ELSEVIER

The Journal of
Heart and Lung
Transplantation

http://www.jhltonline.org

A novel non-invasive method to assess aortic valve opening in HeartMate II left ventricular assist device patients using a modified Karhunen-Loève transformation

Corey J. Bishop, BSBME, Nathan O. Mason, Abdallah G. Kfoury, MD, Robert Lux, PhD, Sandi Stoker, RN, BSN, Kenneth Horton, RCS, RDCS, FASE, Stephen E. Clayson, MD, Brad Rasmusson, MD, and Bruce B. Reid, MD

From the Utah Artificial Heart Program, Intermountain Medical Center, Murray, Utah.

KEYWORDS:
aortic valve;
PCA;
Karhunen-Loève transform;
HeartMate II;
neurological events;
thrombus formation;
automation

BACKGROUND: Thrombus formation on or near the aortic valve has been reported in HeartMate II (Thoratec, Pleasanton, CA) left ventricular assist device (LVAD) patients whose aortic valves do not open. With an akinetic valve, thrombogenesis is more likely. Thrombus formation may lead to neurologic events, placing the patient at greater risk. Aortic valve stenosis and/or regurgitation have also been observed with akinetic aortic valves. Assessing aortic valve opening is crucial when optimizing rotations per minute (rpm) to minimize embolic risk and aortic valve stenosis but presently relies solely on echocardiography, intermittent decreases in rpms to force aortic valve opening, and monitoring of pulse pressure. We hypothesized the electrical current waveforms of the HeartMate II would reveal whether the aortic valve was opening due to pressure changes in the left ventricle to allow for continuous monitoring and control of aortic valve opening ratios.
METHODS: Electrical HeartMate II current waveforms of patients from 2008 to 2009 that were recorded at the time of echocardiograph procedures were analyzed using a modified Karhunen-Loève transformation with a training set of electrical waveforms from 8,860 HeartMate II electrical current recordings from 2001 to 2009.
RESULTS: The study included 6 patients. The electrical current magnitude of the projection of the electrical current waveforms onto the training set's eigenvectors was statistically significantly greater in 4 of the 6 patients when the aortic valve was closed, confirmed by echocardiography. The 2 patients who did not have a large increase in the magnitude had mild aortic valve regurgitation.
CONCLUSION: Electrical current analysis for rotary non-pulsatile pumps is a means to develop a physiologic feedback algorithm for an auto-mode, which currently does not exist. Constant regulation and optimization of rotary non-pulsatile LVADs would minimize patients' risk for neurologic events and aortic valve stenosis.
J Heart Lung Transplant 2010;29:27–31

Heart failure is one of the world's leading causes of death, affecting more than 4.5 million people in the United States. The prevalence of heart failure is expected to increase 10% to 15% by the year 2020.[1] In severe cases, heart failure conditions cannot be medically managed, and the patient's only option is to receive a heart transplant; however, there is a tremendous shortage of transplantable hearts worldwide. Patients now have an additional option of receiving a left ventricular assist device (LVAD), which is used for bridging patients to heart transplantation or as destination therapy (implanting the LVAD indefinitely).

The LVAD decreases the workload of the LV by producing both pressure and volume unloading of the heart.

Reprint requests: Corey J. Bishop, Intermountain Medical Center, Utah Artificial Heart Program, 5121 S Cottonwood St, Murray, UT 84157. Telephone: 801-718-9962.
E-mail address: coreyjbishop@gmail.com

doi:10.1016/j.healun.2009.08.027

First-generation LVADs were made to pump blood in a pulsatile manner because the manufacturing companies believed that pulsatility was optimal for the circulatory system. These pulsatile LVADs have bearings and moving parts that limit the durability and life of the pump. To overcome durability issues, LVADs with fewer moving parts were designed. These second- and third-generation LVADs, which are continuous-flow rotary LVADs that contain no bearings, now have an estimated life of 6 to 8 years. Patient outcomes are not adversely affected by the lack of pulsatility.[2]

However, when the non-pulsatile LVADs operate at rotations per minute (rpms) that are too high, most or all of the blood that enters the LV exits through the inflow conduit of the LVAD and essentially no blood volume flows through the aortic valve (AV), its native route. When blood pressure or volume in the native heart is decreased, the LV cannot generate enough pressure to open the AV. This may lead to adverse neurologic events,[3] including transient ischemic attacks and cerebrovascular accidents due to thrombus formation because of an akinetic AV.[4–8] In addition, fusion may occur when the AV is not opening, resulting in stenosis and/or regurgitation, which further promotes disturbances in blood flow.[9]

When LVAD rpms increase and decrease, the apparent native heart contractility decreases and increases, respectively. There is a balance between the degree of LVAD mechanical circulatory support and the LVAD's rpms. The rpms need to be low enough that the AV is opening, but high enough that the patient receives adequate systemic circulation and unloading of the native heart. A current method of assessing this balance is to perform echocardiograms at regular intervals every few months after LVAD implantation.

Frazier et al[10] has shown that when the pulse pressure is $<$ 15 mm Hg, there is a 24% probability the AV is opening with the Jarvik 2000 continuous-flow pump (Jarvik Heart Inc, New York, NY), whereas that probability jumps to 65% when the pulse pressure is $>$ 15 mm Hg.[10] This method is advantageous in determining what rpms are necessary to minimize the risk of complications. However, this method of measuring blood pressure and interfacing the LVAD circuitry for automation would prove difficult in terms of size constraints and extraneous wires. In addition, a Jarvik controller is capable of increasing the probability of AV opening by intermittently dropping the rpms. This is feasible but continuous control of the AV opening ratios would be superior.

This proof of concept article for continuous regulation of rpms describes a novel approach to determine whether the AV is opening to control the AV opening ratios by analyzing the LVAD's electrical current.

Methods

The Karhunen-Loève transform, also known as principal component analysis (PCA), was performed on 6 HeartMate II (Thoratec, Pleasanton, CA) patients using their electrical current waveforms. To train the PCA algorithm to teach the system what consistency is in electrical waveforms, 8,860 electrical waveforms recorded for HeartMate II patients from 2001 to 2009 at our large single-center institution were used. With 8,860 electrical training data samples from our patients, the calculation accuracy in detecting change is greatly improved.

Recording electrical current waveforms

Electrical current waveforms for the HeartMate II LVAD were recorded using Thoratec's external display modules. All electrical current waveform files were saved in *.tci format. To extract the *.tci files' data, we used MinGW (Minimalist GNU for Window), a Minimal SYStem (MSYS) console, and C++ code. The MSYS console pointed the desired *.tci file into the C++ code to output a *.dat file which was then loaded into MatLab (The MathWorks Inc, Natick, MA) and analyzed.

The analysis was begun by calibrating the unscaled *.dat file values, which are proportional to current, into values with units of amps by a multiplication factor of 0.00146. This amp calibration factor was determined by comparison of the known pre-determined Thoratec amp values calculated from Thoratec's Current Waveform Viewer application. The application's output is unfiltered current data in amps. This current data must be intercepted at an earlier stage in order to collect actual values for each data point, thus the need to calibrate before our analysis. An expanded schematic of the electrical current collection phase is shown in Figure 1.

Fast Fouriér transform analysis

The 10-second current waveform shown in Figure 2 is the electrical current in amps after the comparison-calibration. The current was filtered using a low-pass filtering fast Fouriér transform until a single waveform capitulated the overall morphology.

Subsequently, the derivative of the filtered current waveform was analyzed to determine when the ventricular contraction (systolic interval) began. A ventricular contraction was detected when a slope of 1.5e-4 amps/msec was sustained in any given 225-msec current interval for 125 msec. These values were determined by maximizing the number of detected systolic intervals that were complete while rejecting the partial systolic intervals recorded at the beginning and the end of the recording interval. When the first systolic data point was skewed due to its position in the recording cycle, it was discarded to avoid calculation errors. Once the beginning of the full recorded systolic intervals was found, the subsequent 600 msec of current data were extracted.

Data organization

These systolic intervals, from the initialization of the heart contraction to 600 msec after initialization, were stored into a master matrix for all calibrated current *.dat waveforms recorded.

Component factor analysis

The components of the symmetric covariance matrix were calculated using the equation: $\mathrm{cov}(Y_i, Y_j) = E[(Y_i - \mu_{xi})(Y_i - \mu_{xj})]$. The i and j indices run from 1 to the number of observations in the data set. The E is the mathematical expectation, $Y = \mu_i = E(Y_{i/j})$, Y = current in amps. The right eigenvalues and eigenvectors of the shown covariance matrix $(\boldsymbol{M})$ were then calculated using the equation: $(\boldsymbol{M} - \lambda_R \boldsymbol{I})\boldsymbol{X_R} = \mathbf{0}$. The variable λ_R represents the right eigenvalues, $\boldsymbol{X_R}$ represents the right eigenvectors, and $\boldsymbol{I}$ is the identity matrix. Once the eigenvectors were determined, the original electrical signal was projected onto each of the 10 eigenvectors.

The raw data projected onto each of the eigenvectors were analyzed using Student's t-tests to determine trends of current and AV movement as rpms of the rotary HeartMate II LVAD were adjusted during echocardiography. Actual AV opening ratios were determined by recording the current waveforms at the time of an echocardiogram using motion mode.

Results

The study included 6 patients. Their electrical waveforms were analyzed with a training set of 8,860 recorded electrical current

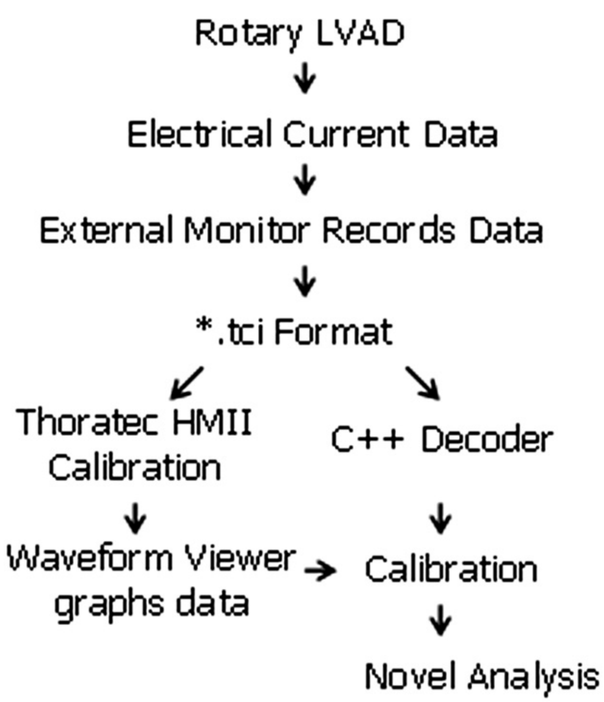

Figure 1 Process of recording and collecting electrical current data from a HeartMate (HMII) rotary left ventricular device (LVAD). Current data are sent from the rotary pump to the external monitor, which records the data in *.tci format. At this point the C++ Decoder intercepts the data and is calibrated for further analysis for our purposes of determining whether the aortic valve is opening.

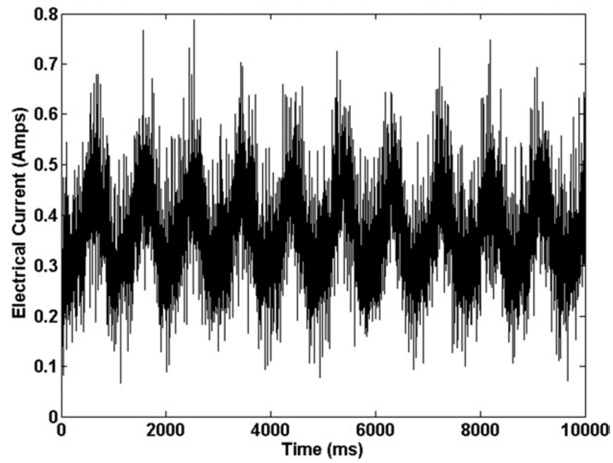

Figure 2 The original 10-second HeartMate II current waveform after calibration in MatLab is shown. Rises in the current depict systolic contraction, whereas the downward slopes depict diastole. The data sampling frequency was 1.00 msec^{-1}. Although the left ventricular assist device is nonpulsatile, pulsatility is introduced into the system because of native heart contractility.

waveforms. The training sets eigenvectors and eigenvalues that satisfied $(\mathbf{M} - \lambda_R \mathbf{I})\mathbf{X_R} = \mathbf{0}$ are shown in Figures 3 and 4, respectively.

One eigenvector correlated with the AV opening. Using the electrical signal projected onto eigenvector 1, we can determine if the AV is opening. The original current signal projected onto eigenvector 1 when the AV was opening and when it was continuously closed is shown in Figure 5. The magnitude of the signal was 0.736 amps when the valve was closed and 1.080 amps when opening.

The ratio of lines in Figure 5 (systolic heart contractions) of the smaller amplitudes to amplitudes that have increased significantly renders the AV opening ratio. This calculation allows the physician the ability to choose what AV ratio is desired for a given patient. The algorithm can then adjust rpms to ensure that the physician-dictated AV opening ratio is maintained by increasing and decreasing the rpms accordingly. To increase the AV opening ratio, rpms decrease until the physician-dictated ratio is reached. On the other hand, to decrease the AV opening ratio, the rpms increase until the

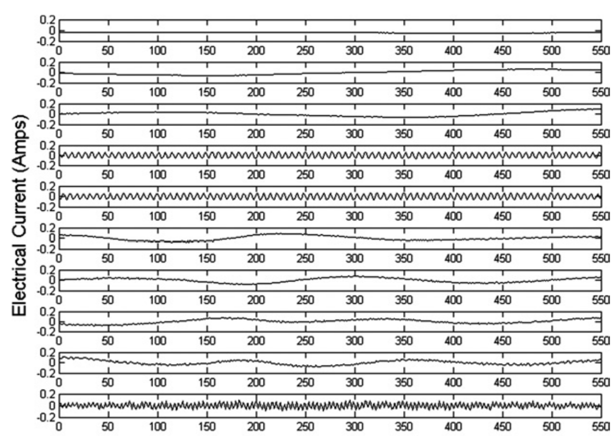

Figure 3 Eigenvectors 1 through 10 are shown.

desired ratio is being maintained. The negative feedback loop allows the appropriate AV opening ratio to be maintained.

When the AV opens, less blood traverses the LVAD compared with when the valve is closed and is seen in the projection of eigenvector 1. Once the valve closes, the LVAD receives more blood and the current increases. This was confirmed using a non-pulsatile mock circulatory system. When we decreased flow to the LVAD by even < 1 mL, the LVAD's current consumption decreased. When we increased flow to the LVAD, the current increased.

Waveforms from 6 patients have been analyzed with motion mode echocardiography validation to date (Table 1). Patients included were those whose AVs were always closed or always opened with adjustments of the rpms. In all cases, the electrical current magnitude change when the AV stopped opening was larger. The current increase in 4 of the 6 patients was statistically significant when the AV stopped opening. The 2 patients whose increase was not statistically significant had mild AV regurgitation. The algorithm currently cannot determine if the AV is opening when there is mild to severe regurgitation, which is a limitation to the algorithm. Further research on AV regurgitation signal characteristics using PCA will hopefully reveal unique signals (perhaps within eigenvectors associated with lower eigenvalues) that will differentiate between AV insufficiency and regurgitation so as to not affect calculations of AV opening ratios.

Discussion

PCA is used to characterize the trends between the AV opening and the current usage of the LVAD by describing a data set using a subset of linear combinations known as eigenvectors. PCA aids visual examination and interpretation of complex data through data reduction and structure detection. Eigenvectors are indicators of shared signal behavior. Associated eigenvalues allow us to rank the order of the importance of contributing eigenvectors to the overall electrical signal. Through echocardiogram comparison, it was possible to determine which eigenvector would reveal behavior that consistently determined if the AV was opening. With this information, using eigenvectors alone, we can determine what the AV opening ratio is without echocardiograms when the AV regurgitation is minimal or zero.

We have been able to identify structural changes in the HeartMate II electric current when the AV is opening and continually closed. These findings have been used to develop a user-friendly waveform viewer for continuous flow, non-pulsatile LVADs for clinical use. However, the implementation of this algorithm in the software would allow for an automated continuous control system of rotary non-pulsatile LVADs to ensure the AV is opening at a particular opening ratio. Doing so will minimize complications associated with the AV not opening for long durations.

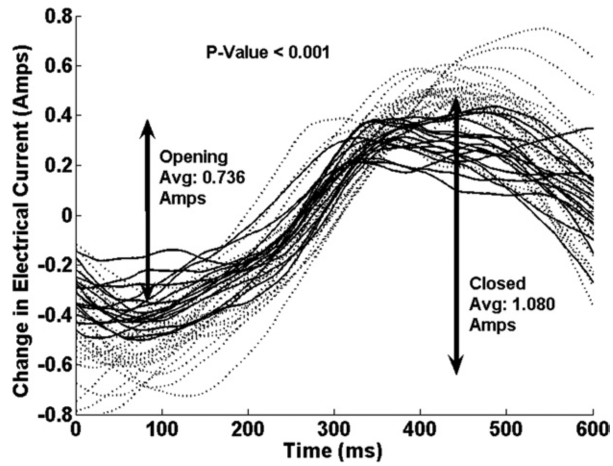

Figure 5 Original current signal was projected onto eigenvector 1 when the aortic valve was opening and closed. The magnitudes are shown with the arrows. The magnitude of the current increases significantly once the aortic valve is closed. The ratio of smaller amplitude lines to larger amplitude lines is the aortic valve-opening ratio. Echocardiography in motion mode confirmed that all heart beats (each line) not opening the aortic valve were larger than when the heart beats opened the aortic valve.

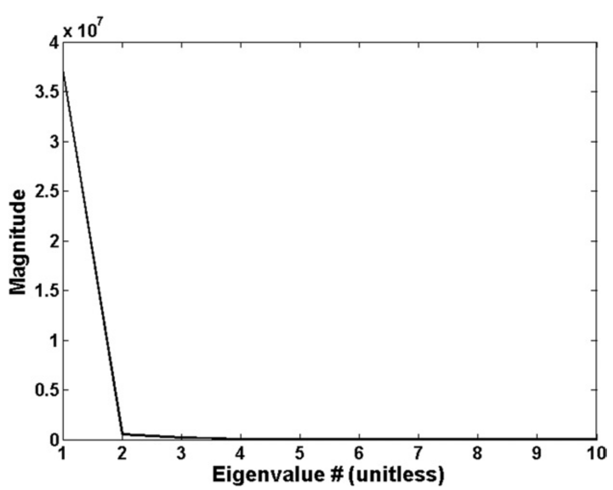

Figure 4 Eigenvalues 1 through 10 are shown. The extremely high values suggest the consistency in the data, which is strong because of the 8,860 samples of data used to train the algorithm. Consistency improves the calculation accuracy.

Table 1 Average Magnitude of the Electrical Current Signal When the Aortic Valve Is Opening vs Closed

	Average magnitude		
Patient	Opening	Closed	p-value[a]
1	0.736	1.080	<0.001
2	1.849	2.366	0.014
3	1.224	1.711	0.003
4	0.883	1.079	0.204
5	1.760	1.894	0.014
6	0.616	0.699	0.242

[a]Values for 4 of the 6 patients were statistically significant ($p < 0.05$). The 2 who were not had mild aortic valve regurgitation.

The automatically regulated continuous control would perform the analysis on multiple rpms within a couple seconds, in the same manner an echocardiogram turndown is performed but in smaller rpm increments and much faster. Through comparing the most consistent portions of the electrical signals at extremely small time intervals, the only changes the algorithm sees in electrical current consistency are due to rpm changes. The quick increase or drop in eigenvector 1 projection magnitudes indicates closing and opening of the AV, respectively. Changes in pre-load, after-load, posture, volume status, blood pressure, medication, heart rate, and contractile reserve of the myocardium, among others, changes over time and cause a change in eigenvector 1 projection magnitudes, but these changes occur over a much longer time period than the algorithm analysis and therefore do not register as opening and closing of the AV. Further clinical studies for further validation in a larger patient population to understand these relationships are underway.

At times, the AV never opens despite adjusting the rpms. For many patients, it is dangerous to decrease the rpms and compromise blood flow to the point that the heart can generate enough comparative pressure to open the AV. Patients whose AVs never open will need an adjunct algorithm to protect the LVAD controller from decreasing the rpms to an excessively low rate. For these situations, we suggest that instead of using the algorithm, the rpms should be lowered to a set interval as with the Jarvik controller.

Although it is possible to determine whether the AV is opening at a given rpm, the scientific community is still endeavoring to determine the ideal opening ratio. With this new current waveform analysis approach, the mechanical circulatory support field will be better equipped with a tool to determine what the ideal ratio is to optimize rotary non-pulsatile LVAD therapy and have the means to choose the ratio best suited for a patient.

Clinical implications and future

This new technology is a user-friendly, non-invasive tool that can be used to automatically regulate the rpms to control LV pressure to allow AV opening at a patient-specific AV opening ratio. The AV opening ratio could be chosen by the physician that would best suit the physiologic needs of each patient as necessary. Adjunct restraints in the algorithm to protect the patient from the dangers of automatic regulation will need to be analyzed further in animal studies. This study is a foundation and stepping stone that will allow the community to better determine how to reduce negative effects of abnormal blood flow due to the AV not opening, through better regulation of rpms. We are in the process of validating our results on a larger scale.

Disclosure statement

The authors acknowledge the support of the Intermountain Medical Center and the Utah Artificial Heart Programs in this research, and the patients and their families.

None of the authors have a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

References

1. Murphy N, Simpson C, Jhund P, et al. A national survey of the prevalence, incidence, primary care burden and treatment of atrial fibrillation in Scotland. Heart 2007;93:606-12.
2. Drews T, Jurmann M, Michael D, Miralem P, Weng Y, Hetzer R. Differences in pulsatile and non-pulsatile mechanical circulatory support in long-term use. J Heart Lung Transplant 2008;27:1096-101.
3. Myers T, Bolmers M, Kar B, Frazier O. Assessment of arterial blood pressure during support with an axial flow left ventricular assist device. J Heart Lung Transplant 2009;28:423-7.
4. Rose A, Park S. Pathology in patients with ventricular assist devices: a study of 21 autopsies, 24 ventricular apical core biopsies and 24 explanted hearts. Cardiovasc Pathol 2005;14:19-23.
5. Crestanello JA, Orsinelli DA, Firstenberg MS, Sai-Sudhakar C. Aortic valve thrombosis after implantation of temporary left ventricular assist device. Interact Cardiovasc Thorac Surg 2009;8:661-2.
6. Horton SC, Khodaverdian R, Powers A, et al. Left ventricular assist device malfunction: a systematic approach to diagnosis. J Am Coll Cardiol 2004;43:1574-83.
7. Rose AG, Park SJ, Bank AJ, Miller LW. Partial aortic valve fusion induced by left ventricular assist device. Ann Thorac Surg 2000;70:1270-4.
8. Lazar RM, Shapiro PA, Jaski BE, et al. Neurological events during long-term mechanical circulatory support for heart failure: the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) experience. Circulation 2004;109:2423-7.
9. Mudd JO, Cuda JD, Halushka M, Soderlund KA, Conte JV, Russell SD. Fusion of aortic valve commissures in patients supported by a continuous axial flow left ventricular assist device. J Heart Lung Transplant 2008;27:1269-74.
10. Myers TJ, Bolmers M, Gregoric ID, Kar B, Frazier OH. Assessment of arterial blood pressure during support with an axial flow left ventricular assist device. J Heart Lung Transplant 2009;28:423-7.