermore, we observed a decrease in the embolic CVA rate for the ePTFE conduit at all time intervals after implantation.

Finally, to assess differences between each of the different conduit models, we performed a Kaplan-Meier analysis (Figure 3) and calculated linearized rates (Figure 4). As previously noted, we found a significant difference between the ePTFE conduits and Polyester conduits ($p = 0.018$). In addition, we noted significant differences between the ePTFE conduit and the

Table 2. Incidence and Linearized Rates of Embolic CVA by Group

	Polyester group ($n = 310$)	ePTFE group ($n = 88$)	ePTFE group excluding non–device-related events* ($n = 88$)
Number of events (embolic CVA)	73	9	7
Support time			
Mean, range (days)	210 (0–1796)	120 (0–921)	120 (0–921)
Total time (months)	2178	354	354
Linearized rate (events/pt-month)	0.034	0.025	0.019
Poisson regression rate ratio (95% CL)		0.76 (0.38–1.52)	0.59 (0.27–1.28)

*As identified by the clinical teams.

CL, confidence level; CVA, cerebral vascular accident; ePTFE, expanded polytetrafluoroethylene.

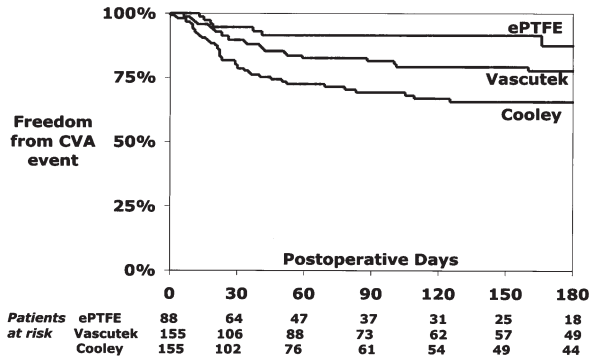

Figure 3. Kaplan-Meier analysis of freedom from embolic CVA for each of the conduit models (Cooley®, Vascutek®, and ePTFE groups). CVA, cerebral vascular accident; ePTFE, expanded polytetrafluoroethylene.

Cooley® conduit ($p = 0.001$), and between the Vascutek® conduit and the Cooley® conduit ($p = 0.012$). These results also clearly show the progression of improvement with each of the subsequent conduit models introduced into clinical use.

DISCUSSION

There are several limitations to the results reported, as outlined below. However, because of the impact of embolic CVA on the patient's quality of life and because of the strength of the results, we deemed early publication to be in the best interest of clinicians and recipients, prompting release of these preliminary results.

The following issues are potential limitations to the analysis; however, because of the small number of events, meaningful sub-analysis of each of these issues is not possible at this time:

1. The anti-coagulation regimen varies widely between individual centers and clinicians.
2. Differences exist in conduit length. The Vascutek® and ePTFE conduits are available in 2 lengths (6 cm and 9 cm), and the Cooley® conduit originally was available in 3 lengths, of which the 9-cm conduit was used in all but 1 center. Although the majority of ePTFE and Vascutek® implantations are performed with the shorter model, some centers use the longer conduit in larger patients. Again this is an area of much intercenter variability. A previous study, however, found no significant differences between Vascutek® conduit lengths in the incidence of embolic CVA.[2]
3. Modifications were made to the ePTFE conduit after the first 52 implantations as previously noted, which could have affected the results. However, the blood pathway was unchanged between these 2 models, and we noted no significant differences in terms of embolic CVA ($p = 0.569$).
4. The ePTFE group had a smaller sample size and shorter support duration, as previously noted. These factors are related directly to the recent use of this conduit.

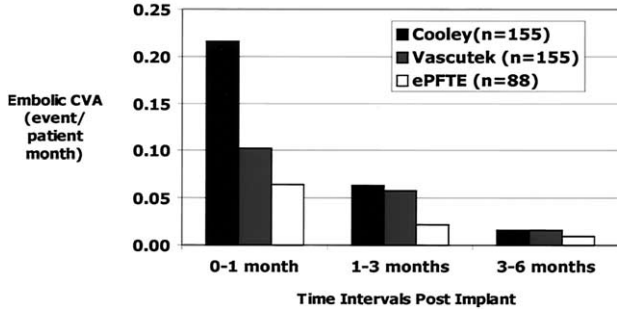

Figure 4. Comparison of linearized rates (events per patient-month) for embolic CVA between each of the conduit models (Cooley®, Vascutek®, and ePTFE groups) at specific time intervals after implantation. CVA, cerebral vascular accident; ePTFE, expanded polytetrafluoroethylene.

The results with ePTFE inflow conduit use in the Novacor LVAS support the hypothesis that the venous nature of the inflow conduit benefits from using a material proven in venous applications. The breadth of these results includes decreases in risk, incidence, and linearized rates at all periods after implantation. Furthermore, the data set consisted of all implantations to date in Europe and Canada, and we noted no special limitations placed on conduit use, which suggests that the results should translate well into even more widespread application.

As noted by Pasque and Rogers,[11] it is impossible to directly compare published embolic rates among various devices because of differences in adverse event definitions, vagaries of reporting, and marketing influence. However, it is clear that use of the ePTFE conduit in the Novacor LVAS now has decreased the embolic CVA rate to rates similar to those reported in comparable cohort studies with other available devices,[12–15] perhaps approaching the baseline event rate expected in this severely ill patient population while receiving circulatory support.

The new ePTFE conduit, with its decreased embolic complication rate, adds to the already established clinical long-term reliability and durability of the Novacor LVAS.[9,16] These characteristics make the system an ideal candidate for the rapidly evolving destination therapy application in which device longevity and reliability is crucial to the recipients' quality and quantity of life.

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APPENDIX I: Contributing Centers and Investigators From Europe and Canada

Austria: AKH des Stadt Wien (E. Wolner, G. Wieselthaler).
Belgium: Cliniques Universitaires Saint-Luc (P. Noirhomme), Gasthuisberg University Hospital (B. Meyns).
Canada: University of Ottawa Heart Institute (P. Hendry).
France: CHU de la Timone (E. Collart), Hopital European George Pompidou (JN. Fabiani), Hopital La Pitie Salpetriere (A. Pavie).
Germany: Albert-Ludwigs Universit Freiburg (F. Beyersdorf), Deutsches Herzzentrum Berlin (R. Hetzer), Herz-und Diabeteszentrum NRW (R. Körfer, A. El-Banayosy), Ludwig-Maximilians-Universität (B. Reichart, P. Überfuhr), Klinikum Universität Regensburg (D. Birnbaum, FX. Schmid), Zentrum für Herzchirurgie Erlangen-Nürnberg (M. Weyand).
Italy: Instituto Clinico Humanitas (R. Galotti, E. Gronda), IRCCS Policlinio San Matteo–Universita di Pavia (M. Rinaldi), Ospedale Borgo Trento, Universita di Verona (A. Mazzucco, G. Faggian), Ospedale Civili di Brescia (A. Muneretto, G. Minzioni), Ospedale Niguarda ca' Granda (E. Vitali), Ospedale Riuniti de Bergamo (P. Ferrazzi), Ospedale Santa Maria della Misericordia (U. Livi).
Netherlands: Leidse Universiteit Medisch Centrum (R. Dion), Utrecht Universiteit Medisch Centrum (J. Lahpor).
Romania: Fundeni Hospital (V. Candea, H. Moldovan, D. Gherghiceanu).
Sweden: Uppsala Akademiska Sjukhuset Hospital (S. Thelin).
Switzerland: Universitätsklinik Basel (HR. Zerkowski).