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Influence of Inflow Cannula Length in Axial-flow Pumps on Neurologic Adverse Event Rate: Results From a Multi-center Analysis

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Background: The application of axial-flow pumps in patients with end-stage heart failure reveals a significantly reduced infectious complication rate as compared with rates observed with pulsatile devices. The remaining adverse event rate relates mainly to thromboembolic complications with neurologic consequences. We investigated the dependence of the neurologic adverse event rate on the length of the inflow cannula.

Methods: A total of 216 consecutive patients with an axial-flow pump (INCOR; Berlin Heart GmbH, Berlin, Germany) were included in a retrospective multi-center analysis. In 138 patients, a short inflow cannula (24-mm tip length into the left ventricle), and in 78 patients a long inflow cannula (tip length 34 mm) was applied.

Results: Patients with a long inflow cannula (LC) demonstrated a better survival rate than those with a short inflow cannula (SC) at the end of the observation period (LC, 63.4%; SC, 52.9%; $p = 0.05$). The thromboembolic adverse event rate was also significantly lower. Only 3 of the 78 patients (3.8%) with an LC had a thromboembolic adverse event (thromboembolic events per patient-year = 0.11) as compared with 32 (23.2%) of SC patients (thromboembolic events per patient-year = 0.50, $p < 0.001$).

Conclusions: Patients with a long inflow cannula had a better survival rate and a lower incidence of cerebrovascular adverse events than patients with a short inflow cannula. J Heart Lung Transplant 2008;27:253–60.

Heart transplantation, the so-called "gold standard" for patients with end-stage heart failure, can no longer be provided in time for many individuals due to the worsening shortage of donor organs. Consequently, short-term mechanical support to bridge patients to transplantation has developed into long-term support with patients being treated for lengthy intervals on an outpatient basis.[1–4] Furthermore, long-term mechanical circulatory support has gained a high level of acceptance with a satisfactory technical reliability of the devices. However, the rate of cerebrovascular events is still a matter of concern. To avoid clot formation and consecutive cerebral infarction, patients need to be treated with anti-coagulants and platelet inhibitors regardless of the type of device.

The INCOR left ventricular assist device (LVAD), a magnetically levitated axial-flow pump, has been available since 2002.[2] Up to now, the INCOR LVAD has shown no instances of serious technical failure, and infection rates have been exceedingly low. Although during the development phase major attention focused on minimizing pump-related activation of the coagulation and platelet aggregation system, the rate of neurologically adverse events was higher than expected in the early cohort of very moribund heart failure patients. A precise analysis of the underlying causes of the adverse events revealed that the length of

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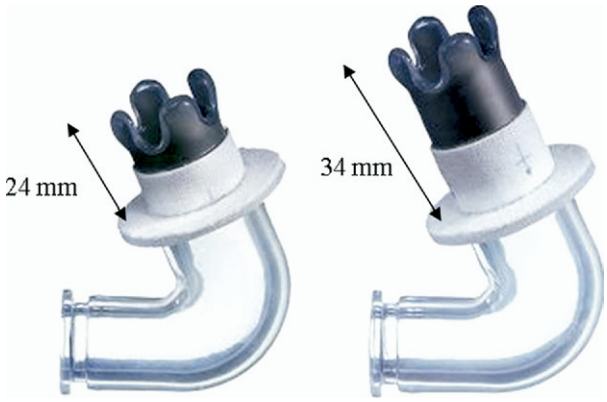

Figure 1. Short inflow cannula (left), long inflow cannula (right).

the inflow cannula had a definite influence on the adverse event rate. The present analysis examines the effect of the intra-cavitary length of the inflow cannula on the rate of neurologic complications.

METHODS

Device

The INCOR LVAD (Berlin Heart GmbH, Berlin, Germany) is an axial-flow pump with a weight of 200 g and an outer diameter of 30 mm. One of the key features of this device is the magnetically suspended impeller, rotating at speeds of 5,000 to 10,000 rpm. A flow of 5 liters can be generated against a pressure of 90 mm Hg at a typical rotational speed of 7,500 rpm. Because the INCOR has no mechanical bearings, friction is absent and there is no mechanical wear. Although the impeller rotates with a constant speed that is individually set for each patient, residual activity of the native left ventricle may propagate through the pump and lead to measurable pulsatility in the patient's circulation. An anti-suction algorithm automatically reduces the rotation speed of the impeller in case of insufficient left ventricular filling to prevent collapse of the left ventricle and suction of its wall. The motor of the INCOR is extremely efficient (>95%), and has an extraordinarily low energy consumption of approximately 3.0 watts under regular operating conditions. All blood contact titanium surfaces are heparin-coated (Carmeda). A percutaneous drive-line connects the pump with the external controller. The control unit and the two batteries are carried in a shoulder-bag, which enables safe keeping and transport of these components. Further details have been described elsewhere.[5,6]

Cannulas

In this analysis two different inflow cannulas were used. The intraventricular part, which is stabilized by a titanium tube with a corona, was manufactured in two different sizes (Figure 1). A long cannula (LC group) was devised when post-transplant evaluation of the inflow cannulas revealed a sometimes inappropriate position of the short cannula (SC group) in the left ventricular cavity. We hypothesized that the long inflow cannula that reaches further into the left ventricle has a lower rate of thromboembolic complications than the short inflow cannula, where the rim sometimes does not surmount the trabeculae of the left ventricular endocardium (Figure 2).

Patients

During a 4-year observation period lasting from the first clinical implant on June 16, 2002 until June 30, 2006,

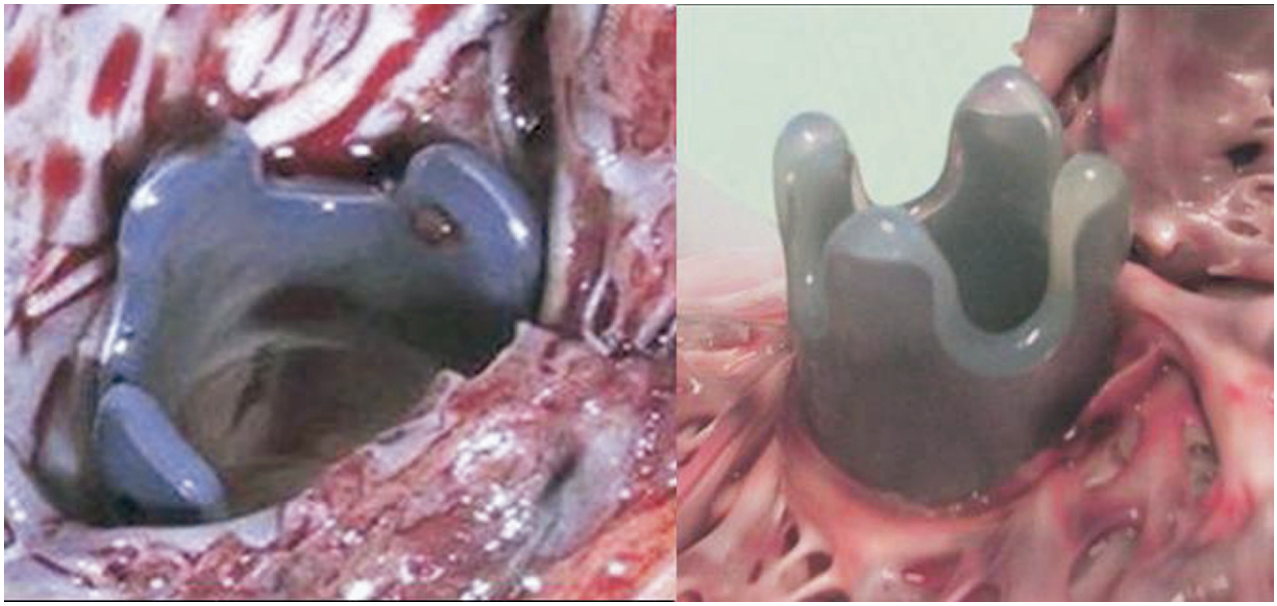

Figure 2. Post-transplant presentation of the short cannula on the left and the long cannula on the right (photos courtesy of Dr. E. Hennig, German Heart Center, Berlin, Germany).

273 patients were provided with the INCOR worldwide. Patients undergoing device implantations via a lateral thoracotomy were excluded from this analysis as were implants in centers with only minimal INCOR experience (fewer than 5 implants) to eliminate a bias originating from a VAD learning curve. Finally, 216 patients would be included into this retrospective analysis.

The first 4 patients were supported with a long inflow cannula. From October 2002 until May 2004 the short inflow cannula was used. Thereafter, the new long cannula was progressively introduced, and use of the short cannula was limited to patients with an extremely thin left ventricular wall at the insertion site. Overall, 138 of the patients received the short cannula (SC), whereas the long cannula (LC) was used in 78 patients. Baseline patient characteristics for both groups are depicted in Table 1.

Surgical Techniques

In the majority of patients, placement of the device was performed employing cardiopulmonary bypass. The anastomotic technique was similar to that used for other implantable LVADs and was usually applied under beating heart conditions[7] or induced ventricular fibrillation.[8,9] The apex of the heart was elevated and an apical hole created in the left ventricle. Non-resorbable interrupted sutures were placed circumferentially with PTFE felt as reinforcement. The inflow cannula was mounted with the aid of a fixation ring. The pump was connected via snap-in connectors and rotated into proper position. The drive-line was guided through the abdominal wall to exit on the right side between the costal arch and the iliac crest. The outflow conduit was trimmed to an appropriate length and anastomosed end-to-side to the ascending aorta. Before connecting the outflow conduit to the pump, both cannulas, as well as the pump, were properly de-aired.

Peri-operative Treatment

During and after surgery all patients received standard care in the intensive care unit. Measures to prevent post-operative right heart failure included positive inotropic drugs, and inhalation of iloprost or nitric oxide[10,11] to lower the after-load, that is, the pulmonary vascular resistance. Excessive unloading of the left ventricle was avoided as right ventricular function may be impaired if the septum shifts to the left side. Fluids and diuretics were carefully balanced and anti–heart failure medication with angiotensin-converting enzyme (ACE) inhibitors and beta-blocking agents was initiated as soon as possible, considering the after-load sensitivity of rotary blood pumps.

Anti-coagulation was started with standard heparinization for extracorporeal circulation. After termination of cardiopulmonary bypass heparin was fully neutralized with protamine. About 12 to 24 hours after surgery, heparin therapy was resumed if drainage losses had declined and the platelet count exceeded 50,000/μl. The heparin dosage was adjusted to achieve a partial thromboplastin time (PTT) of 60 to 80 seconds. Once the patient had recovered further, platelet inhibitors (acetyl-salicylic acid and/or clopidogrel and/or dipyridamol) were added. The appropriate dosage of anti-platelet therapy was adjusted using thromboelastography and aggregometry.[12] With removal of all drains and

Table 1. Demographic Data of 216 Patients With Classical Medial Implantation of the INCOR LVAD in High-volume Centers

	Short cannula (n = 138)	Long cannula (n = 78)	p
Age (years), mean (range; SD)	49.3 (16–72; ±12.6)	53.1 (25–70; ±10.9)	0.025
Male gender, n (%)	119 (86.2)	68 (87.2)	0.510
Height (cm), mean (range; SD)	176.3 (152–221; ±8.8)	176.1 (150–196; ±9.6)	0.887
Weight (kg), mean (range; SD)	80.2 (45–152; ±15.3)	81.1 (55–132; ±15.6)	0.667
BSA (m^2), mean (range; SD)	1.96 (1.50–2.72; ±0.20)	1.97 (1.58–2.54; ±0.21)	0.777
BMI (kg/m^2), mean (range; SD)	25.8 (15.57–42.55; ±0.72)	26.2 (16.95–37.75; ±0.51)	0.506
Etiology, n (%)			
Dilative CMP	62 (44.9)	37 (47.4)	0.415
Ischemic CMP	45 (32.6)	31 (39.7)	0.506
Acute infarction	16 (11.6)	7 (9.0)	0.362
Acute myocarditis	9 (6.5)	0 (0)	0.016
Other	6 (4.3)	3 (3.8)	
LVEF (%), mean (range; SD)	16.7 (4–40; ±6.2)	17.0 (5–40; ±7.5)	0.755
LVEDD (mm), mean (range; SD)	71.8 (33[a]–90; ±10.7)	74.1 (54–110; ±11.4)	0.300
CI ($liters/min/m^2$), mean (range; SD)	1.7 (0.7–2.8[a]; ±0.4)	1.7 (0.8–3; ±0.5)	0.634
mPAP (mm Hg), mean (range; SD)	36.7 (7–90; ±11.5)	37.4 (17–74; ±13.6)	0.744
CVP (mm Hg), mean (range; SD)	14.6 (3–30; ±5.5)	14.1 (1–33; ±7.0)	0.625

BSA, body surface area; BMI, body mass index; CMP, cardiomyopathy; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; CI, cardiac index; mPAP, mean pulmonary artery pressure; CVP, central venous pressure.

[a]One patient presented with severe RCMP.

Table 2. Support and Survival

	Short cannula (n = 138)	Long cannula (n = 78)	p
Support interval (days), mean (range; SD)	186 (1–805; ±187)	171 (0–1128; ±211)	0.603
Outcome of all, n (%)			
Ongoing	7 (5.1)	30 (38.5)	<0.001
HTx	60 (43.5)	18 (23.1)	0.002
Weaned	6 (4.3)	3 (3.8)	0.582
Deceased	65 (47.1)	27 (34.6)	0.05
Cause of death, n (%)	(n = 65)	(n = 27)	
MOF	34 (52.3)	14 (51.9)	0.167
CVE	9 (13.8)	4 (14.8)	0.464
Cancer	2 (3.1)	0	
Trauma	2 (3.1)	0	
RVF	4 (6.2)	4 (14.8)	
PA embolus	1 (1.5)	0	
Bleeding	1 (1.5)	0	
Other	10 (15.4)	5 (18.5)	
Unknown	2 (3.1)	0	

HTx, heart transplantation; MOF, multiple-organ failure; CVE, cerebrovascular event; RVF, right ventricular failure; PA, pulmonary artery.

central lines, oral anti-coagulation was initiated with an international normalized ratio (INR) range of 2.5 to 3.0. In short, the anti-coagulation protocol was similar to those of other axial-flow devices.[13]

Cerebrovascular Events

The main focus of the study was major cerebrovascular events, including stroke and cerebral bleeding. Stroke was a clinical diagnosis, defined as cerebral ischemia with consecutive neurologic symptoms persisting for >24 hours, irrespective of findings in cranial computed tomography (CT). Cerebral bleeding, caused either by spontaneous rupture of a blood vessel within the head or after stroke, mandated confirmation by CT scan, regardless of present symptoms.

Data Retrieval and Statistical Analysis

The study was designed as a retrospective, international, multi-center data analysis. Data were retrieved from the Berlin Heart database, where results from implantation and post-operative surveillance from all INCOR implant procedures had been collected without patient identification. A second audit of the data was performed by each center and approval of all local institutional review boards was obtained.

Statistical analysis was performed utilizing SPSS software, version 14.0 (SPSS, Inc., Chicago, IL). Baseline characteristics of both patient groups were expressed as mean, range and standard deviation, and were compared by t-test for unpaired groups. Logistic regression was used to show the equality of both groups. The chi-square test was used to compare data regarding etiology, outcome and adverse events. The Cox proportional hazard model was used to get an overview on the dependency structure. Survival curves and freedom from stroke were calculated according to the Kaplan–Meier test, whereas the differences between groups were compared using the log-rank test.

RESULTS

Baseline characteristics were similar in both (SC and LC) groups by direct comparison and logistic regression analysis (Table 1). Mean support interval (SC, 186 ± 187 days; LC, 171 ± 211 days; p = 0.603) was not significantly different between the two groups, but at the end of the observation period 38.5% of patients in the LC group were still on mechanical support as opposed to 5.1% in the SC group ($p < 0.001$; Table 2). This difference is explained by an increased waiting time on the transplant list, a more recent implantation date, and a larger number of destination therapy patients in the LC group. Consequently, fewer patients in the LC groups underwent heart transplantation (SC, 43.5%; LC, 23.1%; $p < 0.002$).

At the end of the observation period, overall survival was better in the LC group as compared with the SC group (SC, 52.9%; LC, 63.4%; p = 0.05). Likewise, the 1- and 2-year survival rates based on the Kaplan–Meier survival curves were better for LC patients (61% and 53%, respectively) than for SC patients (50% and 33%, respectively) (p = 0.27; Figure 3). In addition, 4.3% of patients in the SC group and 3.8% in the LC group could be weaned from the device (p = 0.582). Causes of death did not differ between the LC and SC groups. The main cause of death was multi-organ failure in >50% patients in each group (SC, 52.3%; LC, 51.9%; p = 0.167). Fatal cerebrovascular events accounted for 13.8% (SC) and 14.8% (LC) of all deaths (p = 0.464).

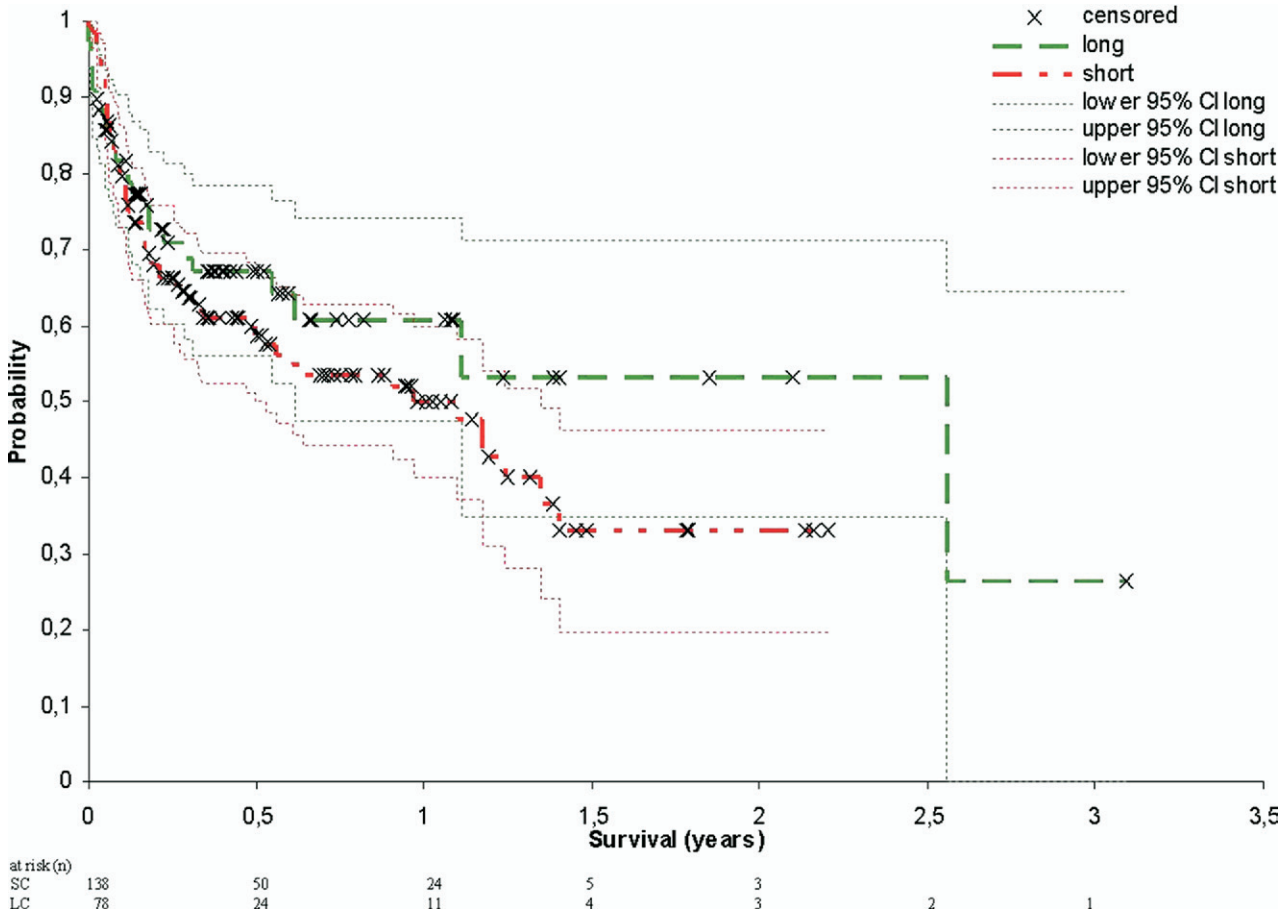

Figure 3. Probability of survival.

A benefit of the long apex cannula was not only seen when evaluating survival, but also with regard to neurologic adverse event rates (Table 3). Cerebrovascular events varied in their clinical appearance, ranging from plegic, aphasic and anoptic symptoms that recovered in most patients over time to severely impacting events. The freedom from stroke was significantly better in the LC group (96.2%) as compared with the SC group (76.8%; $p < 0.001$). As shown in Figure 4, freedom from stroke at 1 and 2 years remained at 95% for LC patients compared with 68% and 64%, respectively, for SC patients ($p < 0.001$). The respective event rate per year was similarly different: 0.11 event per patient-year in the LC group vs 0.50 event per patient-year in the SC group. In the Cox proportional hazards model, the type of inflow cannula turned out to be the most significant variable ($p = 0.005$) with regard to stroke (Table 4). The relative risk of stroke was 6.03 times higher in the SC group than in the LC group.

The number of patients suffering from intracerebral bleeding was also lower in LC patients. The incidence and event rates for cerebral bleeding declined from 10.1% to 5.1% ($p = 0.152$), and from 0.21 event per patient-year to 0.11 event per patient year when switch-

Table 3. Adverse Events

	Short cannula ($n = 138$)	Long cannula ($n = 78$)	p
Stroke (n)	35	4	
Patients effected, n (%)	32 (23.2)	3 (3.8)	<0.001
Events per patient-year	0.50	0.11	
Time to event (days), mean (range; SD)	73 (2–429; ±86)	38 (4–66; ±31)	
Intracerebral bleeding (n)	15	4	
Patients effected, n (%)	14 (10.1)	4 (5.1)	0.152
Events per patient year	0.21	0.11	
Time to event (days), mean (range; SD)	118 (18–330; ±110)	271 (15–933; ±442)	

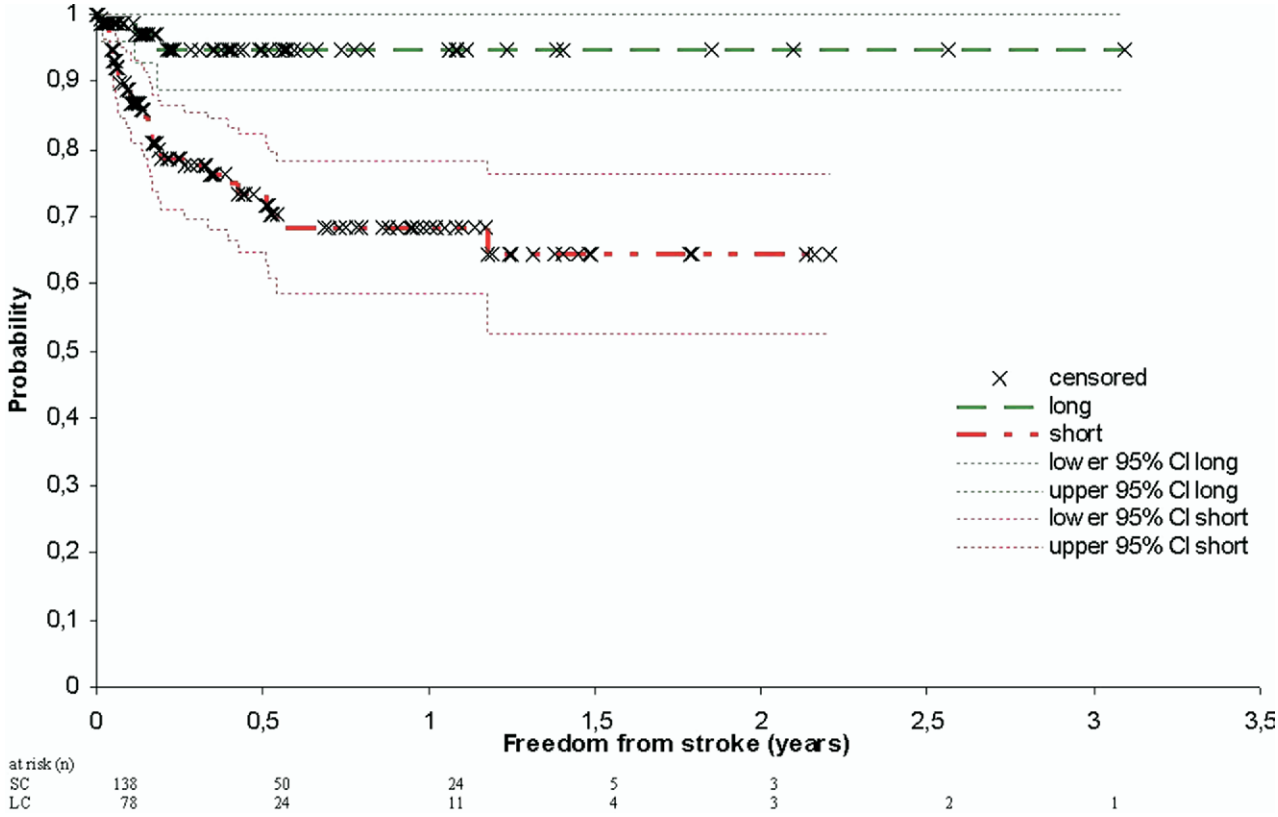

Figure 4. Freedom of stroke.

ing from the short to the long inflow cannula. The relative risk of intracerebral bleeding was 1.98 times higher in the SC group.

DISCUSSION

The problem of thrombus formation in cardiac implants has been known for many years from insertion of mechanical valves as well as from pacemaker and defibrillator lead placement.[14] In mechanical assist devices, technical advances led to the introduction of axial-flow pumps and further optimization of blood flow, with minimal dead space promoting blood stasis. Again, cumbersome progress was made with inflow cannulas. Suction of septal myocardium into the inflow conduit and pump thrombosis had to be overcome.[15]

Table 4. Cox Proportional Hazard Model for Freedom of Stroke

Variable	*p*
Inflow cannula	0.005
Age at implant	0.261
Height	0.320
Weight	0.605
Gender	0.607
Myocarditis	0.936
Acute infarction	0.937
Ischemic CMP	0.944
Dilative CMP	0.949

Nowadays, the inflow cannulas are still a crucial component in ventricular assist devices with regard to thrombus formation. As most emboli spread to the brain and lead to transitory ischemic attacks (TIAs) and strokes, this subject has been a major focus of research in the field of ventricular assist devices.[16–18]

The idea behind modification (length reduction) of the inflow cannula was to have a smooth and step-free transition from the endomyocardium into the cannula, ignoring the effects of cell growth, blood flow pattern, individual endomyocardial anatomy, varying thickness of the ventricular apex and individual surgical techniques. Further clinical observations during device explantation prior to heart transplantation or post-mortem demonstrated that the inflow cannula was not properly inserted in some cases, and interfered with the myocardial trabeculae. These cases were frequently associated with increased thrombus formation (see Figure 2). Thus, the length of the inflow cannula and its extension into the left ventricular cavity was identified as a contributing factor for the nascency of thrombus formation.

At a first look, it seems reasonable that a cannula that sticks between the trabeculae and that has a partially occluded inflow tip will have an extremely unfavorable effect on the flow pattern and, therefore, would quite easily generate thrombi. At transplantation or autopsy

we have also seen cannulas that extended absolutely freely into the ventricular cavity in patients who had suffered thromboembolic complications. Accordingly, other mechanisms must play a role in thrombus formation. In some patients we observed growth of fibroblastic tissue from the left ventricular apex along the cannula into the lumen. The underlying causes are unclear, but patient-specific causes, surgical technique and blood flow pattern may be involved. Pannus formation inside the cannulas has never been observed.[19]

The unique sensoring function achieved with the magnetic bearing provides a specific alarm ("E22") that appears if a particle develops in or passes through the pump. This alarm never occurred in patients who remained free from neurologic events, whereas it was very sensitive in patients who experienced a stroke. The nature of this alarm (abrupt vs slow development) indicates that all stroke events originated in particles that passed through the pump and not in thrombi that formed inside the pump.

Based on the aforementioned findings, the need for proper cannula placement was made clear; however, in this study, we have also highlighted the utility of a longer inflow cannula. Further, our retrospective analysis of 216 patients demonstrated clearly superior results in the patient group with the long inflow cannula. This was true for survival, thromboembolism and intracerebral bleeding, although the average age of the LC group was higher as a consequence of the growing number of patients with an INCOR for destination therapy. The causes of death, especially those induced by cerebrovascular events, among both groups were not significantly different. Thus, a direct relationship between cerebrovascular cause of death and length of inflow cannula cannot be established. Nevertheless, the proportion of patients dying from cerebrovascular events (13.8% and 14.8%) was much lower than the 22.0% indicated by INTERMACS.[20]

The dramatic decline in the overall number of thromboembolic complications in the LC group was impressive and highly significant. The thromboembolic event rate per patient-year had dropped to almost 20% and the relative risk dropped by a factor of 6. During explantation, transplantation or autopsy, there was neither thrombus formation nor fibroblastic tissue observed around the intraventricular part of the LC. Accordingly, it seems that the increased intraventricular length prevented thrombus formation by trabecula interference, and the different flow pattern prevented growth of fibroblastic tissue around the cannulation site.

The incidence of cerebral bleeding was also much lower in the LC group. The rate of cerebral bleeding per patient-year, as well as the relative risk for an intracranial bleeding, decreased by 50%. With the observation of lower stroke rates some physicians somewhat lowered the level of anti-coagulation and anti-aggregation. Thus, one may speculate that the improved results reflect a learning curve, but all 12 participating centers had some experience with other assist devices prior to the study.

As the length of the cannula inside the left ventricular cavity was the decisive factor in this study, the long inflow cannula has become standard equipment. For patients with a very thin apical myocardium, the short cannula is still available. In comparison to other left ventricular assist devices, the overall rate of cerebral thromboembolic and bleeding complications with the INCOR device has improved dramatically. The 5% level indicates the limit of complication rates usually considered satisfactory. However, even with the newer devices, these goals are only rarely achieved.

In conclusion, INCOR patients with a long inflow cannula demonstrated significantly better survival and a significantly lower incidence of cerebrovascular adverse events. The overall rate of cerebrovascular complications has declined to a very acceptable level, rendering the INCOR an excellent tool for long-term mechanical support in cases of acute or chronic heart failure.

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