Supplemental methods

Study design, patient enrollment, and follow-up

This study was a prospective cross-sectional study with follow-up. Patients with HeartMate II who consented to participate in this study were cross-sectionally assigned for transcranial Doppler (TCD) examinations and were enrolled from November 2014 to October 2015. All subjects were asymptomatic and stable while entering the study so that no patient had any acute neurological symptoms or thromboembolic symptoms except for two cases with elevated lactate dehydrogenase (LDH) levels (> 600 IU/l) on blood chemistry. All enrolled patients were completely followed-up until June 2016 and the patients who encountered thromboembolic events and/or hemolytic events during the follow-up period were assigned to additional TCD examinations (not only a single examination, but sometimes two or more examinations). Patients who did not develop any hemolysis and/or thromboembolic events during the follow-up period did not undergo additional TCD examinations.

Transcranial Doppler examinations

TCD was performed using the Nicolet SONARA system (Natus Medical Incorporated, San Carolos, CA, USA) using a 2.0-MHz transducer. The right middle cerebral artery (we evaluated the left middle cerebral artery when there was no bone window in the right side) was insonated at a depth of 50–65 mm from the trans-temporal acoustic bone window. The sample volume (generally 10 mm), power, and gain (as low as possible) were adjusted to ensure an optimal embolic signal to background signal relationship.

The Nicolet SONARA system (Natus) utilizes an emboli detection algorithm to identify embolic signals automatically. Microembolic signals (MES) were identified based on the following criteria of the International Consensus group on Microembolus Detection (1): (i) a short duration signal (less than 300 milliseconds), (ii) high intensity signal compared to the background blood flow signal (detected by the system), (iii) unidirectional signal within the Doppler velocity spectrum, and (iv) the presence of an audible noise (heard as a snap, chirp or moan) (Supplemental figure). Two neurologists (K. F. and K. S.) performed the TCD examinations and reviewed all MES manually on the basis of the aforementioned criteria to distinguish MES suggestive of microemboli from artifacts, and MES were

quantified by counting them for 30 minutes.

The TCD examination was considered positive for the presence of microemboli if one or more MES were detected during the 30-minute monitoring period.

In patients with a large number of MES counts (>15 counts/30 min), another set of TCD examinations under oxygen inhalation was performed to discriminate between solid and gaseous emboli. Oxygen was administered at a dose of 6 L/min by a facial mask and MES counts were recorded more than 5 minutes after initiating oxygen inhalation (2). Patients were instructed to breathe normally, and immediately notify if they developed breathing or chest complaints. Significant reduction of MES suggesting gaseous emboli was defined as decrease to less than 50%.

References for supplemental methods

1) Basic identification criteria of Doppler microembolic signals: Consensus committee of the Ninth International Cerebral Hemodynamic Symposium. *Stroke* 26: 1123, 1995.

2) Droste DW, Hansberg T, Kemény V, et al: Oxygen inhalation can differentiate gaseous from nongaseous microemboli detected by transcranial Doppler ultrasound. *Stroke* 28: 2453-2456, 1997.