High level of cerebral microembolization in patients supported with the DeBakey left ventricular assist device

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Objective: Microembolic signals detected by transcranial Doppler ultrasonography have been demonstrated to be clinically relevant in patients supported with pulsatile left ventricular assist devices. We prospectively investigated the quantity of microembolic signals in patients supported with the continuous-flow DeBakey left ventricular assist device (MicroMed DeBakey VAD; MicroMed Technology, Inc, Houston, Tex) including the refined Carmeda BioActive Surface system (Carmeda AB, Stockholm, Sweden).

Methods: Twenty-three patients (20 male) aged 14 to 62 years supported with DeBakey left ventricular assist devices (n = 6 with Carmeda) were enrolled in this study. Microembolic signal monitorings were performed twice weekly by insonating the middle cerebral artery for 20 minutes without and 20 minutes with oronasal application of oxygen (6 L/min). Evidence of clinically manifest thromboembolic events was based on regular questionnaires, clinical examinations, and results of diagnostic procedures.

Results: Despite a low incidence of thromboembolic complications (0.24 per 100 left ventricular assist device days), 20 patients (87%) showed circulating microemboli. Overall, microembolic signals were found in 175 of 499 transcranial Doppler ultrasonographic examinations (35.1%), with mean counts of 81.2 ± 443 (range 0-5042 signals/h). Both microembolic signal prevalence (25% vs 34%, $P = .01$) and absolute signal counts (46.5 vs 104 , $P < .01$) significantly declined with oxygen delivery. There was no significant correlation between the individual microembolic signal activity and the incidence of clinical thromboembolism or the intensity of antihemostatic treatment. Patients supported with the Carmeda device did not show reduced rates of clinical thromboembolization or cerebral microemboli.

Conclusion: In patients with DeBakey left ventricular assist devices, a high load of clinically silent microemboli can be detected within the cerebral arteries despite a low incidence of embolic complications. It needs to be investigated whether such continuous, presumably gaseous microembolization causes cognitive or neuropsychologic deficits.

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Left ventricular assist devices (LVADs) have become an accepted therapy to bridge patients with severe heart failure to cardiac transplantation.¹ Advances in LVAD technology have not only improved clinical outcome but have enabled better patient mobility,² allowing LVAD use even in an outpatient setting.^{3,4} Moreover, several reports have shown recovery of native ventricular

function in a subgroup of patients after long-term LVAD support.^{5,6} LVADs have even been proposed as a definite treatment option for end-stage heart failure.³

Various serious complications (eg, thromboembolism, bleeding, and infection) represent major limitations to the widespread application of LVADs.^{1,7,8} The risk of thromboembolic events seems to be device specific, directly related to the characteristics of the blood-contacting surface.⁹ In the past, most patients have been treated with pulsatile LVADs. Lately, the novel continuous-flow DeBakey LVAD (MicroMed DeBakey VAD; MicroMed Technology, Inc, Houston, Tex) has been developed and is believed to cause less thromboembolism because of its chamberless and valveless design.¹⁰ The newest DeBakey LVAD is endowed with a covalently bonded heparin surface (Carmeda system; Carmeda AB, Stockholm, Sweden), which is intended to reduce its thrombogenicity further. However, there are no robust diagnostic tools enabling us to define the individual risk of LVAD-associated complications. It has therefore not been possible thus far to discriminate low-risk patients who may be suitable for long-term LVAD-support from high-risk patients who rather require early heart transplantation.

During recent years, it has been recognized that microembolic signals (MESs) are noninvasively detectable by transcranial Doppler ultrasonography (TCD) in patients with increased risk of embolic stroke.¹¹⁻¹³ It has been shown for various patient groups that these clinically silent microemboli may possess prognostic information with respect to future risk of thromboembolism.¹⁴ Recently, we found a significant correlation between the quantity of MESs and the individual risk of clinical thromboembolic complications in 20 patients supported with the Novacor N100 LVAD (Baxter Healthcare Corp, Novacor Div, Oakland, Calif).¹⁵ In this study we present an analysis of the long-term follow-up of 23 patients supported with the nonpulsatile MicroMed DeBakey LVAD. The following questions were addressed: (1) How many MESs are detectable in patients with the DeBakey LVAD? (2) Do MESs represent prognostic markers that reflect the individual risk of clinical thromboembolization in this population? (3) Do MESs correlate with type and intensity of antithrombotic treatment? (4) Are circulating microemboli in these patients solid or gaseous in nature?

Methods

Subjects

From July 2000 to July 2002, a total of 23 patients who had undergone implantation of the DeBakey LVAD were enrolled in this study. The last 6 patients were supported with the latest developed pumps equipped with the Carmeda system. After the purpose and protocol of this study had been explained comprehensively, all patients gave informed consent. The patients had dilated cardiomyopathy (n = 12), chronic ischemic heart disease (n = 10),

and postpartum cardiomyopathy (n = 1). The LVAD implantation procedure and the perioperative management have been described elsewhere.^{10,16}

Antithrombotic Treatment

After implantation, all patients were effectively anticoagulated using with (target activated partial thromboplastin time 60-80 seconds). One patient had heparin-induced thrombocytopenia and was therefore anticoagulated with danaparoid sodium (target anti-factor Xa ≥ 0.35 U/mL). After stabilization of the clinical situation, oral anticoagulation with phenprocoumon was started (target international normalized ratio 2.5-3.5). In addition, oral therapy with platelet antiaggregation drugs was initiated either with aspirin at 100 mg/d or with the combination of aspirin at 330 mg/d and dipyridamole at 75 mg/d. The rationale for these two differing antiplatelet regimens was that as yet no approved therapy with antiplatelet drugs for DeBakey LVAD patients is known to reduce the risk of thromboembolic events. So far, varying approaches of different antiplatelet drugs and dosages in diverse DeBakey studies have been done (Potapov and colleagues¹⁶ no antiplatelet drugs, Salzberg and associates¹⁷ aspirin at 100 mg/d, Vitali and colleagues¹⁸ 100 mg/d aspirin with dipyridamole at 800 mg/d), but without any investigation regarding the exact drug combination and dosage for clinical use. Recently, Bonaros and coworkers¹⁹ showed the necessity of antiplatelet therapy in patients with the DeBakey device because platelet activation markers were upregulated in the postoperative period.

Six patients were discharged from the hospital with LVAD support and were seen at least once weekly in the outpatient clinic. In some cases, blood was drawn only once or twice weekly to monitor the coagulation status. Therefore an attempt was made to perform the MES monitoring on the day of the coagulation test. If no blood was drawn on the day of the TCD examination, the blood test closest to this TCD examination (<3 days) was taken for further statistical analysis.

MES Monitoring

Repeated MES monitoring was performed with the patient in a supine position with a 2-channel 2-MHz probe of a commercially available TCD machine (TC 4040; EME, Überlingen, Germany). The 40-minute examination period included 20 minutes of TCD monitoring while the patient was breathing room air and another 20 minutes with oxygen delivery (6 L/min) by facial mask, arranged in random order. The rationale for this procedure is that in patients with artificial heart devices, large numbers of microemboli are gaseous and caused by cavitation processes at the rims of the valves.^{20,21} Through 100% oxygen delivery at 6 L/min instead of air at atmospheric pressure, the rate of cavitation-induced MESs could significantly be reduced. The physiologic explanation is that the nitrogen present in air bubbles is replaced by oxygen, and because oxygen bubbles have a shorter life span because of oxygen's higher solubility in blood, the number of MESs reaching the brain is strongly reduced. Thus comparison of MES counts detected with and without oxygen delivery provides an estimate of gaseous microemboli.

The main stem of the right middle cerebral artery was unilaterally identified through the temporal skull in a depth of 45 to 60 mm, with a sample volume kept at 10 mm. With the 2-channel

TABLE 1. Survey of the clinical characteristics and results of repeated MES monitoring

											MES monitoring		
Basic characteristics						Treatment and clinical course					MESs		
	Age		Body mass	Primary			Effective	Antiplatelet					
No.	(y)	Sex	index	heart	Carmeda	LVAD	anticoagulation*	treatment†	Embolic	Patient	Exams	Prevalence	Signals/h
			(kg/m ²)	disease	system	time (d)	(%)	(%)	events (No.)	outcome	(No.)	(%)	(mean ± SD)
1	47	M	26	ICM	No	106	100	62	0 (0%)	HTX	5	60	6.6 ± 11.7
2	42	M	29	ICM	No	167	90	88	0 (0%)	HTX	24	25	263.7 ± 809.7
3	18	M	23	DCM	No	280	85	99	0 (0%)	HTX	43	49	189.8 ± 658
4	40	M	22	DCM	No	245	67	9	0 (0%)	HTX	27	26	15.2 ± 33.5
5	28	M	25	DCM	No	200	58	73	0 (0%)	HTX	22	36	322.2 ± 991.8
6	41	M	24	DCM	No	254	72	64	1 (0.4%)	Death	18	0	0 ± 0
7	46	M	34	ICM	No	145	73	85	0 (0%)	HTX	21	33	152.6 ± 481.2
8	62	M	26	ICM	No	81	46	100	0 (0%)	Death	7	43	6.6 ± 15.1
9	50	M	23	ICM	No	299	73	80	0 (0%)	Death	11	9	0.7 ± 2.3
10	54	M	24	DCM	No	74	72	92	0 (0%)	Death	8	38	6.4 ± 9.7
11	57	M	25	ICM	No	108	47	74	1 (0.9%)	Death	6	0	0 ± 0
12	24	F	20	DCM	No	60	43	43	0 (0%)	Death	6	50	27.3 ± 57.6
13	20	M	21	DCM	No	274	100	73	0 (0%)	HTX	11	36	33.1 ± 62.1
14	47	M	26	ICM	No	123	64	100	1 (0.8%)	Death	11	36	54 ± 152
15	56	M	24	ICM	No	387	80	24	2 (0.5%)	Death	72	31	24.3 ± 134.3
16	28	M	21	DCM	No	421	95	62	2 (0.5%)	HTX	56	30	49.1 ± 250.4
17	59	M	30	DCM	No	413	85	25	0 (0%)	HTX	36	22	5.8 ± 28.7
18	50	M	25	DCM	Yes	134	70	59	1 (0.8%)	Death	33	39	70.1 ± 259.7
19	57	M	37	ICM	Yes	9	100	0	0 (0%)	Death	3	0	0 ± 0
20	18	M	23	DCM	Yes	329	73	94	0 (0%)	HTX	53	66	128.8 ± 695.9
21	14	F	22	PPCM	Yes	50	22	11	1 (2%)	Death	9	33	11.3 ± 22.4
22	42	F	29	ICM	Yes	36	50	42	0 (0%)	Death	7	14	0.9 ± 2.1
23	28	M	21	DCM	Yes	54	67	87	1 (1.9%)	LVAD	10	60	11.1 ± 23.2

ICM, Ischemic cardiomyopathy; HTX, heart transplantation; DCM, dilated cardiomyopathy; PPCM, postpartum cardiomyopathy. *Effective anticoagulation is the percentage of time within target range (see Methods section). †Antiplatelet treatment is the percentage of time with antiplatelet therapy.

probe, MES monitoring was performed simultaneously at two depths (45-50 and 55-60 mm) of the middle cerebral artery. Thus true MESs (time delay of the signal appearance in accordance with the flow direction from the proximal to the distal channel) could be distinguished from artifact signals (simultaneous appearance of the signal within both channels).²² The ultrasonographic data were processed with a 128-point fast Fourier transformation with time window overlap of at least 50%. During the entire monitoring period, an experienced investigator was present to watch for patient movements and to detect MESs acoustically on-line. In addition, the MES detection software of the TCD machine was used with a detection threshold greater than 7 dB. Identification of MESs was in accordance with recent consensus statements.^{23,24} An attempt was made to perform MES monitoring twice weekly until the end point (transplantation or death) was reached. In cases of severely unstable clinical situations or reduced patient cooperation, TCD examination had to be postponed until appropriate conditions could be regained. For ambulatory patients, TCD monitorings were performed on the days of clinical follow-up.

Before each TCD examination, a standardized questionnaire was performed to disclose clinically manifest cerebral thromboembolic events (eg, transient focal loss of vision, sensory or motor

dysfunction, and speech disturbance). Furthermore, evidence of peripheral and cerebral thromboembolic complications was based on the regularly screened medical records and patient files. In cases of cerebral or peripheral thromboembolism, results of the respective diagnostic procedures (eg, computed tomography of the head and angiography of the abdominal or peripheral arteries) were noted.

Statistical Analysis

All statistical analyses were done with SPSS 11.0 for Windows (SPSS Inc, Chicago, Ill). Descriptive statistics were based on standard parameters, such as mean ± SD and maximum and minimum values. For nonnormally distributed data, comparisons of two and more groups were performed with the Mann-Whitney and Kruskal-Wallis tests. Frequency distributions were statistically assessed by the χ^2 test (with Yates correction if necessary). Linear regression analysis and the Pearson product moment correlation test were used to evaluate correlations between two parameters.

Results

Basic characteristics of the 23 patients are given in Table 1. The mean duration of LVAD therapy was 188 ± 142 days

Figure 1. Comparison of individual MESs with room air and with oxygen delivery. Strong reduction in MESs was observed in all patients with external oxygen supply. Patients 1 through 17 were supported with regular LVADs and 18 through 23 with Carmeda devices.

(individual range 9-421 days). Twelve patients died of multiorgan failure ($n = 5$), intracranial bleeding ($n = 4$), or right heart failure ($n = 3$). The range of time between the onset of multiorgan failure and death was 3 to 15 days, with a median of 6 days. Ten patients reached heart transplantation, whereas 1 patient was still receiving LVAD support at study's closure. In 78% of the time during LVAD support, patients were effectively anticoagulated (individual range of time 22%-100%), and in 66% of the period patients received antiplatelet therapy (individual range 0%-100%). During a cumulative follow-up of 4249 days, 10 clinically manifest thromboembolic complications occurred in 8 of 23 patients (34.8%) and 6 events of intracranial bleeding occurred in 6 patients (26.1%). This led to overall incidences of 0.24% embolic events (0.24 events/100 LVAD-days) and 0.14% hemorrhagic events. There was no statistical association between the intensity of effective anticoagulation and the occurrence of thromboembolism ($P = .7$). The additional application of platelet inhibitors was likewise not associated with a reduced incidence of thromboembolism, neither with aspirin at 100 mg ($P > .9$) nor with aspirin at 330 mg in combination with dipyridamole at 75 mg ($P > .6$). In a subgroup analysis, the 6 patients with the Carmeda LVADs did not show significantly different frequencies of throm-

boembolic events (0.49%) than did those with conventional DeBakey LVADs (0.19%, $P = .6$).

A survey of the main TCD results is also given in Table 1. A total of 499 TCD monitorings (range 3-72 per patient) were performed. This led to an average examination rate of one TCD monitoring every 8.5 days. MESs were detected in 20 of 23 patients (87%) and in 175 monitoring sessions (35.1%). Thus only 3 patients (13%) remained completely free of MESs on repeated examinations throughout the entire study period. The overall mean MES number was 81.2 ± 443 signals/h (individual range 0-5042 signals/h), with a significant positive correlation between individual prevalences and absolute counts of MESs ($P < .001$). The Carmeda device was not associated with lessening of MESs (81.8 ± 495 signals/h, range 0-5042 signals/h) relative to the conventional DeBakey LVAD (81.5 ± 426 signals/h, range 0-4710 signals/h, $P > .1$).

A significant decline in MESs was evident with oxygen application. When compared with monitoring periods while the patient was breathing room air, both MES prevalence (25% vs 34%, $P = .01$) and absolute MES counts (46.5 ± 283.5 vs. 104 ± 538.4 , $P < .01$) were significantly lower during oxygen supply. Thus at least some subset of the

microemboli must be caused by cavitation processes and therefore gaseous in nature (Figure 1).

There was no statistical association between the individual MES activity and the thromboembolic events, neither when using the MES prevalences ($P > .5$) nor when using the MES counts ($P > .1$). Likewise, the prevalence ($P > .5$) and the quantity of MESs ($P > .3$) did not correlate with the incidence of intracranial bleeding. The MES counts were not related to the intensity or effectiveness of anticoagulation ($P > .9$) or to the application of antiplatelet drugs, neither with aspirin ($P > .9$) nor with aspirin in combination with dipyridamole ($P > .4$). The 8 patients who had one ($n = 6$) or two ($n = 2$) embolic events did not have significantly higher MES prevalences (28.8%) or MES counts ($35.6 \pm 185.7/h$) than did the 15 symptom-free subjects (33.5% and 115.9 ± 562.4 signals/h, respectively, $P > .5$). Over time we observed a large variability of the MES counts for both LVAD systems without a clear trend towards increase or decrease of the MES activity (Figure 2.). There was no correlation between MES activity and patient etiology of heart failure, age, or body mass index (all $P > .8$).

Discussion

The shortage of donor organs has led to expanding waiting lists and has caused a rise in mortality among candidates for cardiac transplantation.²⁵ Consequently, mechanical circulatory support by different types of devices is now a standard clinical procedure for bridging to transplantation. Recently, the novel continuous axial-flow DeBakey LVAD has been introduced to clinical practice.¹⁰ Certain properties of this device are believed to reduce its thrombogenicity: (1) There is no compliance volume shifting chamber. (2) No residual blood volume remains in the device. (3) The rapid rotation of the impeller ensures fast blood flow.²⁶ (4) The specific coating of the newest types of pumps with the Carmeda system may additionally inhibit thrombus formation.²⁷

The aims of this study were to assess the amount of MES detected by TCD and to evaluate their clinical relevance in patients with the nonpulsatile DeBakey LVAD. In two previous studies on patients supported with the pulsatile Novacor LVAD, Nabavi and associates^{15,28} reported a significant correlation between individual MES activity and the clinical manifestation of thromboembolism. Repeated TCD monitoring allowed identification of patients at low risk of clinical thromboembolism. In this study of patients with the DeBakey LVAD, however, we found large quantities of circulating microemboli in roughly every third of 499 examinations during a cumulative follow-up of almost 12 years. Individual peak counts were as high as 5042 signals/h (>1 signal/s), with an overall mean count of 81 MESs per hour, compared with only 2 MES per 30 minutes in patients with the Novacor device.¹⁵ Remarkably, we were unable to

find a correlation between this very high microembolic activity and clinical course. Patients with a higher MES activity did not show a higher risk of thromboembolic complications. In 2 patients (cases 6 and 11) with clinical stroke events, we could not detect any MESs at all during their LVAD time. In fact, the very low incidence of clinically apparent embolism (0.24%) made a valid statistical analysis difficult. In addition, the high numbers of microemboli in our LVAD population could not be related to hemostaseologic alterations. MES rates were completely independent of mode and intensity of anticoagulation or antiplatelet therapy. Even the DeBakey device with the Carmeda system was not associated with reduced MESs.

Recently, unlike these findings with the DeBakey LVAD, we have reported on low MES activity (0.5 signals/30 min.) in stroke-free patients with severe left ventricular dysfunction not being supported with any LVAD.¹² Thus low cardiac output with reduced left ventricular function appeared to be an independent risk factor for microembolic generation.

Gaseous microemboli have been well described in patients with different types of prosthetic cardiac valves.^{29,30} Their gaseous nature has been nicely proved by use of the oxygen inhalation method, leading to almost disappearance of MES in patients with prosthetic cardiac valves.^{20,21} Accordingly, we likewise noted a significant drop in MES counts of more than 50% with oxygen delivery in our patients with DeBakey LVADs. Thus there is strong evidence that most microemboli in our patient cohort are gaseous and not solid. Summarizing all our very latest results, we suggest that microemboli in patients with the pulsatile Novacor LVAD are predominantly solid and carry the risk of thromboembolism, whereas microemboli in patients with the continuous-flow DeBakey LVAD are most likely gaseous in nature and induced by the cavitation processes.

Still, there are important reasons to perform MES detection in patients supported with DeBakey LVADs. First, it is totally unclear why some patients obviously did not produce microemboli at all, whereas in others as many as several thousands per hour appeared. Moreover, some patients had a strongly fluctuating microembolic activity, whereas others had a more or less continuous release. Most likely, properties of the LVAD dynamics play a critical role in the generation of microemboli. We are currently investigating whether certain pump characteristics (eg, power, speed, and output) are associated with increased generation of microemboli. Thus MES monitoring may support technical refinements in LVAD technology. Second, in patients with prosthetic heart valves³¹ and those undergoing heart surgery,^{32,33} it has been demonstrated that the quantity of gaseous microembolization is associated with cognitive impairment and neuropsychological dysfunction. Apparently, a high level of

Figure 2. Time course of microemboli in 23 patients supported with DeBakey LVADs. On *vertical axis*, average number of MESs per hour in a week is given; that did not show significant change with time. **A**, Results of patients with regular LVAD systems. **B**, Results of those with Carmeda devices. Because only 4 patients with regular LVADs had support longer than 40 weeks and only 1 with Carmeda device had support longer than 20 weeks, time axes were restricted to 40 weeks and 20 weeks, respectively.

clinically “silent” microembolization is not as benign as it seems. More sophisticated clinical methods, including repeated neuropsychologic testing, are needed to investigate whether continuous microembolization may produce cortical dysfunction, resulting in chronic encephalopathy. Especially if permanent LVAD support is being considered, the quantity of cerebral microemboli may be an additional criterion to identify suitable candidates for heart transplantation. Finally, even with oxygen delivery and subsequent suppression of cavitation-induced microemboli, large MES counts persisted. Thus a certain fraction of microemboli could still be solid, caused by in situ thrombosis within the native heart or the LVAD. There are several promising new techniques under development that allow classification of MESs according to their acousticophysical properties. In the near future, we will be able to identify the fraction of solid microemboli composed of platelets and plas-matic coagulants. Then we can assess whether hemodynamic, rheologic, or rather inflammatory parameters are involved in the generation of solid microemboli in patients receiving LVAD support.

So far, there is only one other study available on MES detection in patients with DeBakey LVADs. Potapov and colleagues¹⁶ conducted serial MES detection during the first 10 weeks after implantation of this device. Whereas we observed MESs in 20 of 23 patients (87%), they found MESs only in 1 of 5 patients (20%). We can only speculate about the reasons for the discrepancy between our study and the results from Potapov and colleagues.¹⁶ In both studies, technical equipment was appropriate and MES identification was based on generally accepted criteria. Thus methodologic factors are unlikely to account for the difference. Most likely, the differing results reflect the large intersubject and intrasubject variability of microembolism in patients receiving LVAD support. More centers should scientifically address silent microembolization in such patients to further increase our knowledge in this important issue.

In summary, we identified a high level of clinically silent cerebral microemboli in most patients supported with the DeBakey LVAD. Several pieces of evidence indicate that the bulk of these microemboli are gaseous and created by cavitation effects within the LVAD system. Although most patients remained free of stroke symptoms, it needs to be investigated whether continuous microembolization could have deleterious effects on cognitive or neuropsychologic functions.

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